STILL SEARCHING FOR THE ORIGIN OF MIGRAINE: FROM COMORBIDITIES TO CHRONICIZATION

EDITED BY: Claudia Altamura, Gianluca Coppola, Linxin Li and Roberta Messina

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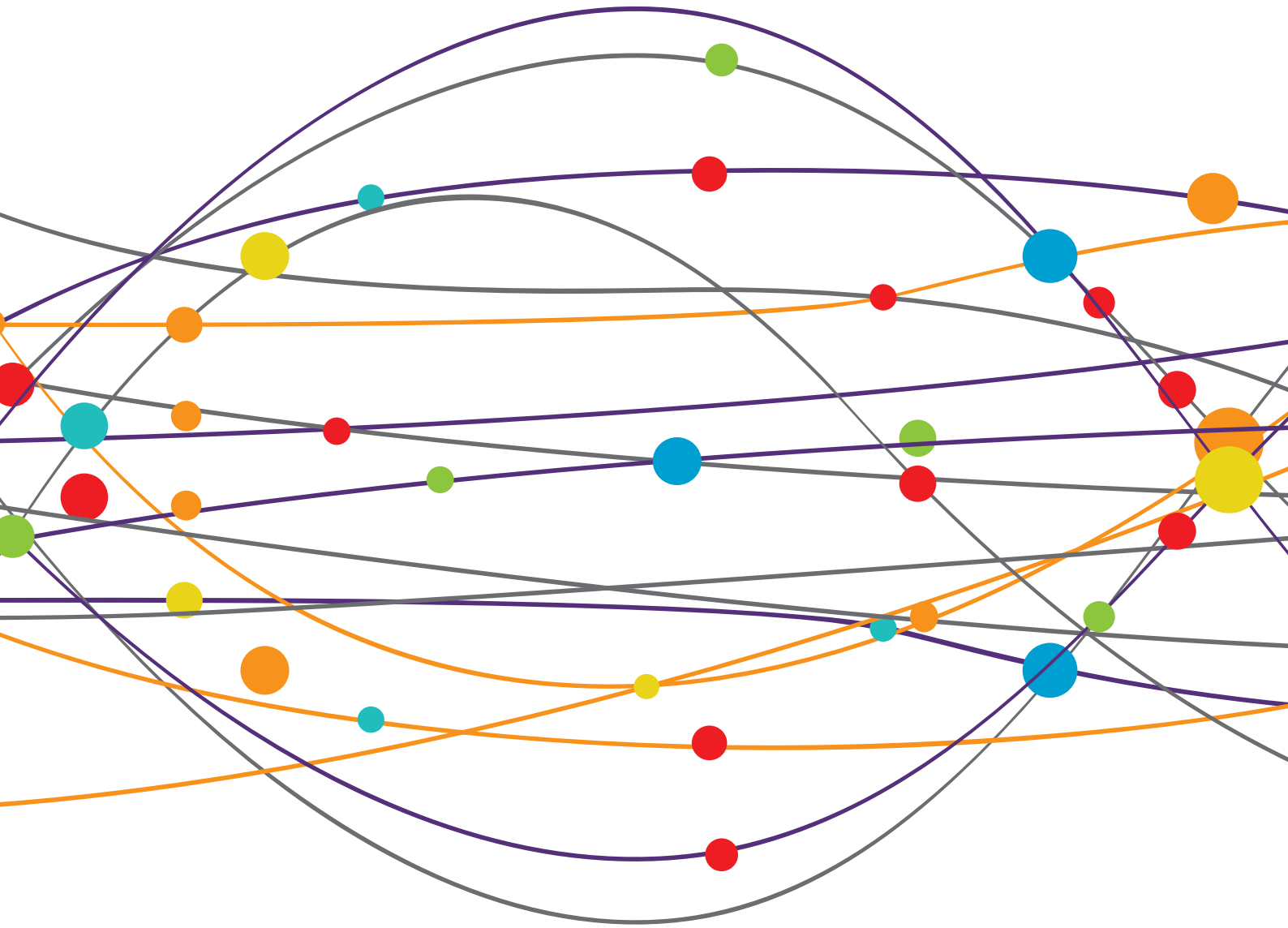

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STILL SEARCHING FOR THE ORIGIN OF MIGRAINE: FROM COMORBIDITIES TO CHRONICIZATION

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EDITORIAL
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Editorial: Still Searching for the Origin of Migraine: From Comorbidities to Chronicization

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Keywords: migraine, comorbid, chronic, physiopathologic mechanism, progression

Editorial on the Research Topic

Still Searching for the Origin of Migraine: From Comorbidities to Chronicization

Migraine is a multifactorial disorder with huge ramifications in the central nervous system. Despite the enormous progress made in recent years in understanding the pathophysiological mechanisms underlying this painful condition, little is known about the factors behind the evolution from the episodic to the chronic form of migraine. One of the main factors subtending this transformation is undoubtedly the excessive, even compulsive, use of symptomatic drugs, whatever they may be. Migliore et al. have shown how complicated the psychopathological profile of medication-overuse headache (MOH) patients is. They are unable to regulate and properly recognize their emotions and are more anxious and depressed. This study also observed that this psychopathological profile influences the severity and impact of the disease in daily life. The tendency to overuse symptomatic drugs most probably has also a genetic basis. The worframin gene (His611Arg) influences drug consumption in psychiatric patients with impulsive addictive behavior. Di Lorenzo et al. observed that the His611Arg polymorphism led to increased use of symptomatic drugs only in patients with MOH, especially those using combination drugs compared with non-medication over-users. Moavero et al. also investigated MOH in a group of children and adolescents with migraine and found that not all patients benefit from drug withdrawal. This finding questions that not all patients with migraine overuse can be correctly classified according to the MOH criteria in the second and third revision of the International Classification of Headache Disorders. These results underline once again how evolving the diagnostic criteria for chronic migraine and its secondary counterpart MOH still are. Nevertheless, these data may indicate the existence of a genetic predisposition underlying the response to withdrawal, a subject not yet investigated.

The existence of episodic syndromes associated with migraine in childhood and adolescence supports the idea that genes play an important additive role in the clinical manifestation of the disease. Cyclic vomiting, an undoubtedly under-diagnosed and very disabling syndrome, about which little is known from a pathophysiological point of view, represents an example. Raucci et al. did a great job in putting together a task force of experts from different disciplines with the valuable aim of reviewing the known salient data on the disease and proposing future research directions.

A child's migraine is undoubtedly an excellent model for studying migraine pathology when it is still in its infancy, i.e., when the pathophysiological mechanisms that abnormally regulate the CNS excitability of the young migraine patient begin to show the first signs of themselves. Rho et al. retrospectively evaluated the EEG of children with different headache types and found a higher frequency of rhythm abnormalities in patients with migraine with aura. Their data also suggest that these patients can experience higher levels of disability in daily life. In general,

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this retrospective study underlines that migraine belongs to central nervous system disorders characterized by cortical dysrhythmia such as epilepsy, an accessual pathology with which migraine is likely to share disease mechanisms. They likely have at least a partial genetic structure in common, as underlined by the most recent genome-wide association studies that have identified a number of gene loci associated with migraine risk, such as those involved in synaptic plasticity, glutamate homeostasis, pain-related pathways, vascular regulation, and vascular tissue. This gene set-up could explain the cardiovascular comorbidity found in particular in migraine with aura patients, in whom patency of the interatrial septum is most frequently seen and whose need for closure is still debated. This is based on the hypothesis that if the patency is broad enough, it may favor the passage of paradoxical embolisms that could trigger cortical spreading depression, the electrocortical phenomenon believed to determine the aura phenomenon. This correlation between patent foramen ovale and migraine is precisely what Liu et al. discuss.

Various disorders may be present in comorbidity with migraine and thus place an additional burden on the patient's shoulders. Anxiety disorder is one of the most frequently detected in studies on the subject, reviewed by Karimi et al. Anxiety disorders are often associated with mood disorders, chronic fatigue, and fibromyalgia, which are again comorbid with migraine, especially when it is chronic (see Karsan and Goadsby). Underlying these disorders may be a shared pro-algogenic terrain, also be favored by the low levels of vitamin D found by Rebecchi et al., especially in patients with chronic migraine. The vitamin D level in the blood correlates with the individual's circadian rhythm. In an fMRI study, Baksa et al. found that different circadian peaks of migraine attack onset are associated with different interictal brain activity in response to threatening fearful stimuli. It is difficult to say whether the same variations could be detected in migraine patients with aura, in whom Carvalho et al. found a delayed motor control response and instability under conditions of external perturbation. The execution of adequate corrective motor responses requires adequate integration between the neural, sensory and musculoskeletal systems. Their dysfunction leads to abnormalities of multiple functional levels in the central nervous system, underlining the extensive central nervous system ramification of migraine pathology.

In conclusion, considering the plethora of pathologies with which migraine, especially when it evolves into a chronic form, is comorbid (see Altamura et al.), we think it is time to move from the original definition of migraine as a "*disease*" to the definition of a "*migraine syndrome*," which incorporates both the pain manifestation and the parade of central and systemic symptoms and pathologies with which it shares comorbidity. In this light, a multidisciplinary approach is necessary to obtain a proficient and persistent relief of pain and other symptoms in people with migraine.

AUTHOR CONTRIBUTIONS

GC drafted the manuscript. CA, RM, and LL reviewed it for intellectual content. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Medication Overuse Withdrawal in Children and Adolescents Does Not Always Improve Headache: A Cross-Sectional Study

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Background: MOH can be diagnosed in subjects with headache occurring 15 days/month in association with a regular medication overuse, but its existence is not universally accepted. ICHD-3 redefined criteria for MOH, removing the criterion associating drug suspension with headache course. The aim of our study was to compare the rate of patients diagnosed with medication overuse headache (MOH) according to ICHD-2 and ICHD-3 criteria, to verify the degree of concordance. The secondary aim was to verify if drug withdrawal was really associated with pain relief.

Methods: In this cross-sectional study, we retrospectively analyzed a sample of 400 patients followed for primary chronic headache at the Headache Center of Bambino Gesù Children's Hospital. We then selected those presenting with a history of medication overuse, and we applied both ICHD-2 and ICHD-3 criteria to verify in which patients the criteria would identify a clinical diagnosis of MOH.

Results: We identified 42 subjects (10.5%) with MOH; 23 of them (55%) presented a relief of headache withdrawing drug overuse. Regarding the applicability of the ICHD-2 criteria, 43% of patients (18/42) fulfilled all criteria, while all ICHD-3 diagnostic criteria were satisfied in 76% of patients (32/42). Eighteen patients (43%) satisfied both ICHD-2 and ICHD-3 criteria, while 10 patients (24%) did not satisfy either diagnostic criterion.

Conclusions: Our study suggests that in children and adolescents, withdrawing medication overuse is not always associated with a clinical benefit. Therefore, though allowing a MOH diagnosis in a higher rate of patients as compared to ICHD-2, the application of ICHD-3 criteria does not guarantee a true a causal relationship between medication overuse and headache worsening.

Keywords: chronic migraine, medication overuse headache, children, ICHD-3 criteria, secondary headache, treatment

INTRODUCTION

Medication overuse headache (MOH) is a headache occurring on 15 or more days/month in a patient with a preexisting primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) for more than 3 months (1). MOH is listed as a secondary headache, in the section focused on "Headache attributed to a substance or its withdrawal."

Although pathophysiologic mechanisms of MOH are still largely unclear, a genetic predisposition likely plays an important role (2, 3). Another potentially significant pathogenetic factor taken into consideration is the interaction between drugs used and neurotransmitters (4) and/or hormonal systems (5). Other factors investigated over time include the presence of abnormal neuronal excitability (6) and changes in gray matter volumes (7) and cerebral metabolism (8–10).

The overall prevalence of MOH in the general population is 0.5–2.6%, although it varies between different studies, probably as a consequence of different diagnostic criteria published over time and different methods used to collect epidemiological data (10, 11). Very few epidemiological studies are available in the pediatric population. Data from Norway and Taiwan report prevalence rate of 0.2 and 0.3%, respectively (12, 13). Data from pediatric populations with chronic primary headache disorders report a medication overuse in 10–60% of cases (14). Both in adults and in children, MOH appears to be more common among females than among males (15, 16). Hopefully, a planned study will clarify some aspect of pediatric MOH (17). This trial plans to evaluate whether the frequency of acute medication overuse is associated with headache frequency in children and adolescents, and the outcomes will be frequency of headache, change in headache frequency in relation to use of acute medications, and headache-related disability (17).

MOH clinical features are usually the same of preexisting primary headache disorder (10). In pediatric patients, it is more commonly associated with chronic migraine (CM) (18). Non-steroid anti-inflammatory drugs (NSAIDs) are the class of drugs more often overused, followed by paracetamol and triptans (15). Historically, the treatment of MOH includes two main strategies: a detoxification program with discontinuation of drugs overused and initiation of pharmacological and non-pharmacological preventive therapy (10).

In the last two decades, diagnostic criteria for MOH were gradually changed. Initially, MOH could be diagnosed only if the headache resolved or reverted to the previous pattern within 2 months after withdrawal of the overused medication (19). In the revision of diagnostic criteria published in 2006 (20), the Headache Classification Committee proposed to remove the criterion concerning the effect of drug suspension on headache course, and this modification was kept in the last published version of ICHD-3 (**Table 1**) (1).

Therefore, MOH can be presently diagnosed in a subject with a history of a preexisting primary headache, presenting with headache occurring 15 days per month in association with a regular medication use exceeding specific thresholds.

TABLE 1 | Diagnostic criteria for MOH by ICHD-2 (2004) [(35) and by ICHD-3 (1)].

ICHD-2	ICHD-3
A. Headache present on ≥15 days/month fulfilling criteria C and D **B.**Regular overuse for ≥3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache **C.** Headache has developed or markedly worsened during medication overuse **D.** Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication	**A.** Headache occurring on ≥15 days/month in a patient with a preexisting headache disorder **B.** Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache **C.** Not better accounted for by another ICHD-3 diagnosis

A direct consequence of new criteria could be an increase in definite diagnosis, since MOH can now be diagnosed even in the absence of improvement after drug withdrawal. However, diagnostic criteria and even the existence of this specific nosographic entity are not universally accepted. For instance, some authors wondered whether medication overuse is the real cause of headache in all subjects fulfilling diagnostic criteria for MOH (14, 19, 21). Indeed, in some individuals medication overuse can increase headache frequency, and discontinuing the medications can have a benefit, but this is not the case in all individuals overusing medications. In some case, increasing headache frequency represents a worsening of the primary headache disorder, and increased use of acute medications is its consequence (14).

The aim of our study was to compare the rate of patients diagnosed with MOH according to the old ICHD-2 and new ICHD-3 criteria, in order to verify the degree of concordance and understand if the new classification really led to different diagnostic rates. The secondary aim was to verify if drug withdrawal is really associated with pain relief and therefore to investigate in a large sample of pediatric patients whether MOH is a true entity.

MATERIALS AND METHODS

In this cross-sectional study, we retrospectively analyzed a sample of patients followed at the Headache Center of the Neuroscience Department of Bambino Gesù Pediatric Hospital in Rome. We included all patients with chronic headache, diagnosed according to the ICHD-3 criteria (1), and followed up at our Headache Center in the period 2010–2018, whose parents gave their informed consent to be contacted for retrospective studies. The sample was partially published in Papetti et al. (18). In particular, 210 out of 377 patients included in the Papetti et al.'s sample (collected between 2010 and 2016) were considered for the present study while the remaining 190 patients were totally original. Moreover, only 20 out 42 of the MOH patients were issued from the Papetti et al. population, while the remaining

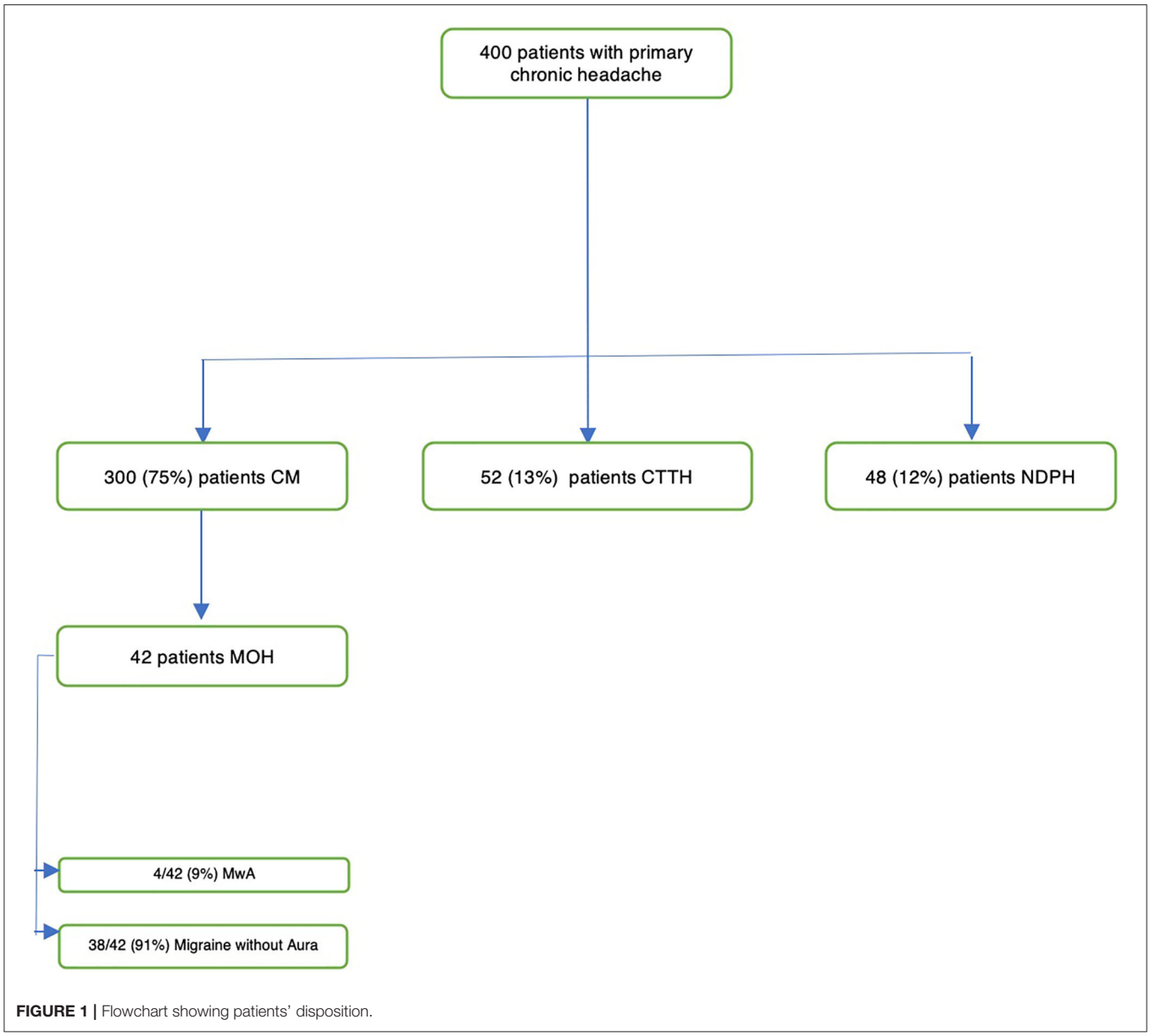

FIGURE 1 | Flowchart showing patients' disposition.

22 patients are totally original. As compared to Papetti et al., the present study investigated different points: (1) the comparison of the applicability of the ICHD-2 and ICHD-3 criteria of pediatric MOH patients and (2) the clinical outcome after medication withdrawal in MOH children and adolescents.

Among these patients, we selected those presenting with a personal history of medication overuse, defined as regular use of abortive therapy: at least 10 days per month for ergotamine, triptans, opioids, or combination-analgesic medication and 15 or more days per month for non-opioid analgesics (paracetamol, non-steroidal anti-inflammatory drug, or acetylsalicylic acid). Overuse should have been carried on for at least 3 months. In all patients, the clinical diagnosis of MOH was tested according to either ICHD-2 or ICHD-3 version criteria, in order to verify the degree of concordance. The diagnoses were made independently by two experienced neurologists, blinded to each other's rating (MV, LP). All these data were initially extrapolated by clinical charts and then confirmed and deeply investigated during follow-up visits and/or telephonic interviews.

Clinical data collected for each patient were the preexisting primary headache type, the clinical characteristics of headache and other symptoms associated, and the treatment used, both symptomatic and prophylactic.

The usual therapeutic strategy was an intensive verbal advice to discontinue the medication overuse, with the suggestion of a different symptomatic treatment than the overused one. In almost all cases, a preventive medication was also proposed, at this same time. Medication withdrawal was considered successful if criteria for overuse were no more satisfied, and it was conducted over a 2-months period. The outcome of medication

withdrawal was assessed after two additional months of follow-up, and it was considered effective if chronic headache reverted to episodic.

Ethical Board approval for retrospective study was obtained.

Statistical Analysis

Statistical analysis was conducted by SPSS version 22.0. To test the hypothesis of a possible association between response to medication withdrawal and sex, type of overused medication, and preventive treatment, we used the χ^2 test. A p-value of ≤ 0.05 was considered significant.

Furthermore, a multiple-regression logistic analysis has been used to evaluate whether age, age at first attack (0–6, 7–10, 11–14, 15–18 years), or type of preventive treatment (topiramate, 5-hydroxytryptophan, flunarizine, amitriptyline) influenced response to withdrawing overused medication. Response to medication withdrawal was selected as a dependent variable, and then all the other variables have been tested as independent variables in a block entry to evaluate the t value, the significance, the standard error, and the upper and lower limit in a confidence interval of 95%.

RESULTS

We collected and analyzed clinical data from a sample of 400 patients (134 M, 266 F) with primary chronic headache. There were no missing data in our sample. Seventy-five percent of patients presented with CM, 13% with chronic tension-type headache, and 12% with new daily persistent headache (NDPH) (**Figure 1**). In 11% of patients (10 patients with NDPH and 37 with CM), migraine with aura (Mwa) was diagnosed.

In this sample, we identified 42 subjects (10.5%, **Table 2**) with symptomatic medication overuse defined as above (at least 10 days per month for ergotamine, triptans, and opioids and 15 or more days per month for non-opioid analgesics). The sample was mainly composed of females (11 M, 26%−31 F, 74%), with a mean age of 13 years at their first medical examination (range: 8–17 years). All patients (100%) presented CM, and 9% (4/42) presented also Mwa. The age at onset of headache was ≤6 years in 9% of patients (4/42), 7–10 years in 29% (12/42), 11–14 years in 48% (20/42), and 15–18 in 14% (6/42). The mean duration of medication overuse was 4.1 months (range 3–6 months).

Photophobia and phonophobia were both present in 81% of patients (34/42), nausea and vomiting in 71% (30/42), and dizziness in 42% (18/42). All patients used NSAIDs as symptomatic treatment; 21% of the sample (9/42) used triptans as further option after a poor response to NSAIDs. Moreover, prophylactic treatment was prescribed in 93% (39/42) of patients, including drug-naïve patients and those who were assuming an ineffective prophylactic therapy. Amitriptyline was the most used drug (79%, 33/42); topiramate was used in 38% (16/42), flunarizine in 28% (12/42), and tryptophan in 15% (6/42). More than one type of prophylactic drug was used in 28% of the sample (12/42; these patients were already assuming one prophylactic drug at the time of our first visit). After withdrawing symptomatic drug overuse, a clear benefit was evident only in 23/42 subjects (55%).

TABLE 2 | Demographic features of patients with chronic migraine and medication overuse.

	N	%
Patients	42	100
Mean age: 13 years (range 8–17 years)	–	–
Sex		
•Males	11	26
•Females	31	74
Diagnosis		
•Chronic migraine	42	100
•Migraine with aura	4	9
Age at onset		
•<6 years	4	9
•7–10 years	12	29
•11–14 years	20	48
•15–18 years	6	14
Symptoms associated		
•Photophobia	34	81
•Phonophobia	34	81
•Nausea and vomit	30	71
•Dizziness	18	42
Symptomatic treatment	42	100
•NSAIDs	42	100
•Triptans	9	21
Prophylactic treatment	39	93
•Amitriptyline	31	79
•Topiramate	15	38
•Flunarizine	11	28
•Tryptophan	6	15

Regarding the applicability of the ICHD-2 criteria, 43% of patients (18/42) fulfilled the diagnosis of MOH while 57% (24/42) did not fulfill all the diagnostic criteria (**Figure 2**). In detail, 21/42 patients (50%) fulfilled criterion A; 35/42 (83%) criterion B, 37/42 (88%) criterion C, and 23/42 (55%) criterion D (**Figure 3A**).

On the other hand, all ICHD-3 diagnostic criteria were fulfilled in 76% of patients (32/42, **Figure 1**). Specifically, ICHD-3 criterion A was fulfilled by 40/42 patients (95%), criterion B by 35/42 (83%), and criterion C by 40/42 (95%) (**Figure 3B**).

Eighteen patients (43%) satisfied both ICHD-2 and ICHD-3 criteria, while 10 patients (24%) did not satisfy either diagnostic criterion.

None of the analyzed variables (age at evaluation, age at first attack, or type of preventive treatment) showed a statistical significance at the multivariate analysis (**Table 3**). The improvement after drug overuse withdrawal was observed in 20/31 (65%) of the females of our sample, compared with 3/8 (38%) of males ($p = 0.03$). However, we have to underline that our sample was mainly composed of females. The type of overused drug was not associated with response to withdrawal ($p = 0.93$).

DISCUSSION

Our retrospective study on a large sample of pediatric patients revealed that the application of ICHD-3 criteria allows a MOH

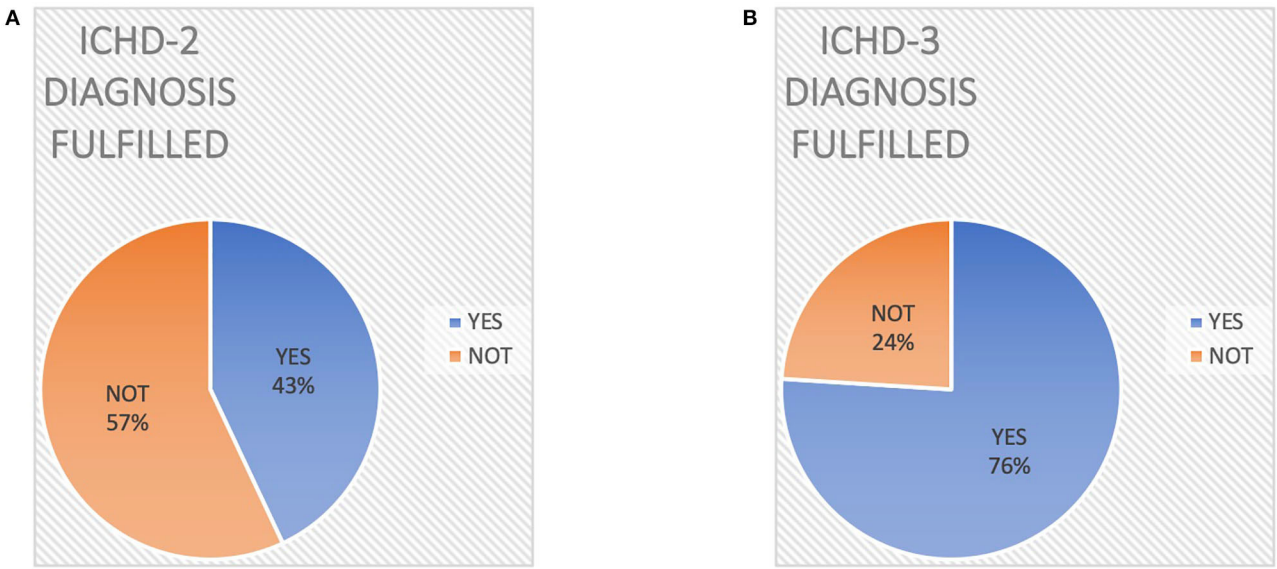

FIGURE 2 | Different diagnostic rate of Medication Overuse Headache according to ICHD-2 criteria **(A)** vs. ICHD-3 criteria **(B)**.

diagnosis in a higher rate of patients (76 vs. 43%), thus proving more sensitive than ICHD-2 criteria. The main difference between the two versions is that ICHD-3 criteria do not require remission or improvement of headache after the regular drugs overuse is stopped. However, ICHD-3 version, removing the relationship between pain and drug overuse, seems to consider the MOH as a fully established diagnosis, while it is still a matter of debate. In ICHD-2, only 50% of patients satisfied criterion A, since many patients did not satisfy criteria C and D. As for ICHD-3, the two patients not satisfying this criterion were adolescents who received the first diagnosis of migraine after initiating the abuse. In both versions of ICHD, only 83% of patients satisfied criterion B, since the remaining 17% of patients presented an overuse of medication for <3 months. Finally, two patients did not satisfy ICHD-3 criterion C since after a careful examination of data it was doubtful if they could be classified as "Headache attributed to non-vascular intracranial disorders."

A second crucial finding of our study is that in our sample symptomatic drug withdrawal was not always sufficient to revert chronic to episodic migraine, thus strengthening the concept that, in turn, medication overuse was probably not sufficient to make our patients' migraine become chronic. Specifically, in our sample, medication withdrawal did not cause any reduction in headache frequency in almost half of patients (45%). Furthermore, 22/23 patients (95%) showing an improvement of symptoms after drug withdrawal (meaning a return to episodic headache) were assuming a preventive therapy at the same time. Therefore, it is very difficult to judge if the positive effect on headache frequency was caused by one or the other therapeutic approach used.

The few studies published on MOH in pediatric age show a response rate to drug withdrawal (defined as a reduction more than 50% of headache frequency) between 40 and 77% (2, 22–24). On the other hand, a lack of improvement after drug withdrawal is reported in 4–41% of patients (**Table 3**). A genetic study on a pediatric population with CM and medication overuse identified statistically significant gene expression differences between responders and non-responders to withdrawal, thus suggesting a possible biomarker to distinguish true MOH patients from chronic migraineurs in whom overused medication does not have a pathophysiological role (2).

Considering also MOH studies in adults, we found limited evidence supporting a clear benefit of discontinuation of symptomatic medications without concomitant introduction of a preventive therapy (25). In particular, clear clinical benefits after only withdrawing overused medication have been described in less than one third of reported patients (26–28). Another important bias of the available studies is represented by patients who pretend to have withdrawn symptomatic treatment, while keeping overusing drugs. Furthermore, randomized controlled clinical trial investigating topiramate (29, 30) and onabotulinumtoxinA (31, 32) for treatment of CM showed that immediate initiation of preventive treatment without early suspension of the overused medication is effective in patients with CM and medication overuse (33). Most of these studies also lacked an adequate control group, thus making it impossible to differentiate patients presenting a benefit due to the typical cyclic pattern of headache, and those really responding to overuse cessation. Some authors hypothesized that medication overuse can be seen as an epiphenomenon of a chronic headache presenting with periods of higher frequency and severity (19), thus suggesting that a combined strategy of preventive therapy and overuse cessation could be more appropriate. Indeed, a recent review of the available literature data concluded that the combined approach of discontinuation of overused acute medications and a concurrent preventive intervention should be

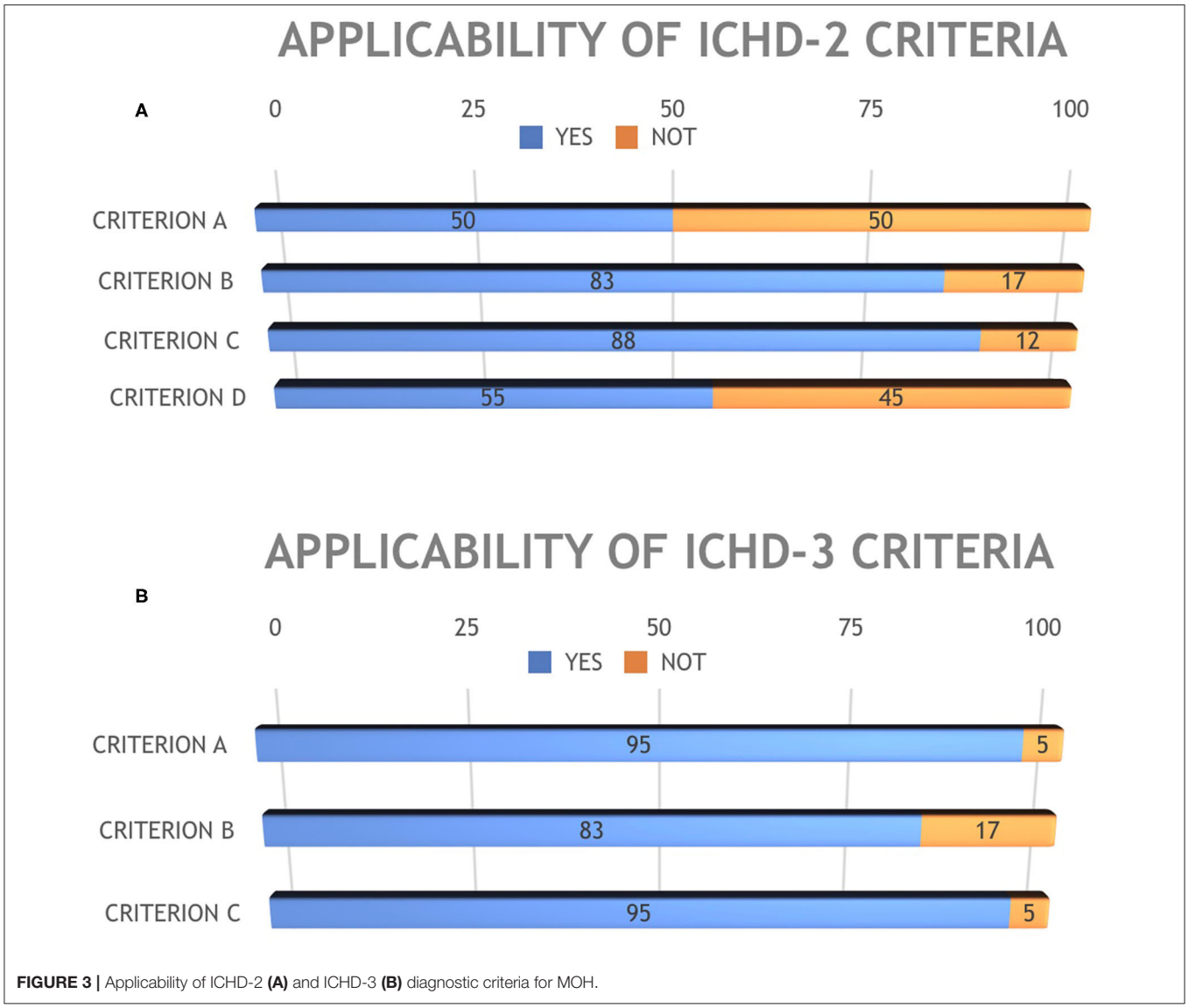

FIGURE 3 | Applicability of ICHD-2 **(A)** and ICHD-3 **(B)** diagnostic criteria for MOH.

TABLE 3 | Results of multiple-regression logistic analysis: beta coefficients and significance, with lower and upper limits at 95% confidence interval.

	β coefficient ± standard error	Significance	Confidence interval (95%)
Age	0.001 ± 0.004	0.882	−0.007; 0.009
Age at migraine onset 0–6 years	−0.483 ± 0.375	0.207	−1.246; 0.280
Age at migraine onset 7–10 years	−0.246 ± 0.232	0.295	−0.718; 0.225
Age at migraine onset 11–14 years	−0.022 ± 0.155	0.213	−0.117; 0.508
Age at migraine onset 15–18 years	−0.005 ± 0.262	0.934	−0.554; 0.511
Topiramate	−0.005 ± 0.207	0.981	−0.427; 0.416
Flunarizine	0.065 ± 0.236	0.785	−0.415; 0.545
TriptOH	−0.339 ± 0.273	0.223	−0.895; 0.217
Amitriptyline	0.179 ± 0.201	0.379	−0.229; 0.587

the standard of care (25), as already recommended by EFNS (European Federation of Neurological Societies) guidelines for MOH (34).

Limitations of the Study

Our study certainly presents some limitations. First of all, the retrospective nature of the study is a limitation in itself.

Furthermore, our population might not be representative of the general population, as patients have been recruited in a tertiary headache center. However, it is also important to underline that patients suffering from chronic headache and medication overuse usually refer to tertiary centers, and therefore, our sample might be overlapping to general pediatric MOH samples. Furthermore, some patients could present with comorbidities, such as obesity, anxiety, and depression, which could influence the outcome but that have not been taken into consideration in the present analysis. Lastly, the information of drug use is based on patients' diary, and especially in case of adolescents, these data might not always be completely reliable.

CONCLUSIONS

In conclusion, our data on a large pediatric population of subjects with chronic headache and medication overuse show that withdrawing medication overuse is not always associated with a clinical benefit. This means that a causal relationship between medication overuse and headache worsening is not always demonstrable, thus suggesting that the concept of MOH might be not universally applicable. Although ICHD-3 criteria for MOH appear to be more sensitive than ICHD-2, allowing a definite diagnosis in a higher number of patients, they do not contribute to make this issue less puzzling, since the new ICHD version considers MOH as a definite nosographic entity, which is not supported by the present literature. In other words, if the effect of drug suspension on headache course is not verified, a sure relationship between medication overuse and headache chronification cannot be demonstrated in all patients. A proposal for a new systematic review on pediatric MOH has been recently published (17) and will hopefully contribute to clarify this issue.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Privacy. Requests to access these datasets should be directed to romina.moavero@opbg.net.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bambino Gesù Ethical Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RM, LP, and MV conceptualized the study. RM, LP, and MS inserted data in the database and analyzed the data. LP, MS, FU, MF, MB, GS, and MV followed up all the patients included in the study. RM drafted the manuscript. FV and MV revised the different versions of the manuscript. All the authors revised and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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EEG Characteristics and Diagnostic Implications in Childhood Headache: A Multi-Center Study

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Introduction: Epilepsy and migraines are frequently observed as comorbidities, with the occurrence of one disorder increasing the probability of the other. The aim of our study was to evaluate the EEG characteristics by the type of headache and the implications of EEGs in headache patients, comparing the clinical characteristics and treatments between the headache patients with normal and abnormal EEGs.

Methods: We conducted a retrospective analysis reviewing the medical records of 259 patients with headaches who visited the pediatrics departments of five university hospitals and underwent EEGs over a period of 3 years. Based on the data entered, analyses of the following items were conducted: (1) comparison of the EEG abnormalities by the type of headache and the characteristics of the EEG findings and (2) comparison of the clinical characteristics between patients with normal and abnormal EEGs.

Results: Of the 259 patients, 31 showed abnormal EEGs, while 228 had normal EEGs. Of the 31 patients with abnormal EEGs, 17 showed epileptiform discharges, and 11 showed rhythmic slowing. The frequency of EEG abnormalities was significantly high in patients with migraines with auras than other types of headache. The Pediatric Migraine Disability Assessment (PedMIDAS) score was significantly higher in the abnormal EEG group compared with the normal EEG group ($p = 0.001$).

Conclusion: The results of this study suggest that the abnormal EEG group had more significant disruptions in their daily lives due to headaches than the normal EEG group and that patients with migraines with aura may need EEGs and they might also have overlapping pathophysiologic mechanisms with epilepsy.

Keywords: headache, migraine, electroencephalogram (EEG), epileptiform discharge, preventive medication, childhood

HIGHLIGHT

- Of the 259 patients, 31 (12%) showed abnormal EEGs, and 228 (88%) had normal findings.
- Of the 31 patients with abnormal EEGs, 17 showed epileptiform discharges (9 had focal spikes and 8 had generalized spikes), and 11 showed rhythmic slowing (7 showed focal slowing, and 4 showed generalized slowing).

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- Migraines with aura showed more EEG abnormalities than other types of headaches. In the patients with headaches with epileptiform discharges, the PedMIDAS scores were higher, and more anticonvulsants were prescribed prophylactically than those of the normal group. These findings imply that patients with migraines with aura may need EEGs, and they might also have overlapping pathophysiologic mechanisms with epilepsy, which can distinguish them from other types of headaches.

INTRODUCTION

A primary headache is diagnosed through medical history and physical examination. If a specific cause, such as a brain tumor or epilepsy, is suspected, the patient undergoes brain imaging or EEG testing to differentiate it from a secondary headache (1). Epilepsy and migraines are frequently observed as comorbidities, with the occurrence of one disorder increasing the probability of the other (2–5). Migraine occurs in about one-fourth of the patients with epilepsy, whereas epilepsy is present in 8–15% of the patients with migraines (6). An EEG is a non-invasive test and is useful for studies of pathophysiology in migraine patients. For these reasons, it is often prescribed as a first-line evaluation in migraine patients. However, the European Federation of Neurological Societies (EFNS) guidelines for the diagnosis of non-acute headaches report that an interictal EEG is not routinely indicated for headache diagnosis (2). The usual indication of an EEG in headache patients is for a differential diagnosis when a serious doubt of epileptic seizure exists. This kind of situation may especially emerge in headache patients with atypical auras or episodic loss of consciousness (7). If a patient has a headache with a visual aura or brainstem aura, an EEG can be performed to differentiate its symptoms from those of epilepsy. Piccinelli et al. reported on electroencephalogram abnormalities in 12.8% of all children with headaches (8) and more commonly in children manifesting migraines with aura (9). Study of electroencephalogram variations in pediatric migraines and tension-type headaches indicate that electroencephalogram abnormalities are particularly prevalent in migraines, especially during headache attacks (10).

The aim of our study was to evaluate the frequency of EEG abnormalities in patients with headaches, the EEG characteristics by the type of headache, and the implications of EEGs in headache patients, comparing the clinical characteristics and treatments between headache patients with normal and abnormal EEGs.

METHODS AND MATERIALS

We conducted a retrospective analysis by reviewing the medical records of 259 patients with headaches who visited the department of pediatrics in five university hospitals and underwent EEGs over a period of 3 years. Electroencephalography was performed when the medical history or physical examination of the patients showed symptoms of a suspected seizure, such as visual or brainstem auras, the patient's lack of response to drug treatment, or continued headaches. Patients with a past medical history of unprovoked seizures, epilepsy, mental retardation, or significant abnormal brain imaging—except incidental benign lesions, such as small pineal cyst, arachnoid cyst, or venous anomaly—were excluded from the study. We retrospectively reviewed the medical records and collected information on age, sex, headache type, headache frequency, severity, duration, EEG and neuroimaging results, and preventive medications. The headache questionnaire form in the medical record included a family history of headache and characteristics of the headaches, such as frequency, duration, location, signs, and accompanying symptoms, severity, and disability caused by the headaches. The headaches were classified according to the International Classification of Headache Disorders (ICHD) criteria. Primary headaches were classified as migraines without aura, migraines with aura, probable migraine, tension headaches, probable tension-type headaches, and other headaches. The severity of headache was assessed using a visual analog scale (VAS: 0–10; 0 = no pain, 10 = most severe pain). Disability in daily life from headaches was assessed using Pediatric Migraine Disability Assessment (PedMIDAS) scores. The scores reflect the number of days that school, home, social, and recreational activities have been hampered by headaches over the past 3 months. We evaluated the following items based on the data of the headache patients who underwent EEGs: (1) the frequency of EEG abnormalities in patients with headaches, (2) comparison of the EEG abnormalities by the type of headache and the characteristics of the EEG findings, (3) comparison of the clinical characteristics and treatment between the patients with normal and abnormal EEGs, and (4) the diagnostic value of EEGs for patients with headaches.

Statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY, USA). A chi-square test was used to compare the frequency of the two groups and mean comparisons were performed by *t*-tests for normal distributions and by the Mann-Whitney *U*-test for non-normally distributed data. The relationship between EEG abnormality and PedMIDAS score or headache type was

TABLE 1 | Clinical characteristics of the headache patients with electroencephalograms (EEG).

Headache patient with EEG (n = 259)	Number (%)
Sex (male/female)	127/132 (1:1.03)
Age	11.3 ± 3.4
Headache type	
Migraine without aura	108 (41.7)
Migraine with aura	41 (15.8)
Probable migraine	45 (17.4)
Tension-type headache	11 (4.2)
Probable tension-type headache	5 (1.9)
Others	49 (18.9)
EEG result	
Normal	228 (88.0)
Abnormal	31 (12.0)

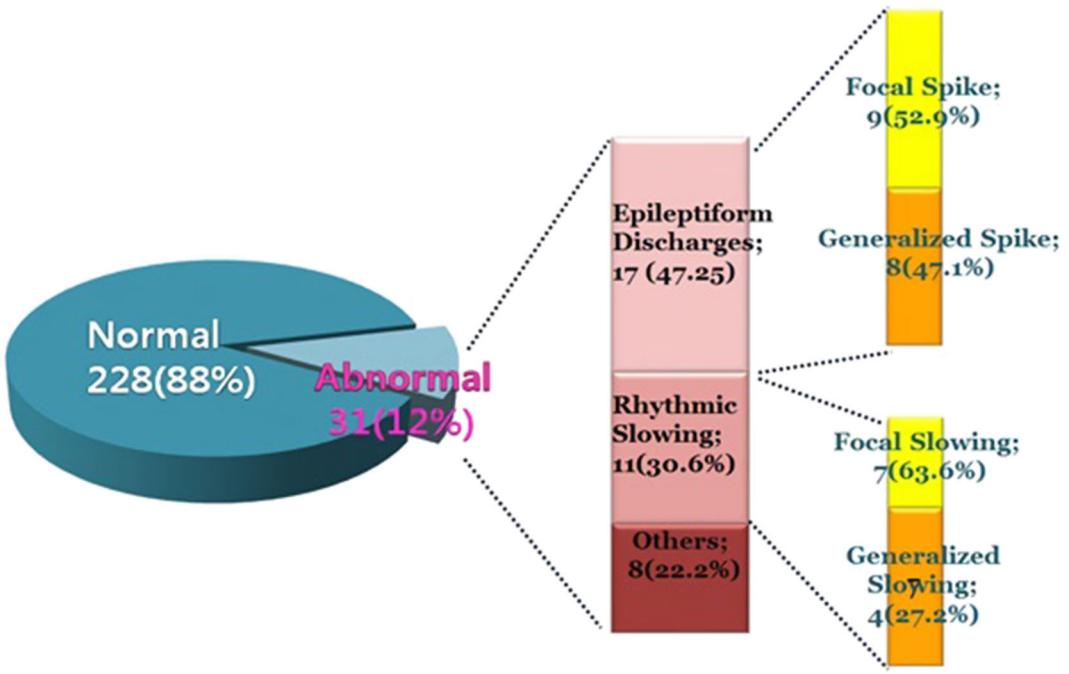

FIGURE 1 | Classification of abnormal electroencephalogram (EEG) findings.

TABLE 2 | Electroencephalogram (EEG) findings according to headache types in the patients.

		Migraine without aura ($n = 108$)	Migraine with aura ($n = 41$)	Probable migraine ($n = 45$)	Tension-type HA ($n = 11$)	Probable tension-type HA ($n = 5$)	Others ($n = 49$)	*P*-value
Abnormal EEG		12 (11.1)	10 (24.4)	1 (2.2)	2 (18.2)	0 (0)	6 (12.2)	0.047
Epileptiform discharge	Focal	6	2	1	0	0	0	
	General	2	2	0	2	0	2	
Slowing	Focal	3	1	0	0	0	3	
	General	3	1	0	0	0		
Others		3	3	0	0	0	2	

analyzed by logistic regression to adjust for age, sex, and headache types.

In all cases, statistical significance was indicated by $p < 0.05$. This study was approved by the Institutional Review Board of Hallym University Dongtan Sacred Heart Hospital. Informed consent was waived due to the retrospective nature of the study.

RESULTS

In 259 patients with headaches who underwent EEGs, the ratio of males to females was 1:1.03 and the mean age was 11.3 ± 3.4 years old. The most common type of headache was migraines without aura (108 patients), followed by 41 patients with migraines with aura, 45 with probable migraines, 11 with tension-type headaches, and 5 with probable tension-type headaches. EEGs were mainly performed for the migraine patients. Of the 259 patients, 31 (12%) showed abnormal EEGs and 228 (88%) had normal findings (**Table 1**). Of the 31 patients with abnormal EEGs, 17 showed epileptiform discharges (9 had focal spikes, and 8 had generalized spikes), and 11 showed rhythmic slowing (7 showed focal slowing, and 4 showed generalized slowing) (**Figure 1**). The frequency of EEG abnormalities was significantly different according to headache types. Ten (24.2%) patients with migraines with aura had abnormal EEGs, and 12 (11.1%) patients with migraines without aura had abnormal EEGs (**Table 2**). There were no differences in sex, age, or family history of headache or epilepsy between the patient groups with normal EEGs and abnormal EEGs. There were also no differences in headache frequency, characteristics, duration, or location (**Table 3**). The PedMIDAS score, which assesses the severity of headaches, was significantly higher in the abnormal EEG group than in the normal EEG group ($p = 0.001$) (**Figure 2**). EEG abnormalities were significantly related to PedMIDAS score

TABLE 3 | Comparison of clinical characteristics between headache patients with normal and abnormal electroencephalograms (EEG).

		Normal (n = 228) (%)	Abnormal (n = 31) (%)	P-value
Sex (M:F)		110:118	17:14	0.491
Age (years)		11.4 ± 3.4	10.5 ± 3.7	0.168
Family history of headache		82 (36)	14 (45.2)	0.320
Family history of epilepsy		3 (1.3)	0 (0.0)	0.521
Duration of illness	24 h	13 (9.4)	0 (0.0)	0.906
	1 to <7 d	33 (23.9)	3 (37.5)	
	1 wk to <1 mo	23 (16.7)	1 (12.5)	
	1 mo to <6 mo	23 (16.7)	1 (12.5)	
	6 mo to 1 yr	18 (13.0	1 (12.5)	
	>1 yr	28 (20.3)	2 (25.0)	
Frequency	< 1/mo	31 (14.0)	1 (3.1)	0.745
	1–3/mo	47 (21.3)	8 (25.8)	
	1/week	7 (3.2)	2 (6.5)	
	2–3/week	37 (16.0.7)	10 (32.3)	
	4–6/week	18 (8.1)	3 (9.7)	
	Every day	81 (36.7)	7 (22.6)	
Headache characteristics	Throbbing	77 (34.5)	4 (13.8)	0.227
	Pressing	75 (33.6)	11 (37.9)	
	Squeezing	16 (7.2)	2 (6.9)	
	Stabbing	32 (14.3)	8 (27.6)	
	Pinching	1 (0.4)	0 (13.8)	
	Others	22 (9.9)	4 (12.9)	
Duration	< 1 min	13 (5.9)	3 (10.3)	0.406
	2–15 min	6 (2.7)	1 (3.4)	
	16–30 min	18 (8.1)	5 (17.2)	
	31–59 min	62 (27.9)	5 (17.2)	
	1–72 h	117 (52.7)	14 (48.3)	
	>3 d	6 (2.7)	1 (3.4)	
Location	Bitemporal	57 (25.0)	7 (22.6)	0.220
	Left temporal	23 (10.1)	5 (16.1)	
	Right temporal	17 (7.5)	6 (19.4)	
	Frontal	47 (20.6)	2 (6.5)	
	Vertex	13 (5.7)	4 (12.9)	
	Occipital	19 (8.3)	2 (6.5)	
	Periorbital	3 (1.3)	0 (0.0)	
	Posterior orbital	2 (0.9)	0 (0.0)	
	Whole	30 (13.2)	3 (9.7)	
	Others	13 (5.7)	1 (3.2)	

and migraine with aura, respectively, when age, gender, and headache types were adjusted with logistic regression analysis (p = 0.007 adjusted odds ratio 1.034, 95% CI 1.009–1.060, p = 0.030, adjusted odds ratio 2.874, 95% CI 1.109–7.447). In a comparison of neuroimaging findings according to EEG findings, MRIs were performed in 76.3% of the normal and 80.6% of the abnormal EEG group and there was also no significant difference between the two groups (**Table 4**). Brain tumors were seen in one case of rhythmic focal slowing on the EEG but were excluded from statistical analysis. Among the 17 headache patients with epileptiform discharges, 8 patients had migraines with aura, 5 had migraines without aura, 1 had a probable migraine, 1 had migraine with aura and epilepsy, 1 had a tension-type headache, and 1 had another type of headache (**Table 5**). The most common preventive therapy for patients with normal EEGs was amitriptyline, followed by flunarizine. The patients with abnormal EEGs were treated most commonly with antiepileptic drugs such as topiramate and valproate (**Figure 3**).

DISCUSSION

EEGs are not routinely recommended for headache patients because they do not help with a primary headache diagnosis. They are helpful only in patients with visual symptoms or brainstem auras. Epilepsy and headaches often occur simultaneously in the same patient. In patients with migraines, epilepsy is present in 5.9% (range 1–17%), which is high compared with the prevalence rate of 0.5–1% in the general population (3). Similarly, 14.7% of the epilepsy patients have migraines (range 8–24%), which is high compared with the prevalence rate of 12% in the general population (4–6). Generally, migraines occur in about one-fourth of the patients with epilepsy, whereas epilepsy is present in 8–15% of the patients with migraines (6). There are a few studies on the characteristics of EEGs according to the type of headache and the implication of EEGs for headache patients. EEG abnormalities were reported to vary (8.8–20%) in pediatric headache patients (8, 10, 11), and the most common abnormalities were epileptiform discharge seen in 0.4–20% of the patients (12–18). Piccinelli et al. reported electroencephalographic abnormalities in 12.8% of all children with headaches (8). In our study, of the 259 headache patients who underwent EEGs, 31 (12%) showed abnormal EEGs, consisting of 17 (6.6%) epileptiform discharges (9 with focal spikes and 8 with generalized spikes) and 11 with slowing (7 with focal slowing and 4 with generalized slowing) while 228 (88%) had normal findings.

The mechanism of the EEG abnormalities seen in headache patients, unlike the general population, may be different in migraine patients. Migraine patients have a potential for intrinsic or genetic predispositions to cortical neuron hyperexcitability. It has been suggested that the threshold of excitability of the cortical neurons causing headaches in migraine patients is lower than the threshold of cortical neuronal excitation causing seizures in epilepsy patients (19). This hypothesis explains why the prevalence of headaches in epilepsy patients was greater than the prevalence of epilepsy in headache patients and the underlying pathophysiologic mechanisms in abnormal EEGs in headache patients.

The EEG abnormalities differed by the type of headache (10) and the characteristics of the EEG findings. According to a previous study, 36% (18/50) of the migraine patients and 12% (6/50) of the tension-type headache patients revealed specific electroencephalogram abnormalities in headache attack electroencephalograms (p < 0.05). In electroencephalograms taken during headache-free periods, 16% (8/50) of the migraine

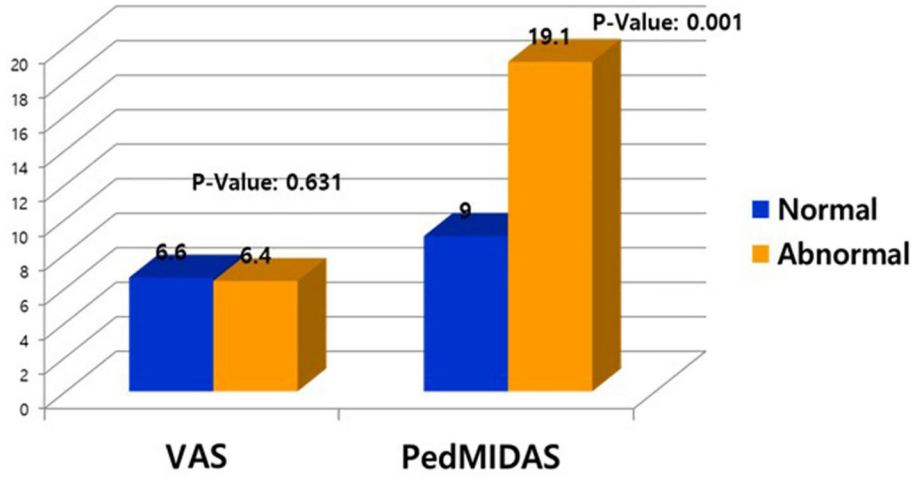

FIGURE 2 | Comparison of visual assessment score (VAS) and Pediatric Migraine Disability Assessment score (PedMIDAS) between patients with normal and abnormal electroencephalograms (EEG).

TABLE 4 | Comparison of neuroimaging findings between patients with normal and abnormal electroencephalograms (EEG).

			Normal ($n = 228$)	Abnormal ($n = 31$)	*P*-value
Neuroimaging	Not done		36 (15.8)	4 (12.9)	0.866
	CT		18 (7.9)	2 (6.5)	
	MRI		174 (76.3)	25 (80.6)	
	Result (total)	Normal	162 (84.4)	19 (70.4)	0.174
		Abnormal	30 (15.6)	8 (29.6)	

CT, computed tomography; MRI, magnetic resonance image.

TABLE 5 | Acute and preventive medication of headache patients with epileptiform discharges.

	Medication	Number	Diagnosis
Focal	No treatment	1	Probable migraine
	Ibuprofen	2	Migaine without aura
	Amitriptyline	1	Migraine without aura
	Flunarizine	1	Migraine with aura
	Valproate	2	Migraine with aura
	Topiramate	2	Migraine without aura
Generalized	Antibiotics	1	Others (sinusitis)
	Ibuprofen	1	Migraine with aura
	Valproate	2	Migraine with aura
	Topiramate	2	Migraine with aura
	Topiramate, oxcarbazepine	1	Migraine with aura with epilepsy
	Topiramate, levatriacetam, Oxcarbazepine	1	Tension type headache

group and 2% (1/50) of the tension-type headache group revealed abnormalities ($p < 0.05$) (17). In our study, according to headache types, there was a significantly high frequency of EEG abnormalities. Ten (24.4%) patients with migraines with aura had abnormal EEGs, and 12 (11.1%) patients with migraines without aura had abnormal EEGs (**Figure 2**). These findings suggest that patients with migraines with aura may need EEGs and they might also have overlapping pathophysiologic mechanisms with epilepsy, which can distinguish them from other types of headaches.

There were no differences in the demographic data and clinical characteristics of the headache patients with normal and abnormal EEGs except for the PedMIDAS scores, which assess the disability in daily life due to headaches. The scores were statistically significantly higher in the abnormal EEG group compared to the normal EEG group in our study (**Figure 3**). Because of this, the headache patients with abnormal EEGs had more significant disruptions in their daily lives due to headaches than the patients with normal EEGs. We may need to be concerned with focal slowing in the EEG that might be due to brain tumors, as was seen in one case of rhythmic focal slowing in the EEG in this study, and even with which cases were excluded from statistical analysis. In a small population study, headache patients with epileptiform discharge could effectively prevent headaches by taking anticonvulsants (20). In our study, headache patients with epileptiform discharges more frequently used anticonvulsants as headache prevention drugs than the patients with normal EEGs. Further prospective studies comparing the effectiveness of preventive therapy with anticonvulsants in patients with normal and epileptiform discharges in the EEGs are needed. Rare cases have been reported of pure or isolated ictal epileptic headaches occurring as the sole epileptic manifestation (21–26). Rho et al. (27) found that one-third of the patients with epilepsy and headaches had a headache first, and more than half had a history of headaches when they first visited a hospital for the evaluation of a seizure. Therefore,

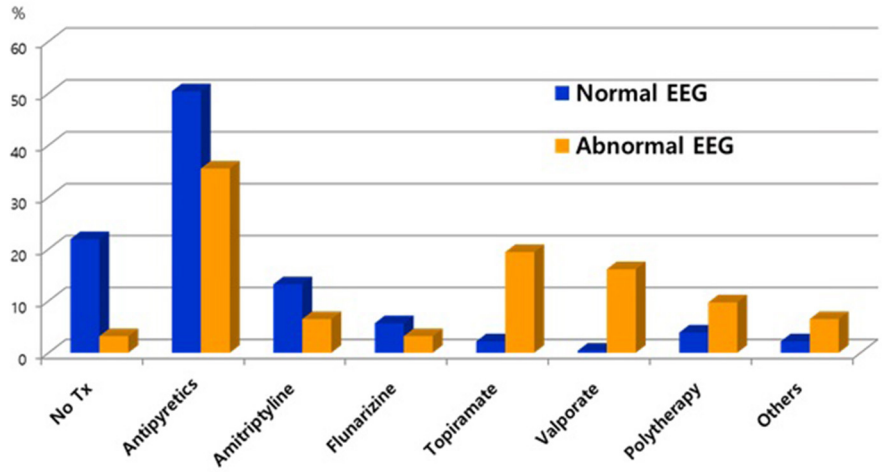

FIGURE 3 | Comparison of preventive therapy between patients with normal electroencephalograms (EEG) and epileptiform discharges.

especially in headache patients with epileptiform discharges in the EEG, the occurrence of epilepsy should be monitored by long-term follow-up. In view of the usefulness of EEGs to differentiate epilepsy in headache patients, our study was limited because only one of the 17 patients with epileptiform discharges was finally diagnosed with epilepsy, but the follow-up period was short, and anticonvulsants were usually used as a headache prevention agent to suppress the occurrence of seizures. Prospective follow-up studies of long-term prognosis and the occurrence of epileptic convulsions in headache patients with abnormal EEGs are needed because epilepsy patients with comorbid migraines initially have a headache as the only symptom (19, 28). Although the patient was not included this study, headache was the only ictal symptom in an epileptic patient who was diagnosed incidentally when an interictal EEG was being recorded with the simultaneous onset of ictal epileptiform discharges and headaches. A limitation of this study was the retrospective nature of the chart review, which made it difficult to determine the long-term prognosis of the patients with abnormal EEGs.

CONCLUSION

We identified the frequency and characteristics of abnormal EEGs according to the type of headache. Migraines with aura showed more EEG abnormalities than other types of headaches. In the patients with headaches with epileptiform discharges, the PedMIDAS scores were higher than those of the normal group, and more anticonvulsants were prescribed prophylactically.

To determine the value of EEGs in headache patients, more follow-up studies are required for headache patients with epileptiform discharges.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of Hallym University Dongtan Sacred Heart Hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The first author and the corresponding author each contributed 30% and the remaining co-authors contributed 10% each. All authors contributed to the article and approved the submitted version.

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Cyclic Vomiting Syndrome in Children

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Cyclic Vomiting Syndrome (CVS) is an underdiagnosed episodic syndrome characterized by frequent hospitalizations, multiple comorbidities, and poor quality of life. It is often misdiagnosed due to the unappreciated pattern of recurrence and lack of confirmatory testing. CVS mainly occurs in pre-school or early school-age, but infants and elderly onset have been also described. The etiopathogenesis is largely unknown, but it is likely to be multifactorial. Recent evidence suggests that aberrant brain-gut pathways, mitochondrial enzymopathies, gastrointestinal motility disorders, calcium channel abnormalities, and hyperactivity of the hypothalamic-pituitary-adrenal axis in response to a triggering environmental stimulus are involved. CVS is characterized by acute, stereotyped and recurrent episodes of intense nausea and incoercible vomiting with predictable periodicity and return to baseline health between episodes. A distinction with other differential diagnoses is a challenge for clinicians. Although extensive and invasive investigations should be avoided, baseline testing toward identifying organic causes is recommended in all children with CVS. The management of CVS requires an individually tailored therapy.

Management of acute phase is mainly based on supportive and symptomatic care. Early intervention with abortive agents during the brief prodromal phase can be used to attempt to terminate the attack. During the interictal period, non-pharmacologic measures as lifestyle changes and the use of reassurance and anticipatory guidance seem to be effective as a preventive treatment. The indication for prophylactic pharmacotherapy depends on attack intensity and severity, the impairment of the QoL and if attack treatments are ineffective or cause side effects. When children remain refractory to acute or prophylactic treatment, or the episode differs from previous ones, the clinician should consider the possibility of an underlying disease and further mono- or combination therapy and psychotherapy can be guided by accompanying comorbidities and specific sub-phenotype. This review was developed by a joint task force of the Italian Society of Pediatric Gastroenterology Hepatology and Nutrition (SIGENP) and Italian Society of Pediatric Neurology (SINP) to identify relevant current issues and to propose future research directions on pediatric CVS.

Keywords: functional gastrointestinal disorders, migraine, vomiting, antiemetics, anticonvulsants, cyclic vomiting syndrome, differential diagnosis, episodic syndromes that may be associated with migraine

INTRODUCTION

Cyclic Vomiting Syndrome (CVS) is identified by acute, stereotyped and recurrent episodes of intense nausea with incoercible vomiting, lasting from a few hours to a few days; both children and adults are affected, although the clinical presentation and natural history vary somewhat with age (1). CVS was first described in 1806 by Heberden (2) and then by Gee in the St. Bartholomew's Hospital Reports (3). Since pediatric CVS evolves into migraine later in life in most patients and based on a high family prevalence of migraines, the effectiveness of anti-migraine therapy and observation of mitochondrial DNA polymorphisms in CVS and migraine patients, CVS has been considered a migraine-related or migraine-equivalent disorder (1, 4, 5). In the International Classification of Headache Disorders (ICHD III beta) (6) considers SVC as a pediatric migraine variant among the episodic syndromes that may be associated with migraine. The recent Rome IV Criteria included CVS among the "functional gastrointestinal disorders" (FGID), idiopathic disorders of gut-brain interaction affecting different parts of the gastrointestinal tract symptoms that are not attributable to organic etiology (7–9).

The etiopathogenesis is likely to be multifactorial. Recent evidence suggests that aberrant brain-gut pathways, mitochondrial enzymopathies, gastrointestinal motility disorders, calcium channel abnormalities, and hyperactivity of the hypothalamic-pituitary-adrenal axis in response to a triggering environmental stimulus are involved in the CVS development (10). Genetic factors have been linked to CVS, but further research is required to better establish the heritable basis of this disorder (11).

This review was developed by a joint task force of the Italian Society of Pediatric Gastroenterology Hepatology and Nutrition (SIGENP) and Italian Society of Pediatric Neurology (SINP) to propose future research directions.

EPIDEMIOLOGY

There are difficulties in obtaining reliable epidemiological evidence for CVS, being an undiagnosed condition (12). In children, a prevalence of 1.9% has been reported by two school-based surveys from Scotland and Turkey (13, 14), while the incidence of new pediatric cases was 3.15 per 100,000 children per year in an Irish population-based study (15). In a primary care cross-sectional, among Colombian children aged 0–48 months, ∼0.5–7% of them received CVS diagnosis (16). Although mainly occurs in pre-school or early school-age, CVS appears to be more common in adults than previously thought (12, 17–19), and delayed diagnosis has been reported. Indeed, patients are frequently misdiagnosed as having recurrent gastroenteritis, food poisoning, and eating disorders (20). In a study from the U.S. mean ages at onset of symptoms and diagnosis were 5.7 ± 0.3 and 8.0 ± 0.3 years (21).

Patients with CVS are predominantly white, followed by African American and Hispanic (22, 23). A recent nationwide analysis conducted in US of over 20,000 adults hospitalized for CVS showed that 63% of patients were white, 18% were African American, and 6% were Hispanic (24). Moreover, CVS appears to be slightly more common in female (13–15, 18, 21, 25, 26) and is associated with family (especially maternal) or personal history of migraines (up to 82%) (27, 28). The highly documented later development of migraine (up to 75% of children) suggests a progressive continuum from CVS to migraine headaches in most children (13, 27, 29–31). Nearly 60% of children outgrow CVS (29) with a reported median overall duration of the disorder of 66 months (range 3–179) (30). CVS determines a worsening in quality of life of children, needing multiple hospitalizations for acute dehydration, missing a mean of 20 days of school each year (32) with an annual cost of ∼$ 17,035 per individual patient (1).

PATHOPHYSIOLOGY

The pathophysiology of CVS is yet to be established although several potential underlying mechanisms have been postulated. The emetic reflex is highly complex, and its final common pathway and its central mechanisms have yet to be fully elucidated. It is widely accepted that several nuclei within the medulla oblongata between the obex and the rostral portion of the nucleus ambiguous play a key role in the central coordination of emetic neurocircuitry (33). Among these nuclei, which collectively are conceptualized as a central pattern generator, the nucleus tractus solitarius (NTS) within the dorsal vagal complex (DVC) represents the main integrative site for modulation of the emetic reflex. Activation of NTS to evoke vomiting occurs via inputs from the GI tract and other visceral organs via the vagus nerve, vestibular system, and higher brain regions including the cerebral cortex, hypothalamus, cerebellum, and the *area postrema* (AP). The latter, defined as chemoreceptor trigger zone (CTZ), is an important component of emetic arc and is located in the floor of the fourth ventricle outside the blood-brain barrier with the potential to detect circulating toxin. Distinct neural input from NTS coordinates the motor pathways driving the visceral and somatic motor events of vomiting by activating nuclei within the hindbrain in a precisely synchronized temporal fashion. NTS has reciprocal direct or indirect projections to several higher CNS centers, including the parabrachial nucleus, hypothalamus, limbic system and forebrain providing the neuroanatomical substrate for the integration of various sensory, affective and emotional responses to nausea and vomiting (34).

CVS is viewed as a final common phenotype driven by synergistic interaction of discrete pathophysiological pathways. Similar to other periodic disorders, such as migraine, CVS might be characterized by a specific-individual "attack threshold" above which the synergistic action of the different pathophysiologic mechanisms induces the distinctive clinical expression. Each mechanism is not necessary pathogenetic, but it can be deemed as essential building unit within a common stimulus of adequate intensity able to breach the threshold for inducing the emetic cycles in susceptible patients (35). As the threshold may widely differ among patients, the development of effective and personalized treatments might rely on recognizing triggers and their underlying mechanisms and in turn either raising or desensitizing the individual threshold.

Several pathophysiologic mechanisms have been postulated, such as autonomic abnormalities, hypothalamic-pituitary-adrenal (HPA) activation, genetic abnormalities, neuronal hyperexcitability, and gastric dysmotility.

Autonomic and Neuroendocrine Dysfunctions

Clinical manifestations of the autonomic nervous system (ANS) activation are dominant clinical features of CVS during both prodromal and acute phase. An increased sympathetic tone with low-to-normal parasympathetic tone during the interspersed period has been reported in both pediatric and adult CVS patients (36, 37). Postural orthostatic tachycardia syndrome (POTS) is diagnosed in up to 50% of the adolescents with CVS, and its treatment is effective in preventing emetic episodes (38, 39). The hypothalamus, which is functionally integrated into the limbic system, is considered the main ANS control center (33).

Stressors, both psychological (heightened emotional state) and physical (intercurrent infection, sleep deprivation, excessive exercise and prolonged fasting) can activate a neuroendocrine stress-mediated response by the HPA axis. Corticotropin-releasing factor (CRF), the major physiological activator of HPA axis and released from hypothalamic paraventricular nucleus (PVN), stimulates the release of ACTH and in turn cortisol from the adrenal cortex. However, CRF can also act in extra-hypothalamic circuits. Different types of CRF and different CRF receptors have been identified not only in CNS but also in the enteric nervous system. CRF-containing neurons from PVN project within NTS, where CRF receptors have been demonstrated as well as to the area postrema (40–42). Both central and peripheral injections of CRF inhibit gastric and proximal small bowel motor activity and induce vomiting in experimental animal and humans (43). Finally, it is also well known that NTS, via both catecholaminergic and non-catecholaminergic neurons, projects to the PVN regulating HPA axis and driving autonomic response to both acute and chronic stressors (44). Sato et al. (45) described a subset of children with CVS with prolonged and severe emetic phase associated with profound lethargy, hypertension and laboratory evidence of HPA axis hyper-responsiveness and increased secretion of antidiuretic hormone (ADH). Noteworthy, CRF exhibits a circadian rhythm, showing an increased secretion starting at 1 a.m. and reaching its peak at 6 p.m., which could account for the early morning onset of emetic phase.

CVS could be the consequence of a dysfunctional allostasis, defined as the physiologic adaptive changes activated by acute and chronic stressors for preserving the body homeostasis (46). Over time and with increasing stressor severity, the allostatic load may impair normal function leading to the development of pathology. The systems mediating allostasis include the HPA axis, ANS, metabolic systems, and the immune system. Hence, the hypothalamus plays a central role in orchestrating the physiological processes of stress adaptation. It has been suggested that early life negative events and negative life experiences might shape the development of neural circuits for cognitive and emotional processing and in turn, lead to disordered allostasis and decreased emetic "threshold" (35).

Gastric Dysmotility

Gastric motor abnormalities have been suggested to play a key role in CVS pathogenesis. Chong et al. studied the gastric myoelectrical activity and gastric emptying time (GET) in 15 CVS children showing the presence of tachygastria in both preprandial and postprandial period and delayed gastric emptying (47). Conversely, Hejazi et al. (48) assessed GET using 4-h scintigraphic methods in 92 adults with CVS during the interspersed period of the disease and found rapid GET in 59% of patients, in 27% normal GET and in only 14% delayed GET, paralleling similar results previously reported in both adults and children (49, 50). It was postulated that rapid GET might reflect underlying autonomic dysfunctions reported in CVS

patients; however, Hejazi et al. (48) failed to show any correlation between gastric emptying and autonomic testing results. Another hypothesis has speculated the role of ghrelin, a gut hormone able to enhance gastric emptying, in the pathogenesis of rapid GET during the remission period. Hejazi et al. (51) found increased ghrelin levels in adults with CVS compared with normal GET. However, the majority of the studies that have identified either rapid or normal GET were performed during the interspersed period, while those performed during the emetic phase have shown a significant gastric emptying delay, which might be related to either the activation of HPA axis resulting in the release of CRF, which inhibits foregut motility, or activation of dorsal vagal complex (DVC), which inhibits gastric motility via the efferent vagal pathway.

Mitochondrial Dysfunction

The role of mitochondrial dysfunction in CVS pathophysiology was postulated based on the striking maternal inheritance pattern, the presence of an energy-depletion pattern on urine organic acid measurements and the efficacy of mitochondrial-targeted therapies, such as coenzyme Q10, L-carnitine, and riboflavin (52–54).

The genotype/phenotype correlation remains unclear as well as the functional role of mitochondrial dysfunction has yet to be determined. A simplistic underlying hypothesis is that mtDNA polymorphisms might impact energy metabolism during both a resting state, by decreasing the ability to preserve transmembrane ion gradients and hence predisposing to a hyperexcitability state, and during stress circumstances by failing to mount a greater energy supply for increased demand.

Ion Channel Disease Abnormalities

Abnormalities in stress-induced calcium channel might also have a significant role in the CVS pathogenesis. Lee et al. found a significant association between the type 2 ryanodine receptor (RYR2), encoding a stress-induced calcium channel present in many central and peripheral neurons, and CVS [OR = 6.0, (95% CI =1.7–22)] (55).

Neuronal Dys-Excitability Disorder

Neuronal hyperexcitability may be a common link between CVS and other episodic CNS disorders (11, 56, 57). Hyperexcitability may represent a consequence of genetic functional variants in mtDNA, ion channel and/or neurotransmitter receptor structure, or may result from aberrant neural circuits development. Alterations in brain network functional connectivity, particularly within networks involving the amygdala and the insular cortex, seem to play a role of brain "dysexcitability" in CVS patients (35).

Endocannabinoid System Dysfunction

The cannabinoid receptor (CB) 1 and 2, their ligands N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), and their biosynthetic and degradative enzymes are the major components of the endocannabinoid system (ECS) (58). The ECS represents an important physiologic regulator of GI motility both centrally and peripherally. CB receptors are densely expressed in CNS areas, such are DVC, and in the enteric nervous system (59). The central inhibition of emetic reflex via CB1 receptor occurs by modulating vagal afferent activity within the DVC in the hindbrain, and vagal efferent activity projecting to enteric nervous system (60, 61). Venkatesan et al. (62) measured serum endocannabinoids and their related lipids, N-oleoylethanolamine (OEA) and N- palmitoylethanolamide (PEA), in 22 adults with CVS patients during both the acute emetic phase and the interspersed period, and 12 matched controls and found increased serum levels of endocannabinoid-related lipids during both phases.

Toward a Unifying Hypothesis?

CVS may be best described as a consequence of dysfunction in the brain stem and hypothalamic nuclei that normally modulate or gate sensory emetic inputs, leading to the failure of brain integration and filtering mechanisms and resulting in the activation of emetic neurocircuitry under normal conditions. A mechanistic search for a common denominator focuses on the generalized central neuronal hyperexcitability, genetically driven by mutations in genes coding for ion-channels and mutations in mtDNA. Mitochondrial dysfunction impacts energy production at rest and fails to mount a greater energy supply during a period of heightened demand. Hence, common physical and psychological stressors might initiate the emetic cascade by stimulating dysfunctional hypothalamic neurons, characterized by high intrinsic energy demands, and consequently activating the autonomic nervous system and HPA axis with CRF release. The hypothalamus projects within NTS, which in turn activates the visceral and somatic motor pathways of the emetic cascade. Similarly, physical and psychological stressors might also initiate the emetic cascade directly activating NTS neurons, which by projecting to the PVN in the hypothalamus might stimulate both the HPA axis and autonomic responses.

CLINICAL MANIFESTATIONS

CVS is characterized by stereotypical episodes of paroxysmal vomiting and intense unremitting nausea with a return to baseline health between episodes (1, 7, 8). This distinctive on-off temporal pattern characterized by four phases is essential for diagnosis (1, 8, 63) (**Figure 1**). Up to 75% of children exhibit symptoms during the night or early in the morning (generally 2.00–7.00 a.m.) (25, 64, 65) lasting several hours to days, although rarely >72 h (1). A study conducted on 181 children reported duration of attacks ranging from few hours to 10 days (mean 4.25 days) with intervals of 0.25–12 months (mean 1.8 months) (25).

Four phases have been identified: prodromal; emetic; recovery, and inter-episodic (63) (**Figure 1**). About 90% of patients experience a prodromal phase (63), that is characterized mainly by signs and symptoms of autonomic dysfunction such as pallor, sweating, lethargy, hot flashes and rarely temperature change and drooling (25, 65). It generally occurs a few hours before the vomit onset, and it might resemble a panic attack; this premonitory phase is similar to that of migraine headache attack (26). Abdominal pain is described in the prodromal as well as in the other phases (66). In approximately three-quarters

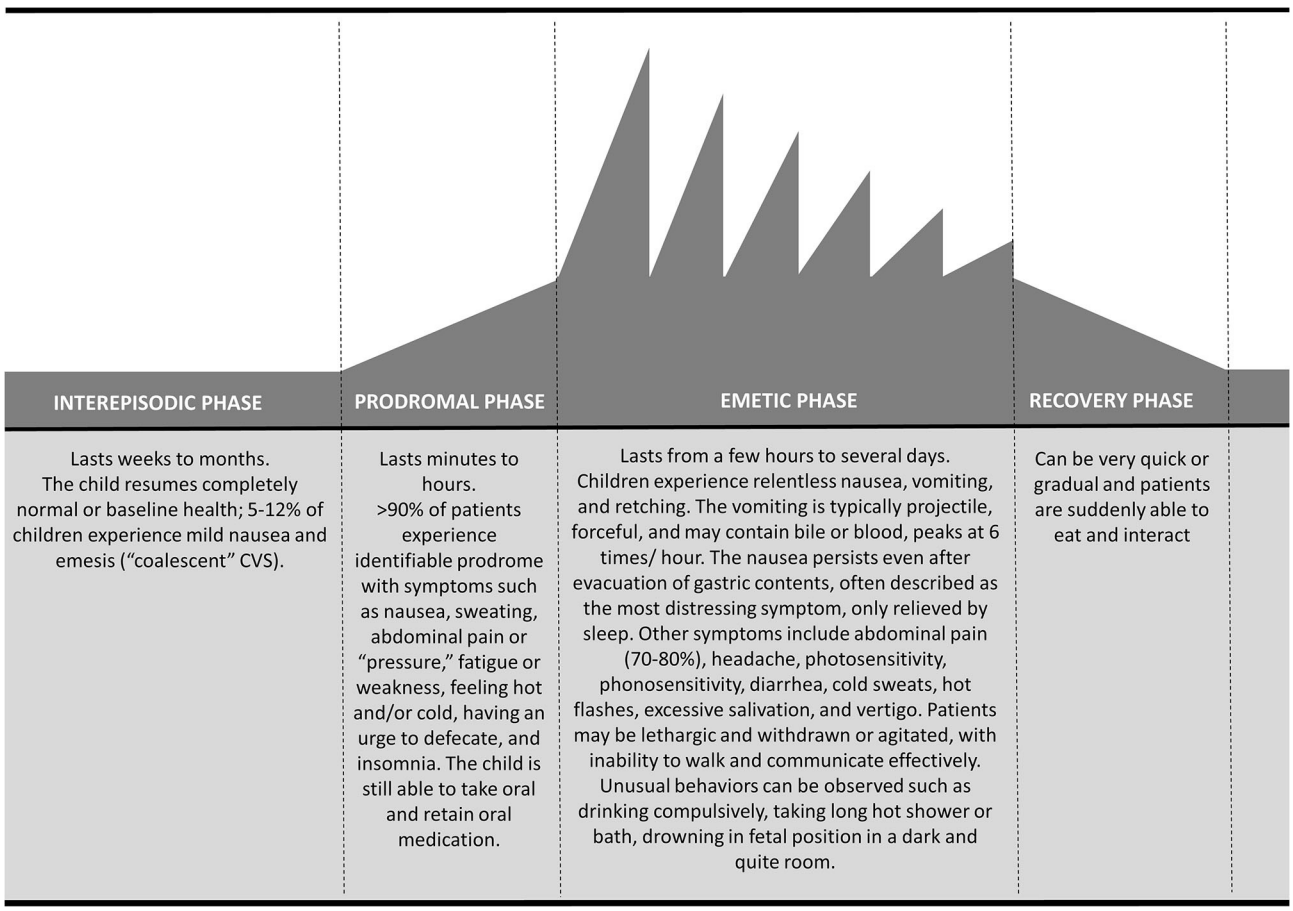


FIGURE 1 | Temporal pattern of cyclic vomiting syndrome: schematic representation of the four phases.

of patients, recurrent stressors can be identified to precede CVS episodes. Emotional stress (generally of an excitatory nature) and infections are the most common triggers. Certain foods (e.g., chocolate, cheese, and caffeine), fasting, fever, lack of sleep, allergies, dietary and menstruation are also common trigger factors (20, 38, 67). The emetic phase is characterized by a projectile, intense vomit, averaging 6 times/hour at the peak (first hour), often leading to significant dehydration (1). Vomiting is often bilious (1) and associated to other gastrointestinal symptoms, such as abdominal pain, which is described in up to 80% of children, retching, anorexia, disabling nausea and diarrhea (68). Autonomic dysfunction can be exacerbated during this phase together with other neurological symptoms like headache, photophobia, phonophobia and vertigo (38, 68). Drowsiness and deep sleep are typical of the recovery phase; subsequently, children slowly start to re-tolerate food and beverages with remission of nausea and restoration of appetite (1). After the episode, children return to normal or baseline state of health lasting weeks to months (inter-episodic phase). Up to 12% of patients might experience interictal nausea and emesis episodes ("coalescent" CVS), usually less severe than those during a full episodes (8, 38).

DIAGNOSIS

There are three main different sets of criteria to consider for diagnosis of CVS in children (**Table 1**). The NASPGHAN (1), and the Rome IV (7, 8) classifications are those mainly used in the pediatric literature. The third classification was provided by ICHD (6), which in its 3rd edition (beta version) includes the CVS among the episodic syndromes potentially associated with migraine.

The key difference between classifications is represented by the number of recurrent episodes of vomiting required for formulating the diagnosis of CVS. Both NASPGHAN and ICHD guideline recommend a minimum of five attacks of intense nausea and vomiting for the diagnosis in children (1, 6), while a minimum of two episodes are required in Rome IV criteria (7, 8). The rationale behind this decision of the Rome IV working group was the possibility to make an early diagnosis of CVS. Moreover, compared to the other classifications, in Rome IV pediatric committee established different sets of criteria for neonates/toddlers (7) and children/adolescents (8). In the former set, the word "nausea" has been left out because of the difficulty in assessing in this symptom in infants (69).

TABLE 1 | Current classification for the diagnosis of pediatric Cyclic Vomiting Syndrome (CVS).

NASPGHAN

All of the criteria must be met

1. At least five attacks in any interval or a minimum of three attacks during a 6-months period
2. Episodic attacks of intense nausea and vomiting lasting 1 h to 10 days and occurring at least 1 week apart
3. Stereotypical pattern and symptoms in the individual patient
4. Vomiting during attacks occurs at least 4 times/h for at least 1 h
5. Return to baseline health between episodes
6. Not attributed to another disorder

ROME IV

Children and Adolescents

Must include all of the following

1. The occurrence of 2 or more periods of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-months period
2. Episodes are stereotypical in each patient
3. Episodes are separated by weeks to months with return to baseline health between episodes
4. After appropriate medical evaluation, the symptoms cannot be attributed to another condition

NEONATES AND TODDLERS

Must include all of the following

1. Two or more periods of unremitting paroxysmal vomiting with or without retching, lasting hours to days within a 6-months period
2. Episodes are stereotypical in each patient
3. Episodes are separated by weeks to months with return to baseline health between episodes of vomiting

ICHD-3

A. At least five attacks of intense nausea and vomiting, fulfilling criteria B and C

B. Stereotypical in the individual patient and recurring with predictable periodicity

C. All of the following:
   1. nausea and vomiting occur at least four times per hour
   2. attacks last ≥1 hour and up to 10 days
   3. attacks occur ≥1 week apart

D. Complete freedom from symptoms between attacks

E. Not attributed to another disorder (In particular, history and physical examination do not show signs of gastrointestinal disease)

Roma IV criteria recognize that some patients may not be completely asymptomatic in between typical episodes. Indeed, inter-episodic nausea, dyspepsia, and IBS symptoms might be experienced in 5–12% of children (38).

A detailed medical history is a key to CVS diagnosis, so extensive and invasive investigations can be avoided. However, since serious metabolic, neurologic and surgical conditions may underlie the clinical picture of recurrent vomiting (1), it is recommended that all children should undergo baseline testing toward identifying organic causes (**Figure 2**). Screening includes basic metabolic profile (electrolytes, glucose, blood urea nitrogen, creatinine), to be performed before administration of intravenous fluids, and upper gastrointestinal tract series to exclude malrotation and anatomic obstructions (1, 7, 8). In children refractory to the initial treatment, transient hydronephrosis should be sought by abdominal ultrasound, preferably during a crisis. Addison disease and disorders of fatty acid oxidation should be excluded if a child has hyponatremia or hypoglycemia (1). An awake and/or sleep EEG should be performed to recognize autonomic seizures (Panayiotopoulos Syndrome) (70–72).

NASPGHAN guidelines indicate alarm symptoms and signs that may help clinicians in identifying those patients in whom further diagnostic testing is appropriate (1) (**Table 2**, **Figure 2**). In general, the occurrence of CVS under the age of 2 years raises the index of suspicion for neurometabolic diseases (1, 7, 8). When attacks are precipitated by acute illness, fasting or high-protein meals, metabolic and mitochondrial disorders need to be considered. Metabolic screening should be promptly performed for urea cycle defects, fatty acid oxidation, amino acid metabolism, and mitochondrial disorders.

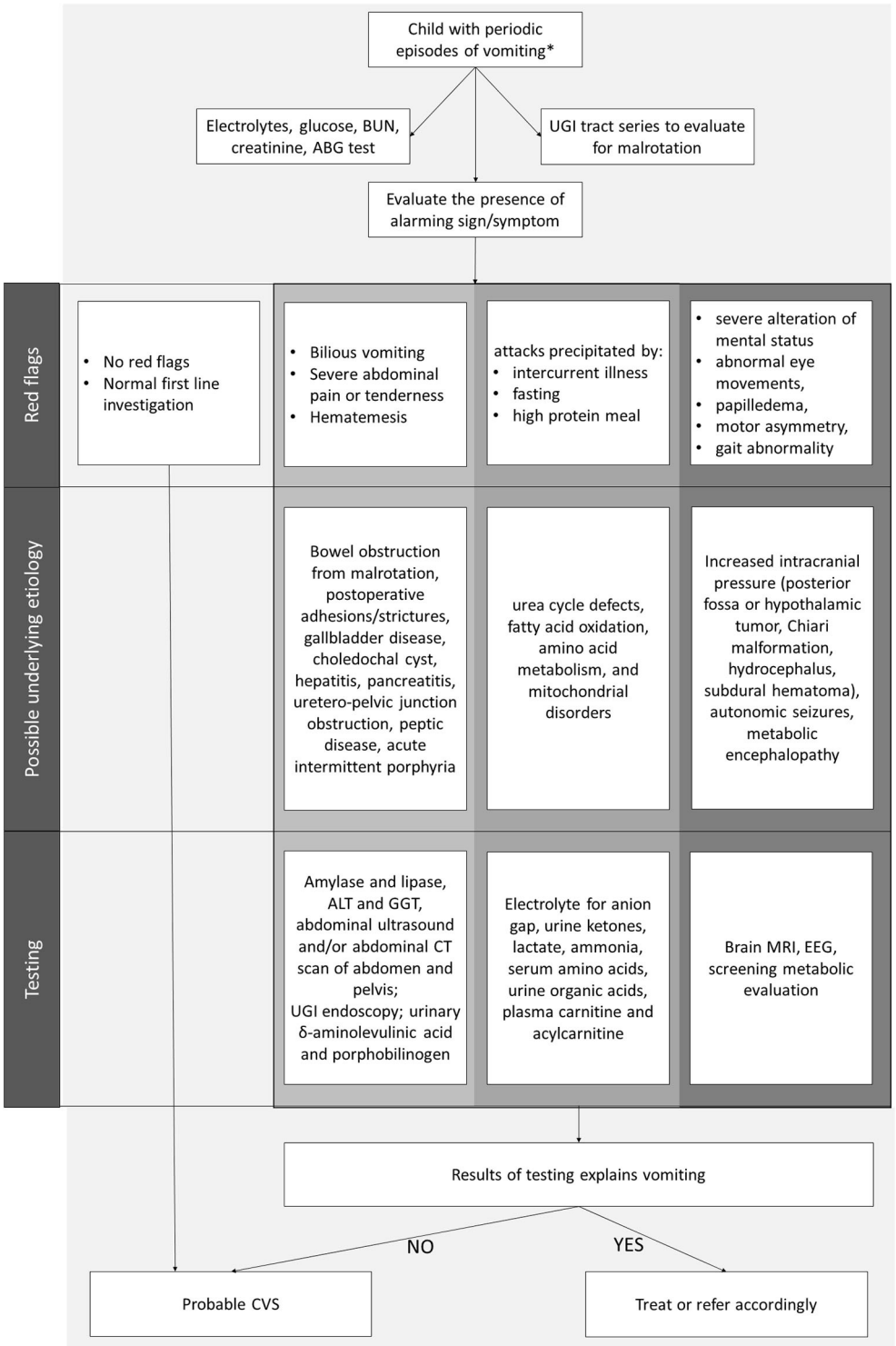
Despite most children with CVS may experience bilious emesis and severe abdominal pain, they might also underline the presence of serious surgical and non-surgical disorders. Therefore, an investigation aimed at ruling out bowel obstruction from malrotation or postoperative complications, gallbladder disease, choledochal cyst, hepatitis, pancreatitis, or ureteropelvic junction obstruction should be performed (**Table 2**). An upper GI endoscopy may be required if patients experience chronic gastrointestinal symptoms or large amounts of hematemesis. If anxiety, depression, hallucination, seizures, cranial nerve weakness, and paresis of the extremities are associated with vomiting and abdominal pain, detection of increased urinary δ-aminolevulinic acid and porphobilinogen in spot urine during the episode confirm the diagnosis of acute intermittent porphyria.

Adolescents should be questioned about the chronic marijuana use to identify a condition termed "cannabinoid hyperemesis syndrome" (CHS) which is characterized by severe cyclical nausea, vomiting, and abdominal pain that are relieved by compulsive long hot water bathing (1, 8, 72).

NATURAL HISTORY/PROGNOSIS

CVS resolves, in most children (50–70%) in late childhood or early adolescence (28–30, 73, 74). In one study among 41 children with CVS, 39% of children reported resolution of symptoms either immediately or within weeks from diagnosis. However, a large number of children from the group whose vomiting resolved continued to have somatic symptoms, with 42% of children suffering regular headaches and 37% having abdominal pain (compared to 50% of the persisting vomiting patients). Overall, 32% of the group had intermittent diarrhea and 54% experienced travel sickness at follow-up. Noteworthy, 78% of parents felt that the provision of a positive diagnosis and information made a significant impact on the severity of vomiting (29).

Resolution of symptoms did not correlate with duration or severity of the disorder at presentation or with any of the other variables analyzed (sex, age at diagnosis, admission to the



* Fulfilling clinical criteria for CVS (Table 1)
Abbreviations: ABG: arterial-blood gas: ALT, alanine aminotransferase; BUN, blood urea nitrogen; CT, computed tomography; CVS, cyclic vomiting syndrome ; EEG, electroencephalography; GGT, gamma-glutamyltransferase; MRI, magnetic resonance imaging; UGI, upper gastrointestinal

FIGURE 2 | Evaluation of children with cyclic vomiting pattern.

TABLE 2 | Clinical features suggestive of organic disorder.

Alarm symptoms and signs	Additional testing
Bilious vomiting, abdominal tenderness and/or severe abdominal pain	Amylase and lipase, alanine aminotransferase and g-glutamyltransferase; abdominal ultrasound and/or abdominal CT scan of abdomen and pelvis; upper GI endoscopy; urinary δ-aminolevulinic acid and porphobilinogen
Hematochezia ± melena	Upper GI endoscopy
Attacks precipitated by intercurrent illness, fasting, and/or high protein meal	Electrolyte for anion gap, urine ketones, lactate, ammonia, serum amino acids, urine organic acids, plasma carnitine and acylcarnitine
Abnormalities on neurological examination including severe alteration of mental status, abnormal eye movements, papilledema, motor asymmetry, and/or gait abnormality (ataxia)	Brain magnetic resonance imaging, electroencephalography, metabolic evaluation
History of head trauma	Brain magnetic resonance imaging
Progressively worsening episodes or conversion to a continuous or chronic pattern	Testing aimed at excluding chronic condition (e.g., inflammatory bowel disease) or metabolic disorders
Prolonged vomiting (>12 h in a neonate; >24 h in children; <2 years; >48 h in older children)	
Poor weight gain or weight loss	

hospital, identification of trigger factors, travel sickness, family history of migraine) (29).

According to another study on 28 cases (adult and children) with CVS, 62% of patients showed a gradual improvement in symptoms and 24% had complete resolution after a mean of 7 years (28).

Many children with CVS stop having emetic episodes as they grow older, although they develop headache throughout clinical history. Less commonly, CVS persists in adulthood or it may even begin in adulthood (75). Adult patients could be divided into subgroups with pediatric-onset (presentation before age 18) or adult-onset of CVS (37). A retrospective study (23) analyzed 101 CVS patients comparing those with pediatric-onset (29%) and those with adult-onset (71%). Pediatric-onset CVS patients were more likely to be female and there was a long delay in diagnosis when compared to adult-onset. Apart from these differences, both groups of patients had similar clinical characteristics and response to standard medications used in the treatment of CVS.

CVS is part of the episodic syndrome that may be associated with migraine (6). They are considered as an early life expression of migraine, thus they may occur without a headache component. A recent study on 1,134 children with tension-type headache (26.8%) or migraine (73.2%) found a previous history of "episodic syndromes" in 70.3% of patients (76). Among them, 6.6% of patients suffered from CVS. While some studies (5, 77) suggested that the episodic syndromes are exclusively associated with migraine, according to Tarantino et al. (76, 78) "migraine equivalents," including CVS, show a similar prevalence in children with either migraine or tension-type headache.

The strict relationship between CVS and pediatric primary headaches is supported by a study (31) evaluating the prevalence of primary headache in children with a history of CVS and benign paroxysmal torticollis (BPT). The authors showed that 79% of patients with the previous history of CVS had developed headache (71% migraine and 29% tension-type headache).

COMORBIDITIES

CVS is probably not the result of a single pathogenetic mechanism, rather the common final clinical picture (cyclical emesis attacks) of different physiopathological pathways, with different threshold, and many triggers can be able to elicit it (79). Anxiety and mood symptoms affect about 59% of school-aged children with CVS and represent the most prevalent comorbidities (1, 80). Anxiety alone has been described in a quarter of CVS population (66); it may lead to school avoidance, worsening CVS-induced disability. Quality of Life has been demonstrated to be correlated with trait anxiety and coping abilities (80, 81).

Autonomic function in CVS has been extensively investigated since many of these patients exhibit autonomic dysregulation; abnormalities in skin sympathetic responses and thermoregulatory sweat tests have also been reported. Postural orthostatic tachycardia syndrome has been described in 14% to 38% of CVS adolescents (39), and many children with CVS showed evidence of altered autonomic tone at baseline with elevated sympathetic tone and low to normal parasympathetic tone (36). Chelimsky et al. (39) suggested that treating the underlying autonomic dysfunction reduces the number of vomiting episodes in CVS and many children can have a reduced number of vomiting episodes from fluid administrations, salt supplementation, fludrocortisone, and low-dose propranolol (82).

Among gastrointestinal comorbidities, a recent survey on an adult population showed that CVS was significantly associated with irritable bowel syndrome, gastroparesis, and gastroesophageal reflux. Pareek et al. (83) found that irritable bowel syndrome and/or a family history of irritable bowel syndrome were more commonly reported in CVS patients (67 vs. 62%) than in general population (10–20 vs. 14%).

Sleep hygiene and melatonin intake before bedtime to induce sleep onset may reduce the triggering effect of sleep deficit. Using frequent or longer-lasting energy sources (protein bars) and coenzyme Q10 (10 mg/kg/day), can improve stamina and participation in school and extracurricular activities (53).

CVS and migraine, both, can be triggered by acute psychological or physiological stress, sleep deprivation and menses (27, 35, 63, 84), and a personal or family history of migraine disorders are frequent in both children and adults with CVS.

Even epilepsy and panic disorder share some clinical features with CVS and it is important to stress that the autonomic manifestations are prominent (or even isolated) features in some

TABLE 3 | Diagnostic tests for ruling out conditions in the differential diagnosis with Cyclic Vomiting Syndrome (CVS).

Condition	Diagnostic testing
GASTROINTESTINAL DISORDERS	
Peptic ulcer disease	Upper GI endoscopy
Gastroparesis	Scintigraphic gastric emptying study
Hepatitis	Abdominal Ultrasound
Pancreatitis	Abdominal Ultrasound
Cholecystitis	Abdominal Ultrasound
Biliary tract anomalies	Hepatobiliary scintigraphy, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography
Malrotation with volvulus, postoperative adhesions/strictures	Upper gastrointestinal series with small bowel follow through, abdominal CT scans, upper GI endoscopy
Chronic intestinal pseudo-obstruction	Plain abdominal X-ray, upper GI series with small bowel follow through, antroduodenal manometry
EXTRA-INTESTINAL DISORDERS	
Central nervous system	
Mass	Brain MRI, Brain CT
Hydrocephalus	Brain MRI, Brain CT
Subdural hematoma	Brain CT
Autonomic seizures	EEG
Renal Disorders	
Uretero-pelvic junction obstruction	Abdominal Ultrasound
Nephrolithiasis	Abdominal Ultrasound, abdominal CT

TABLE 4 | Differential diagnosis between Cyclic Vomiting Syndrome and intracranial masses.

	Cycling vomiting syndrome	Intracranial masses
Prodromal symptoms	Always present	Rarely present
Dehydration	Always present	Rarely present
Warning signs*	Absent	Often present
MRI alterations	Absent	Present

**Headache, altered sensory, papilledema, hypertension, bradycardia or tachycardia, signs of herniation, retinal hemorrhages, bluish skin lesions, fractures, ataxia, cranial nerve deficits, motor/sensory deficit, seizures, visual dysfunction.*

TABLE 5 | Relevant causes of vomiting in metabolic disorders.

ASSOCIATED OR NOT WITH ENCEPHALOPATHY
Organic acidurias
Urea cycle disorders
Fatty acid oxidation disorders
MCT1 defect
MELAS
Glutaric aciduria type I
ASSOCIATED WITH ACIDOSIS/KETOACIDOSIS
Organic acidurias
Mitochondrial diseases
ASSOCIATED WITH KETOSIS ONLY
Ketolysis defects
ASSOCIATED WITH SEVERE ABDOMINAL PAIN
Phorphyrias (acute intermittent porphyria, coproporphyria)
ASSOCIATED WITH HEPATOPATHY
Organic acidurias
Urea cycle disorders
Galactosemia
Hereditary fructose intolerance
Tyrosinemia type I
Fatty acid oxidation disorders

epilepsy with onset in pediatric age such as PS and rolandic epilepsy, requiring sometimes a challenging differential diagnosis (70, 71). Additional neurologic findings such as developmental delay, seizures, hypotonia with or without neuromuscular disease manifestations, cognitive impairment, myopathy, and cranial nerve dysfunction have been reported in up to 29% of CVS patients allowing to propose a subtype called CVS plus (85).

DIFFERENTIAL DIAGNOSIS

It includes seven main disorders that can be grouped in the acronym "URGENTIME": URologic, Gastrointestinal, Endocrine, Neurologic disorders, Toxins/medications, (recurrent) Infections, and MEtabolic diseases. Specifically, renal colic and/or pelvic-ureteric junction obstruction may cause recurrent vomiting of urologic origin with possible symptom-free interval periods. Many gastrointestinal disorders may determine recurrent vomiting due to bowel obstruction (malrotation with volvulus, duplication cyst, and intermittent intestinal intussusception, chronic intestinal pseudo-obstruction), allergic or inflammatory process (food allergy, eosinophilic esophagitis, gastritis, duodenitis, hepatitis, biliary tract dysmotility, pancreatitis, pancreatic pseudocyst, appendicitis, peptic disease, inflammatory bowel disease); Pheochromocytoma, diabetes and Addison disease and different neurological disorders (epilepsy, migraine, autonomic nervous system disorders, brain tumor), should also be considered in children presenting with vomiting. Besides, toxins (such as the use of cannabis) and medications (antibiotics, NSAID, laxatives, hormones) need to be excluded. Also, recurrent infections, particularly enteritis, hepatitis, otitis media and chronic sinusitis may manifest with vomiting. Finally, several metabolic diseases such as aminoaciduria, organic aciduria, urea cycle and fatty acid oxidation defects, mitochondrial disorders and acute intermittent porphyria should be ruled out (86).

Because of the wide range of underlying conditions and lack of a specific sign and biomarker of CVS, the selection of first step and progression of investigations is often challenging and tests should be selected based on clinical presentation and suspicion (**Tables 3–5**).

Neurological Disorders

Epilepsy

Vomiting may be an "ictal" manifestation, as a part of the seizure semeiology (87, 88), and in young children, autonomic phenomena such as nausea and vomiting are common symptoms of PS, an age-related childhood-onset focal idiopathic epilepsy. PS is often misdiagnosed as encephalitis, migraine, gastroenteritis, gastroesophageal reflux or CVS (70, 71, 89). Carbonari et al. showed that CVS is a common misdiagnosis in children with PS and other non-convulsive epilepsies (90). Other epilepsies such as temporal lobe epilepsy (TLE) or symptomatic epilepsies related to posterior regions of the brain can manifest with vomiting as the main manifestation and mimic CVS (91).

Migraine

As CVS and migraine share common pathogenic mechanisms (39), many clinical features of CVS, as well as a family history of migraine, are in common with migraine; moreover, patients with CVS often manifest migraine later in life.

Abdominal pain is one of the key symptoms of cyclic vomit and it is also the major feature of abdominal migraine, moreover, abdominal migraine and CVS can co-exist in the same child (13). Abdominal migraine is a migraine subtype where children have attacks presenting predominantly with abdominal, rather than headache symptoms. The International Classification of Headache Disorders defines abdominal migraine as recurrent attacks of moderate to severe midline abdominal pain lasting 2–72 h, associated with flushing, pallor, anorexia, nausea, or vomiting without headache. At least five episodes are needed to fulfill the diagnosis. Children are normal between attacks and gastrointestinal or renal disorders are ruled out (6–8). Despite all the confusing overlaps, in abdominal migraine pain predominate over vomiting, while nausea and vomiting predominate over abdominal pain in CVS (92); also, certain pain characteristics are more likely in CVS such as burning, non-midline, mild and not interfering in daily activities, and duration of >1 h (13).

Autonomic Nervous System Disorders

Many of the symptoms of CVS that are associated with episodes of vomiting such as pallor, increased salivation, nausea, abdominal pain and unwillingness have been attributed to autonomic imbalance (39, 82). Thus, CVS should be distinguished from dysautonomic disorders, such as acute autonomic neuropathy (93) and hereditary sensory or autonomic peripheral neuropathies.

Cannabinoid Hyperemesis Syndrome (CHS)

This condition is characterized by paroxysmal episodes of abdominal pain, nausea and vomiting in individuals addicted to daily cannabis or marijuana use. Screening for cannabinoid use has to be considered in adolescents with unexplained CVS (91). Often, individuals suffering from CHS report temporary cessation of symptoms after hot bathing and showers, a helpful clue to differentiate CHS from CVS (92).

Brain Tumors and Other Intracranial Masses

Brain tumors and other intracranial masses (hydrocephalus, posterior fossa tumors, subdural hematoma, and subdural effusion) represent a differential diagnosis of cyclic vomiting.

They can cause nausea, vomiting, or both, by increasing the intracranial pressure (ICP) at the area postrema of the medulla. Vomiting, often present in the morning, occurs due to increasing of ICP during the night while the patient is sleeping and venous drainage is decreased (32). Acute elevation of ICP needs timely treatment, so it's important to look for some warning signs such as headache, altered sensory, papilledema, hypertension, bradycardia or tachycardia, signs of herniation, retinal hemorrhages, bluish skin lesions and fractures.

While CVS is characterized by stereotypical episodes with prodromal symptoms such as nausea, abdominal pain, anorexia and pallor, emesis in brain tumor or other intracranial masses occur without prodromal symptoms and is triggered by a rapid change in body position and nausea is rarely present (15). Brain tumors and strokes may present with focal neurologic deficits and the type is depending by location and disease stage (**Table 4**).

Another differential diagnosis is idiopathic intracranial hypertension (pseudotumor cerebri) (94). In these patients, ICP is increased with normal cerebrospinal fluid (CSF) content, normal neuroimaging and absence of other neurological signs. It mostly affects obese adolescent girls and is typically described by other authors with headache and sometimes nausea and vomiting. In summary, intracranial expansive masses are often associated with neurological findings, including ataxia, cranial nerve deficits, motor/sensory deficit, seizures, visual dysfunction, papilledema, so it is important never to ignore pediatric patients with these symptoms.

Metabolic Diseases

Recurrent vomiting is a characteristic clinical sign of inborn errors of metabolism (IEMs), such as organic acidurias (usually in association with acidosis), disorders of urea cycle (with hyperammonemia) and fatty acid oxidation defects (**Table 5**). Laboratory investigation for metabolic causes of vomiting should include glucose, ketonemia, acid-base balance, lactate, ammonia, acylcarnitine and urinary organic acid. The association of other clinical and biochemical abnormalities may direct the differential diagnosis.

Vomiting With Encephalopathy

Chronic or recurrent vomiting in infancy is particularly common to the organic acidurias (OAs) due to a defect in the metabolism of branched-chain amino acids isoleucine, leucine and valine, in which the accumulation of small molecules proximal to the metabolic block, which are toxic for the body, especially for the brain and are therefore defined intoxication-type IEMs (95). Neurological damage is characteristic with associated symptoms ranging from poor feeding to slow growth, lethargy, vomiting, dehydration, malnutrition, hypoglycemia, hypotonia, metabolic acidosis, ketoacidosis, and hyperammonemia.

Vomiting may be due to the hyperammonemia associated with disorders of the urea cycle (UCDs), inborn errors of ammonia detoxification/arginine synthesis (96). In severe cases,

a rapid deterioration of the level of consciousness can be observed, but, in milder affected patients, vomiting can be the only presenting symptom and/or be intermittent. Fatty acid oxidation disorders can also manifest with hyperammonemia and vomiting, because of metabolic decompensation due to prolonged fasting or infections. As recurrent vomiting leads to alkalosis, the evidence of acidosis at acid-base analysis should raise the suspicion of an OAs or other causes of loss of bases; conversely, vomiting in UCDs is associated with alkalosis. Along with recurrent metabolic vomiting, some patients with OA and UCDs present with focal neurological signs or cerebral edema. These patients can be mistakenly diagnosed as having brain tumors or cerebrovascular accidents. Another rare organic aciduria, Glutaric Aciduria type I. frequently presents with encephalopathic episodes and vomiting, mimicking encephalitis, in association with an intercurrent gastrointestinal or viral infection. This disorder is caused by an inherited deficiency of glutaryl-CoA dehydrogenase, which is involved in the catabolic pathways of L-lysine, L-hydroxylysine and L-tryptophan (97). Prompt recognition of this disorder permits the start of a low lysine diet and carnitine supplementation, improving neurological outcome (98).

Noteworthy, in several countries, these conditions are included in the panels of Expanded Newborn Screening, allowing earlier diagnosis and treatment.

Cyclic Vomiting With Severe Abdominal Pain

The Porphyrias are IEMs due to defect of the biosynthesis of heme, which enters in the composition of cytochromes as well as hemoglobin. Diffuse crampy abdominal pain and constipation are present in all the three most common acute intermittent porphyrias, variegate and hereditary coproporphyria (99). Acute neurovisceral symptoms are due to increased activity of the first step of porphyrin synthesis and can be aggravated by certain drugs. The abdominal pain may be intense, similarly to that which occur in diabetic ketoacidosis. Striking accumulations and excess excretion of heme pathway intermediates and their oxidized products give a characteristic red (or dark) urine color. Hepatic porphyrias are transmitted as an autosomal dominant trait. Diagnosis is often difficult and a positive urine screening test (Watson –Schwarts test) may be present only during acute illness. Concomitant study of blood, urine, and stool for porphyrins is the best diagnostic approach, followed by genetic analysis (99).

Vomiting With Ketosis

While ketonuria should always be considered abnormal in neonates, it is a physiological result of catabolism in late infancy, childhood, and even adolescence. However, hyperketosis >6 mmoles/l of total plasma ketone bodies that cause metabolic acidosis (serum bicarbonate <18 mmol/l) is always pathological. Ketosis in absence of other biochemical abnormalities such as acidosis, hyperlactatemia, or hypoglycemia, rarely is due to an IEMs and is likely to be a normal physiological response to fasting, catabolism, vomiting, medium-chain triglyceride enriched or other ketogenic diets). Conversely, ketoacidosis with or without hypoglycemia could be seen in several metabolic disorders, especially OAs and mitochondrial diseases.

Persistent ketosis (both in fasting and in fed state) suggests a genetic defect of ketolysis. This category includes deficiency of Beta-Ketothiolase, due to mutation of ACAT1 gene, and defect of succynil-CoA:3 Oxoacid CoA transferase, caused by pathogenic variants in SCOT gene (100). Both disorders are characterized by acute episodes di nausea and vomiting, often leading to encephalopathy and coma. Metabolic studies show in both disorders an increase of 3OH-butyrate in serum and urine. Beta-Ketothiolase is also associated with a characteristic profile of acylcarnitine and urinary organic acids.

Monocarboxylate transporter type 1 deficiency (MCT1) is caused by mutations in the *MCT1* gene (*SLC16A1*) on chromosome 1p13. MCT1 has been reported as a cause of recurrent episodes of severe ketoacidosis often associated with cycling vomiting without consciousness depression (101).

Vomiting With Hepatopathy

Galactosemia, Hereditary Fructose Intolerance (HFI) and Tyrosinaemia type I, are the main conditions in this category characterized by vomiting plus acute liver failure, requiring immediate and specific treatment (102). Patients may show acute deterioration, vomiting, seizures, dehydration, hypoglycaemia, liver failure and tubulopathy. Other biochemical abnormalities associated with liver disease are mellituria, hyperammonaemia, hyperlactatemia, hypoglycaemia, hypertyrosinaemia, and hypermethioninaemia. The presentation of Tyrosinaemia type I is usually after the 3rd week of life, whereas galactosaemia usually presents in the newborn period and HFI after weaning, since fructose is not normally part of infant formulas. In the suspect of one of these conditions, galactose, fructose and proteins must be excluded from the diet, pending confirmation of the diagnosis. When galactosaemia or HFI is confirmed, proteins can be reintroduced (102). If Tyrosinaemia type I is confirmed, patients should start immediate treatment with NTBC, along with a low-phenylalanine and low-tyrosine diet, to help a rapid recovery from acute liver failure (103).

Differential Diagnosis With Cyclic Vomiting of Childhood

Cyclic vomiting of childhood, often triggered by fasting and in the setting of infection, needs to be differentiated from IEMs. In some children, episodes can also be provoked by intense exercise. Typically, episodes begin in the second year and usually end within puberty. Urinary organic acid analyses show prominent ketosis, but no pathological metabolites, and acylcarnitine analysis shows prominent acetylcarnitine. Treatment with intravenous glucose usually results in rapid resolution of the symptoms. Ondasentron can be effective, whereas phenotazine antiemetic is of limited use. A substantial number of children with this phenotype cannot be included in a precise disease category (104). Some authors have suggested an impaired uptake of ketone bodies into the peripheral tissues. This disorder could be sometime confused with ketotic hypoglycemia, but blood glucose is not abnormally low, and the treatment for ketotic hypoglycemia (avoiding fasting, cornstarch at bedtime, etc.) is not particularly beneficial (105).

GENETICS FINDINGS IN CVS

CVS running through generations has been sporadically reported (106–109). Moreover, inherited inborn errors of metabolism, including fatty acid oxidation disorders, urea cycle defects mitochondrial and amino acids disorders, have been associated with pediatric CVS (4, 55, 110–114). However, so far, CVS has an entry [MIM # 500007] in the online catalog of Mendelian Inheritance in Man (115), currently attributed in this catalog to mutations in the mitochondrial transfer RNA-leucine [*MTTL1*; MIM # 590050] gene (107). Mitochondrial dysfunction [i.e., mitochondrial DNA polymorphisms [including A3243G, C16519T, and G3010A mtDNA polymorphisms and mutations in the *MTTL1* mitochondrial gene (MIM # 590050) or mitochondrial DNA rearrangements or deletions] has been demonstrated in some patients (4, 53, 67, 91, 107–109, 111–113, 116–121). The functional significance of these single nucleotide polymorphisms remains unknown. Furthermore, these mitochondrial associations have not been replicated in adults with cyclic vomiting (112) suggesting the role of other non-mitochondrial factors (11).

Individuals with CVS may also harbor (polymorphic) mutations in single genes, including: (1) *RYR2* (ryanodine receptor 2) [MIM # 180902; on chromosome 1q43] (2) (55) *SCN4A* (sodium channel voltage-gated, type IV subunit alpha) [MIM # 603967; on chromosome 17q23.3] (3) (11) CNR1 (cannabinoid receptor 1) [MIM # 114610; on chromosome 6q15] (122); and (4) OPRM1 (opioid receptor MU1) [MIM # 600018; on chromosome 6q25.2] (122).

The *RYR2* gene encodes for a stress-induced calcium release channel receptor two, which is part of the ryanodine receptor [RYR: a tetramer composed of 4 RYR2 polypeptides and four FK506-binding proteins or FKBP12.6], present in the sarcoplasmic reticulum of (a) cardiac muscular cells [where it acts as the major source of calcium, required for cardiac muscle excitation-contraction coupling], being responsible for (type 2) right ventricular dysplasia with cardiac arrhythmia type 2 [MIM # 600996] and (type 1) catecholaminergic polymorphous ventricular tachycardia [MIM # 604772]; and (b) autonomic and other neurons. Marx et al. (123) demonstrated that protein kinase A [PKA; MIM # 176911; on chromosome 7p22.3] phosphorylation of RYR2 dissociates FKBP12.6 and regulates the channel open probability: in defective hearts RYR2 is PKA hyperphosphorylated, resulting in defective channel function due to increased sensitivity to calcium-induced activation.

The *SCN4A* gene encodes for a component (i.e., the alpha subunit four) of the voltage-gated sodium channel integral membrane protein, which form a pore in the cytoplasmic membrane conducting sodium ions through the membrane and is responsible, so far of: (a) a group of related muscular disorders, including hyperkalemic periodic paralysis [HYPP; MIM # 170500], paramyotonia congenita [PMC; MIM # 168300]; and (b) a group of disorders classified as potassium-aggravated myotonia [MIM # 608390], and hypokalemic periodic paralysis type 2 [HOKPP2; MIM # 613345].

The *CNR1* gene encodes for the G-protein coupled pre-synaptic cannabinoid receptor 1 ($\mathbf{CB_1}$), which is expressed in glutamatergic and GABAergic interneurons, located prevalently in the central (e.g., hippocampus, basal ganglia, cerebellum, neocortex, and spine), peripheral and autonomic (e.g., heart and gut) nervous system but also in the endocrine and sexual glands, and is activated by endocannabinoids acting as a modulator, which in turn decreases the release of glutamate and GABA. Interestingly, the use of cannabinoids is relatively common among individuals with CVS and chronic cannabis use has been associated paradoxically with cannabinoid hyperemesis syndrome (124–126).

The *OPRM1* gene encodes for the primary site of action for the endogenous enkephalins and beta-endorphins, and is located in the pre- and post-synaptic regions of neurons distributed over the brain (e.g., periacqueductal region, dorsal horns of the spine, olfactory bulb, and neocortex) and intestinal tract.

An unifying genetic-related pathogenic mechanism infers that the synergic roles of these nuclear DNA mutations and single-gene sequence variants may result in aberrant stress-induced calcium release [RYR2-mediated] into the mitochondria (11), or sodium release/balance [SNN4A-mediated] across the cytoplasmic membrane, or neurotransmitter modulation [e.g., CNR1- or OPRM1-mediated] or axonal transport (KIF1B) or energy production (TRAP1) of autonomic neurons, resulting in an increased risk to develop autonomic/functional disease such as cyclic vomiting, and related conditions such as migraine, epilepsy and gut dysmotility: this model incorporates the existing hypotheses regarding CVS pathogenesis into a cohesive mechanism, and might have treatment implications (52, 127).

Chew and al. (128) expanded a "TUBB3 E410K phenotype" originally known as type 3 congenital fibrosis of the extra-ocular muscles [CFEOM; MIM # 600638; on chromosome 16q24.3] due to mutations in *TUBB3* [tubulin beta-3; MIM # 602661], which encodes for the two heterodimer proteins that compose microtubules, by adding, besides congenital fibrosis of the extra-ocular muscles, facial weakness, developmental delay and progressive sensorimotor peripheral neuropathy, Kallmann syndrome [i.e., hypogonadotropic hypogonadism and anosmia; MIM # 308700], stereotyped midface hypoplasia, intellectual disabilities and, in some cases, vocal cord paralysis, tracheomalacia and cyclic vomiting. They inferred that the c.1228G > A mutation in the *TUBB3* gene and subsequent E410K amino acid substitution in the beta-tubulin 3 protein, defines a new genetic etiology for Moebius syndrome [MIM # 157900], Kallmann syndrome and cyclic vomiting (128).

Larger genetic and functional studies of CVS in both adults and children will be needed to better establish the heritable basis of this disorder. These studies must involve well-characterized patient sub-sets to better delineate genotype-phenotype relationships.

FOCUS ON EMERGENCY DEPARTMENT

Evaluation and recognition of etiology of pediatric patients with recurrent vomiting in the emergency department (ED) can represent a challenge because a broad differential diagnosis is present. While the most common causes are benign, it can be due

to potentially disabling or life-threatening conditions, requiring early diagnosis, and prompt intervention. Misdiagnosis is not uncommon (129) with consequent ED discharge with a non-specific diagnosis and consequent diagnostic delay, quantified in 2.5 years (38). It has been described that patients may have up to 10 ED visits per year, with over 5 ED visits before the correct diagnosis (130). The emergency physician should use a systematic approach that has to be age and developmentally appropriate to be able to identify life-threatening emergencies, such as bowel obstruction, diabetic ketoacidosis, adrenal crisis, toxic ingestion, or increased intracranial pressure (131). Diagnosing CVS efficiently and cost-effectively can be achieved by early clinical recognition based upon clinical criteria (**Table 1**), followed by a limited diagnostic workup to exclude alternative disorders in all patients, even in the absence of warning signs for organic causes (132) (**Figure 2**).

In ED setting biochemical, radiographic assessments, and potentially endoscopic/ultrasound assessment should be considered. Biochemical testing should include arterial-blood gas test, complete blood count, serum electrolytes and glucose, liver panel, lipase, blood urea nitrogen, creatinine and urinalysis, also to exclude possible dehydration (132). So especially in urgent care, the physicians should: (1) investigate for the etiology of vomiting, taking into account the child's age (serious disorders are more frequent in children younger than 2 years); (2) look for the possible consequences or complications of vomiting (e.g., fluid depletion, hypokalemia, and metabolic alkalosis) and correct it; (3) provide a targeted therapy, when possible or, in other cases, the symptoms should be treated (131). The NASPGHAN Consensus on pediatric CVS proposed in 2008 a diagnostic workup (1), in which especially during the acute phase, the tendency toward an "exclusion" diagnosis prevails through the execution of first level investigations. A careful anamnestic collection and physical examination can orientate toward the identification of those children with warning signs/symptoms in which level II investigations are necessary (**Table 6**).

It is recommended that in the presence of red flag further evaluation is performed. Once life-threatening causes are excluded and acute alterations are treated, the patient should be referred to an appropriate pediatric specialist (e.g., gastroenterologist, surgeon, neurologist, metabolic experts), to avoid inappropriate further ED visits and a delay in the diagnosis and preventive therapy in case of CVS (130).

Further evaluation:

1. If the acute onset of unilateral or flank pain, severe abdominal pain, abdominal tenderness bilious vomiting, perform ALT/GGT (LFT's), lipase ± amylase, an abdominal and pelvic ultrasound to exclude e.g., gallstones or acute hydronephrosis should be performed (132). Large amounts of upper gastrointestinal bleeding may warrant endoscopic evaluation. Persisting upper gastrointestinal symptoms between episodes suggest performing an upper endoscopy at any time between episodes to rule out other causes (e.g., coeliac disease, IBD). In case of suspected obstructive disorders (e.g., bilious vomiting, severe discomfort) in addition to LFTs, lipase, ultrasound, also a plain abdominal X-ray or CT abdomen should be performed.
2. If metabolic warning, blood and urine tests should be obtained, followed by delivery of 10% dextrose-containing intravenous fluid at a rate of 1.5 times maintenance (simultaneously with fluid boluses as necessary) (1). During the early part of the episode (before IV fluids are administered) physicians should measure: serum concentrations of lactate, pyruvate, ammonia and serum amino acids, blood gas in addition to serum electrolytes (for anion gap) as well as urine organic acids (in addition to urine ketones already done); eventually carnitine, acylcarnitine and urine catecholamines,

TABLE 6 | Pediatric emergency department protocol for patients with recurrent vomiting regardless of an established diagnosis of Cyclic Vomiting Syndrome (CVS).

Medical history and physical examination

- individuate the presence of warning signs/symptoms (**Table 2**)
- evaluate for the presence of clinical criteria for CVS (**Table 1**)
- evaluate the change in the typical vomiting pattern (if previous CVS diagnosis)
- evaluate previously performed investigations

Emergency Department management

1. Clinical assessment: pulse rate, temperature, breathing rate, blood pressure, level of consciousness, state of hydration, and body weight
2. Investigations for all patients:
   - complete blood count, electrolytes, glucose, blood urea nitrogen, creatinine, arterial-blood gas test, urinalysis
   - upper gastrointestinal tract series to evaluate for malrotation (if not done before)
3. Other laboratories and diagnostic imaging guided by warning symptoms/signs at discretion of attending physician:
   - Attack with bilious vomiting, severe abdominal pain, abdomen tenderness, hematemesis
     - *At any time*
       - ultrasound of abdomen and pelvis, lipase/amylase, EGDS
     - *During the attack*
       - Amylase and lipase, alanine aminotransferase and g-glutamyltransferase
       - Upper GI endoscopy if large hematemesis
   - **Attack precipitated by fasting, intercurrent illness, high protein meal**
     - *Before IV fluid*
       - glucose, electrolytes for anion gap, lactate, pyruvate, ammonia, serum amino acid, urine organic acid, urine ketones, plasma carnitine, acylcarnitine
   - **Abnormal neurological exam (severe altered mental status, abnormal eye movement, papilledema, motor asymmetry, gait abnormality)**
     - Brain MRI, Brain CT
     - EEG
4. Reassess after treatment for emetic phase of CVS (see treatment) or for complications of vomiting
   - *Treatment failure*: intensify treatment as indicated (see treatment) or admit patient
   - *Positive treatment response*: discharge with treatment advice and eventually referral to specialist

This ED protocol represents a sample template and should be tailored based on individual needs.

δ-aminolevulinic acid and porphobilinogen should be carried out especially in patients with supporting symptoms (e.g., anxiety, depression, hallucination, seizures, cranial nerve weakness, and paresis of the extremities). After obtaining the appropriate specimens for testing (before IV fluids are administered), emergency treatment must be instituted. If it not possible to carried out these tests in the ED or to save a small amount of frozen urine and plasma for later evaluation. Moreover, an upper gastrointestinal series to the ligament of Treitz (a small bowel follow-through or CT/MR enterography) should be performed in all children to exclude malrotation or non-fixation with possible intermittent volvulus.

3. If neurologic signs, perform magnetic resonance imaging (MRI) of the brain or computed tomography (CT) to rule out intracranial lesions, brain tumors or referral to a neurologist. Moreover, in those patients with neurologic signs an electroencephalography (EEG) recording should also be performed to rule out PS, a benign epileptic syndrome, characterized by predominantly autonomic symptoms (including emesis): the availability of EEG recording in pediatric ED might be useful for a prompt and not-cost-consuming diagnosis (133).
4. Children who present in ED with a CVS diagnosis (Rome IV criteria) and without any additional warning symptoms require only a limited set of further investigation. During each episode, laboratory testing should be performed, consisting of electrolytes, glucose, blood urea nitrogen (BUN), creatinine, and urinalysis to primary monitor for acute hypovolemia and electrolyte disturbances. It is clear, e.g., that mild metabolic acidosis, hypoglycemia, and ketosis are consistent with CVS while severe acidosis or hypoglycemia (in particular non-ketotic hypoglycemia) warrant further evaluation for an inborn error of metabolism, especially in infants and toddlers. It is also important to identify triggers (in particular infections), and recognize comorbid (132).

TREATMENT

The management of CVS requires an individually tailored therapy that takes into consideration the frequency and severity of attacks, and resultant disability balanced against the potential side effects of treatment. The two key treatment arms are prophylactic measures and medications administered in the interictal period and acute and supportive interventions given during attacks (1) (**Table 7**).

Acute Treatment

Therapeutic management of acute phase is mainly based on supportive and on symptomatic care aimed to correct fluid and electrolyte deficits, provide antiemetic therapy, analgesics, and sedation for relief of unrelenting nausea, vomiting, and pain. Moreover, early intervention with abortive agents during the brief prodromal phase can be used to attempt to terminate the attack (79, 134).

Sumatriptan ($5HT_{1B/1D}$agonist) can be used intranasally (10 mg <40 Kg−20 mg >40 kg) or subcutaneous [(age × 4 + 20)/100 × 3 mg] in children 12 years and older (127, 135). It has also been shown that it is more effective when there is a family history of migraines. Uncommon side effects include neck pain/burning and coronary vasospasm and it is contraindicated in basilar artery migraine (134, 135).

Aprepitant, a neurokinin (NK1) receptor antagonist, can be used during the prodromal phase as abortive therapy. In a retrospective study, 25 pediatric patients refractory to conventional CVS therapies were treated with aprepitant at the beginning of the prodromal phase (**Table 7**), resulting in a decrease in vomiting duration and frequency in 76% of the patients (136). Once the vomiting starts, patients should be admitted to the hospital to provide supportive care and interventions aimed to stop the emetic phase (79).

Supportive care includes: (1) decrease stimulation in a dark, quiet, private room with minimum vital sign measures; (2) replacement of fluids, electrolytes and energy balance. It has been reported that the use of 10% dextrose solutions is associated with an improvement of the catabolic state and of ketosis that could exacerbate nausea (134). Vomiting can lead to hypokalemia and potassium replacement might be necessary. In case of prolonged fasting with minimal energy and/or protein intake, temporary nasojejunal feedings or parenteral nutrition can hasten recovery (1, 79) Treatment of pain and complications. Ketorolac (0.4–1 mg/kg per dose intravenously every 6 h, max dose 30 mg, max daily dose 120 mg) is considered the first-line analgesic treatment for pain. In selected severe cases, morphine or fentanyl can be used (134). The association with intravenous H2-receptor antagonist or proton pump inhibitors at conventional dosage can be helpful to treat epigastric pain and also to prevent esophagitis and hematemesis from Mallory-Weiss tear (1). Transient hypertension found in the SATO subset of CVS should be treated with short-acting ACE inhibitors (e.g., captopril) during the episode only. If secretion of the antidiuretic hormone with hyponatremia, low serum osmolality, and high urine specific gravity occurs, water intake should be restricted until values normalize (1). Metabolic acidosis can occur for several causes and should be checked taking arterial blood gas and treated if needed (134). Ondansetron iv (0.3–0.4 mg/kg/dose every 4–6 h, max 20 mg/day) has been shown to decrease vomiting duration or frequency during the acute phase by more than 50% (38). It can be used at a dose of 0.15 mg/kg per dose oral/sublingual in those patients with milder symptomatology; main side effects are constipation, dry mouth, headache, drowsiness (20). Moreover, since QT prolongation can occur with the administration of this medication, a baseline ECG is recommended.

When ondansetron fails to control nausea and vomiting, sleep induced by sedatives may be the only way to provide symptomatic relief. The most effective combination is ondansetron and lorazepam (0.05–0.1 mg/kg/dose iv every 6 h). Alternatively, chlorpromazine (0.5–1 mg/kg/dose every 6 h) and diphenhydramine (1–1.25 mg/kg/dose every 6 h) can be used together, but this provides less antiemetic and more sedative effect (38). In extreme cases, dexmedetomidine has been successfully used to treat three pediatric CVS patients by a continuous infusion in the intensive care setting (137).

TABLE 7 | Medications available for pharmacological treatment of Cyclic Vomiting Syndrome (CVS) in children.

Medications	Class	Mechanism of action	Goal and indication	Dose	Route of administration	Side effects
Sumatriptan	Antimigraine	5HT1B/1D agonist	Prodromal phase as abortive therapy	10 mg < 40 Kg 20 mg > 40 kg (age × 4 + 20)/100 × 3 mg, in children 12 years and older	Intranasal subcutaneous	Neck pain/burning and coronary vasospasm and it is contraindicated in basilar artery migraine
Ondansetron	Antiemetic	5-HT3 receptor antagonist	Abortive therapy	0.3-−0.4 mg/kg/dose every 4–6 h, max 20 mg/day) 0.15 mg/kg per dose recommended.	Intravenous oral/sublingual in patients with milder symptomatology	constipation, dry mouth, headache, drowsiness, QT prolongation
Cyproheptadine	Antimigraine	Anti-histamine, serotonin (5HT2) and calcium channel antagonist	Preventative First choice in children ≤ 5 years	0.25–0.5 mg/kg/day Single night-time dose or divided bid or tid.	Oral	Increased appetite, weight gain and sedation
Pizotifen	Antimigraine	Serotonin (5HT2) antagonist and anti-histamine	Preventative alternative to cyproheptadine Available only in Canada and the UK	0.5–1.5 mg at night	Oral	increased appetite, weight gain and sedation
Propranolol	Antimigraine	β-blockers	Preventative	0.25–1 mg/kg/day, most often 10 mg bid or tid	Oral	lethargy, reduced exercise tolerance, bradycardia
Erythromycin	Antiemetic	Prokinetic agent	Preventative	20 mg/Kg/day	Oral	
Aprepitant	Antiemetic	Neurokinin (NK1) receptor antagonist	Preventative Phase as abortive therapy	40 mg orally twice/week in children < 40 kg, 80 mg in children 40–60 kg, and 125 mg in children > 60 kg 125 mg 30 min before the emetic phase, followed 80 mg/day 2–3 >20 kg, 80 mg for 3 days 15- 20 kg, 80 mg/day 40 mg day 2–3 <15 kg.	Oral	hiccups, fatigue, increased appetite, mild headache and severe migraine
Amitriptyline	Antidepressant	Tricyclic antidepressant	Preventative	Starting dose should be 0.2–0.3 mg/kg/day and increases of 5–10 mg/week should be done up to the highest dose of 1–1.5 mg/kg/day	Oral	Dry mouth, constipation, weight gain, morning tiredness, behavioral changes, cardiotoxicity (tachyarrhythmia)
Phenobarbital Valproic acid Topiramate	Anticonvulsants	Barbiturate either multiple mechanism of action	Preventative	2–3 mg/kg/day at bedtime 10–40 mg/kg/day 2 mg/kg/day divided in 2 daily doses	Oral	Sedation, cognitive impairment, Hyperactivity, disruptive behavior Irritability, Anorexia/weight loss, Hypertermia/dehydratation
Flunarizine	Antimigraine	Non-selective calcium channel blocker	Preventative	5 mg per day	Oral	Hypotension, Weight gain and appetite
Fluoxetine	Antidepressant	Selective serotonin reuptake inhibitor	Preventative	20 mg/day as anxiolytic treatment (not enough evidence)	Oral	Gastrointestinal symptoms, Sleep changes, Headaches. Restless legs. Appetite changes
Carnitine		Mitochondrial supplements	Alternate preventive	50–100 mg/kg/day, adults 1 g tid	Oral	Diarrhea, fishy body odor
Co-enzyme Q10		Mitochondrial supplements	Alternate preventive	5–10 mg/kg/day, adults 100 mg tid	Oral	Diarrhea

(Continued)

TABLE 7 | Continued

Medications	Class	Mechanism of action	Goal and indication	Dose	Route of administration	Side effects
Riboflavin		Mitochondrial supplements	Alternate preventive	400 mg daily or divided twice daily	Oral	Not described
Ketorolac	Analgesic	Non-steroidal anti-inflammatory	Supportive	0.4–1 mg/kg per dose every 6 h, max dose 30 mg, max daily dose 120 mg	Intravenous	gastrointestinal bleeding and dyspepsia
Omeprazole	Decreases stomach acid production	Proton pump inhibitors	Supportive	0.1 mg/kg	Intravenous	
Lorazepam	Sedatives	5-HT3 receptor antagonist	Supportive as rescue therapy	0.05–0.1 mg/kg/dose iv every 6 h, max 4 mg.	Intravenous	Disorientation, dizziness, hypotension, respiratory depression
Chlorpromazine	Sedatives, antiemetic, antipsychotic	D_2-antagonist	Supportive as rescue therapy	0.5–1 mg/kg/dose every 6 h, max 40 mg/day <5 years; max 75 mg/day 5–12 years	Intravenous	Drowsiness, hypotension, seizure, extrapyramidal symptoms, arrhythmias
Diphenhydramine (only in association with chlorpromazine)	Sedatives, antiemetic, antihistamine	H_1-antagonist	Supportive as rescue therapy	1–1.25 mg/kg/dose every 6 h	Intravenous	Respiratory depression, hallucinations, hypotension, nausea, blurred vision

If a child does not respond to one of the discussed regimens or the episode differs from previous ones by greater severity, longer duration, or different symptoms, then the clinician should consider the possibility of an underlying disease (e.g., acute appendicitis, pancreatitis, brain tumor) and the need for new or to repeat diagnostic testing (e.g., abdominal ultrasound, brain TC/MRI) (79).

The recovery phase from the last emesis to the successful retention of food and drink typically lasts a few hours. Once children want to eat food, they can generally return to a normal diet without gradual progression. However, some children experience protracted symptoms including intractable nausea with the inability to eat, persistent dizziness and hyperesthesia with allodynia; antiemetics, proton pump inhibitors or anticholinergic agents, and analgesics respectively are of little help (79).

Prophylactic Treatment and Lifestyle Changes and Dietary Restrictions

During the interictal period, lifestyle changes and the use of reassurance (e.g., attacks are not self-induced) and anticipatory guidance (e.g., improvement with age and knowledge that effective therapies are available) can themselves have a significant therapeutic effect reducing the frequency of attacks (138). In patients with anxiety, cognitive behavioral therapy and biofeedback may be needed (137).

A careful history and a detailed vomiting diary recording frequency of episodes, type of meal before episodes, and potentially aggravating life events can help to identify and avoid potential triggers in 70% of children (38). For these reasons, a short-term trial of 1–2 months to assess the impact of these conservative measures may be established synchronized with the diagnostic workup aimed to exclude organic causes of vomiting.

Lifestyle changes include: (1) avoidance of excessive excitement (e.g., birthdays, holidays, and overexertion); (2) avoidance of triggering foods. Although extensive dietary restriction of potential triggering foods is not recommended, it is reasonable to test eliminating foods or chemical substances that appear to be aggravating factors for migraines (e.g., cheese, chocolate, hot dogs, aspartame, monosodium glutamate. and alcohol) (139). Also, children with documented food sensitivities to specific foods (e.g., cow, soy, or egg white proteins) have been shown to improve following specific dietary elimination (3) (140) Consumption of high-carbohydrate snacks between meals, before physical exertion, and at bedtime should be used when a patient's history suggests fasting-induced attacks (38). Furthermore, given that CVS is considered to be within the migraine spectrum, it is appropriate to suggest migraine lifestyle interventions that include good sleep hygiene (e.g., regular sleep schedules, avoidance of sleepovers), regular aerobic exercise, regular meal schedules, maintenance of good hydration, and moderation or avoidance of caffeine (141). Finally, marijuana consumption should be checked in adolescents because its use was found to worsen the cyclic hyperemesis and its cessation decreased episodes of vomiting (142).

The indication for prophylactic pharmacotherapy depends on attack intensity (more than every 1–2 months) and severity (exceeding 2 days or requiring hospitalization), the impairment of the QoL (e.g., frequent school absences) and if attack treatments are ineffective or cause side effects. The choice of prophylactic pharmacological treatment should take into account the age of the child, psychological comorbidities and formulation and safety profile of the drug. The low initial dose is recommended, and increase incrementally, titrating to effect (1).

Cyproheptadine is a first-generation antihistamine used in GI disorders for its serotonin (5HT2) and calcium channel antagonist effects (143, 144). Cyproheptadine is effective in young children with CVS and is the first choice for children 5 years old or younger (145–147). The recommended dose is 0.25–0.5 mg/kg/day divided twice or three times per day. Common side effects include increased appetite, weight gain and sedation. Increased weight due to enhanced appetite makes this drug the best choice in an underweight patient but not recommended in school-age girls. To reduce the sedation experienced during the school day it can be successfully used as a single night-time dose (147).

Pizotifen 0.5–1.5 mg at night is an alternative to cyproheptadine with the same side effects. However, it is available only in Canada and the United Kingdom (148).

Propranolol is a β-blockers recommended as the second choice in children of all ages (1). Haghighat et al. (25) showed in a randomized trial that propranolol was effective in 74 out of 83 (92%) patients and appeared to be more effective than amitriptyline). Interestingly, the addition of a daily oral dose of erythromycin 20 mg/Kg to propranolol showed a significant increase in response rate in a randomized trial (149, 150).

Recommended propranolol dose is 0.25–1 mg/kg/day, most often 10 mg twice or three times per day. Main side effects are lethargy and reduced exercise intolerance, moreover, the resting heart rate should be monitored for potential bradycardia and when discontinued, it should be tapered for 1–2 weeks. It is contraindicated in patients with asthma, diabetes, heart disease and depression.

Only one uncontrolled study evaluates erythromycin alone (20 mg/kg/day) as a prokinetic agent but the strength of this data is limited by the poor quality of the study (151).

An interesting approach when standard agents are either ineffective or poorly tolerated is the use of aprepitant. Aprepitant was approved for the prevention of chemotherapy-induced nausea and vomiting (152, 153) (see **Table 7** for aprepitant dose); at 12 months follow-up, 13 children (81%) achieved either complete (3/16, 19%), or partial (10/16, 62%) clinical response. Adverse effects to aprepitant included hiccups, fatigue, increased appetite, mild headache, and severe migraine; only one patient stopped the medication for severe migraines (135).

Amitriptyline, a tricyclic antidepressant, is the most widely prescribed prophylactic medication for the treatment of CVS (52). North American Society for Pediatric Gastroenterology, Hepatology and Nutrition suggests amitriptyline as the first-line treatment in children older than ≥5 years (1). In literature, several studies are supporting the efficacy of amitriptyline in large pediatric case series (23, 25, 27, 30, 145, 154). Badihian et al. (147) found that amitriptyline and cyproheptadine showed the same efficacy in CVS prophylaxis. A retrospective study (52) reported a similar level of efficacy for amitriptyline and CoQ-10. Bagherian et al. (155) showed that amitriptyline is a better choice to reduce the severity of CVS attacks compared to topiramate. Response rates of amitriptyline in the available case series range from 70 to 90 per cent (52, 147). Amitriptyline should be started at a low dose and slowly titrated up to the desired effect if tolerated. Starting dose should be 0.2–0.3 mg/kg/day and increases of 5–10 mg/week should be done up to the highest dose of 1–1.5 mg/kg/day (79, 156). Since the most common amitriptyline side effect is represented by sleepiness, the drug should be administered at bedtime. Amitriptyline can have also anticholinergic, arrhythmogenic, and behavioral side effects, thus it can cause constipation, dry mouth, sedation, QT prolongation, increased appetite. Although half of the children experience at least one side effect, only 19% have to stop the drug (52).

If a patient does not respond to the first-line therapy (amitriptyline, cyproheptadine, and/or propranolol) the following options should be considered: (1) presence of persisting triggers (e.g., psychological stressors) and comorbid conditions (e.g., anxiety, POTS) or missed underlying disorders (e.g., hydronephrosis, chronic sinusitis, acute appendicitis, intestinal malrotation with volvulus, CNS tumors, metabolic crises) and toxic exposure (e.g., cannabis); (2) inadequate compliance which is common in adolescents and can be documented by testing blood levels for amitriptyline; (3) response to specific medications in CVS is quite variable and often requires serial medication trials and dose escalation before efficacy is achieved; (4) use of combination therapy with 2 drugs (e.g., amitriptyline with propranolol or an anticonvulsant); (5) use of complementary therapy such as carnitine, coenzyme Q, estrogens, acupuncture, or psychotherapy.

The use of antiepileptics in CVS prophylaxis has been studied in a few clinical trials (30, 155, 157–160) (**Table 7**). Valproate (10–40 mg/kg/day) is effective for the prophylaxis of severe CVS (30, 159). Sezer and Sezer (160) compared topiramate with propranolol as a long-term treatment option. The responder rates were 81% for the propranolol group and 94% for the topiramate group. Topiramate should be started with 25 mg at night for 1 week, then increased in 25 mg increments at weekly intervals at the usual dose 50–100 mg per day in two divided doses (max. 200 mg per day) until to clinical control.

Flunarizine is a non-selective calcium channel blocker commonly used as a prophylactic treatment for episodic migraine (75, 161–163). The recommended dose in migraine prophylaxis is 5–10 mg daily. Common side effects include increased appetite, weight gain and sedation. Its use in CVS patients is supported by anecdotal cases.

The use of mitochondrial supplements (co-enzyme Q10, L-carnitine, and riboflavin) may be helpful in a subset of patients with suspected mitochondrial or metabolic dysfunction (53, 54, 164). Boles et al. (53) suggested that a protocol consisting of mitochondrial-targeted cofactors (co-enzyme Q10 and L-carnitine) plus amitriptyline (or possibly cyproheptadine in preschoolers) is highly effective and safe in the prevention of vomiting episodes. The dose of drugs used in CVS is summarized in **Table 7**.

Low estrogen oral contraceptives can be used to treat girls with menstrual-related CVS (165). Anecdotal experience suggests that acupuncture may attenuate the severity of CVS attacks

(166). Psychotherapy, especially stress reduction, may help as adjunctive therapy (167, 168).

CONCLUSION

In the first description of CVS, Dr. Samuel Gee in 1882 wrote: "These cases seem to be all of the same kind, their characteristic being fits of vomiting, which recurs after intervals of uncertain length. The intervals themselves are free from signs of disease." His observations were later included in the definition of "the periodic syndrome of childhood" described by Wyllie and Schlesinger in 1933. CVS is now typified by stereotyped intense bouts of vomiting, at least 4 times per hour, lasting for hours to days followed by stretches of wellness. Although the recognition of CVS has been facilitated by the recently defined diagnostic criteria, many patients are still misdiagnosed. Moreover, at present, there are no specific tests for diagnosing CVS. Therefore, CVS is currently classified as an idiopathic disorder and the diagnosis relies on fulfilling clinical criteria.

CVS pathophysiology is still not well-understood; however, given the link between migraine and cyclic vomiting, it is assumed that there are similarities in the underlying cause. Over the last years, there have been some advancements in understanding the etiology and pathogenesis of CVS. However, CVS is currently still classified as an idiopathic disorder. Indeed, enlightening the pathophysiological mechanisms could unfold intriguing aspects of the syndrome, such as its periodicity, the mechanisms of actions of emetic triggers, and the heterogeneity in symptom severity and treatment response despite the phenotypic similarity.

There are no known ways to prevent or mitigate the risk in those with cyclic vomiting syndrome. The inheritance pattern is partial and there are no clear predictive markers of the disorder. If a child presents for a first or second episode of severe vomiting and there is a strong family history of migraine it might raise cyclic vomiting syndrome higher on the differential list and allow for earlier identification. Moreover, as CVS is a relatively uncommon condition there are no therapeutic controlled or open trials in the management of CVS and treatment recommendations are mainly based on expert opinion. Further clinical studies are crucial to assessing the efficiency and safety of the different treatment options and how the quality of life, the attack-free interval and the acute phase of the disease change with the antiepileptic drug compared to standard therapy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

UR, OB, GDN, RT, SSal, PS, and PPar conceived and planned this project inviting all the experts in this field from both the Italian Society of Pediatric Gastroenterology Hepatology and Nutrition (SIGENP) and Italian Society of Pediatric Neurology (SINP), they have also written the first draft of the manuscript. All the other involved authors participated in writing and improving, according to their specific expertise and experience, the final version of the manuscript.

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Psychopathological Comorbidities and Clinical Variables in Patients With Medication Overuse Headache

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The psychopathological profile of patients with medication overuse headache (MOH) appears to be particularly complex. To better define it, we evaluated their performance on a targeted psychological profile assessment. We designed a case-control study comparing MOH patients and matched healthy controls (HC). Headache frequency, drug consumption, HIT-6, and MIDAS scores were recorded. All participants filled in the following questionnaires: Beck Depression Inventory-II Edition (BDI-2), trait subtest of State-Trait Anxiety Inventory (STAI-Y), Difficulties in Emotion Regulation Scale (DERS), Barratt Impulsiveness Scale (BIS-11), Toronto Alexithymia Scale (TAS-20). The primary endpoint was to establish if MOH patients have an altered psychopathological profile. The secondary endpoint was to establish whether the worst profile correlates with the worsening of headache and disability measures. We enrolled 48 consecutive MOH patients and 48 HC. MOH patients showed greater difficulty in recognition/regulation of emotions (DERS, TAS-20), depression (BDI-2), anxiety (STAI-Y), and impulsiveness (BIS-11). We found a positive correlation among DERS, BDI-2, STAI-Y, and BIS scores and MIDAS and HIT-6 scores and among DERS and headache frequency and drug consumption. MOH patients showed a high rate of emotion regulation difficulties, depression, and anxiety, which may negatively affect their headaches. The ability to regulate/recognize emotions may play a central role in sustaining medication overuse.

Keywords: emotion regulation, emotion recognition (ER), psychopatological profile, medication overuse headache (MOH), behavioral approach

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INTRODUCTION

The daily or almost daily frequent use of symptomatic drugs in patients with high frequency or chronic migraine, and less frequently with chronic tension-type headache, leads to the development of medication overuse headache (MOH).

The psychopathological profile of patients with MOH is very complex: together with mood and anxiety disorders, it can be observed as tending to obsessive-compulsive disorders and the occurrence of dependance-related behavior (Cupini et al., 2009; Radat and Lanteri-Minet, 2010; Lampl et al., 2016), and it has yet been suggested that a psychological profile assessment should be included in patients' evaluation (Sarchielli et al., 2016).

A negative prognostic value for psychiatric comorbidities has been suggested putting forward the hypothesis that these can represent a risk factor for the evolution of episodic into chronic headaches (Radat and Swendsen, 2005; Guidetti et al., 2010). Psychopathological disturbances are also seen as a potential predictor of relapse and poor response to treatment, and this can, in turn, complicate headache management facilitating MOH development (Cupini et al., 2009; Radat and Lanteri-Minet, 2010). Finally, some studies raised hypotheses about the potential comorbidity between psychiatric disorders and chronic headaches, but the presence of psychiatric disorders in MOH patients has been verified only in some of these (Buse et al., 2013; Sarchielli et al., 2016).

Our study aimed at evaluating the prevalence of psychopathological profiles in MOH patients through a comprehensive psychopathological battery to assess depressive symptoms and anxiety disorders, emotions' recognition and elaboration, and impulsiveness' level. We also investigated potential correlations between the psychopathological profile and some clinical variables (i.e., headache frequency, drug consumption, the impact of headaches on abilities of daily living). We expected MOH patients to show higher scores in psychopathological questionnaires compared with healthy controls (HC). Moreover, we hypothesized that psychopathological scores correlate with different clinical variables (i.e., monthly days of headache, medications taken per month, disease duration, and migraine-related functional disability).

MATERIALS AND METHODS

Participants

We designed a case-control study comparing patients affected by MOH with HC, regarding possible differences in psychopathological profile. During the enrollment period (November 2015–May 2017), participation in the study was proposed to every outpatient with a MOH diagnosis that visited our Headache Center. MOH was diagnosed according to the International Classification of Headache Disorders, 3rd edition, beta version [Headache Classification Committee of the International Headache Society (IHS), 2013], based on clinical characteristics and the headache frequency resulting from personal headache daily diaries. Every other headache diagnosis was based on the ICHD criteria. Patients with suspected symptomatic headaches were investigated and excluded if needed.

Inclusion criteria for patients were age $\geq$18 years old, and fulfilling the ICHD 3rd edition, beta version criteria for MOH. Exclusion criteria were secondary headaches, and lack of inclusion criteria.

HC matched by age and gender were recruited among employees of the University Campus Bio-Medico. They all were free of medications at the moment of the assessment. Moreover, based on a clinical interview, we excluded those subjects who reported any known medical condition and neurological or psychiatric disease.

All patients had been under the care of our Headache Center for at least 3 months before the enrolment in the study and regularly completed their headache daily diary. We prescribed preventive therapy if patients were not taking it or a new one if they were. Patients were suggested not to overuse painkillers. Acetaminophen/paracetamol was allowed to treat the attacks. However, when patients were unable to refrain to take their usual symptomatic drugs, they were recommended to record in their diaries the number of triptans or NSAIDs or other analgesics they were forced to take. We reassessed patients after 3 months from the first visit. Mean headache frequency and symptomatic drug consumption in the previous 3 months were extracted from the diaries. If patients still overuse painkillers and the MOH diagnosis was confirmed, they had to start a bridge therapy protocol (Paolucci et al., 2017) for helping the withdrawal of symptomatic drugs. The protocol consisted of a 5-day iv infusion of saline solution NaCl 0.9% 250 ml with methylprednisolone 125 mg plus diazepam 10 mg, infused at 100 ml/h, and daily monitoring in a Day Hospital setting. Patients had not to take the overused symptomatic drug(s) and at the end of these 5 days received a new prophylactic therapy.

After informed consent was given, patients and controls were enrolled. At the moment of inclusion in the study, patients were asked to fill in a set of questionnaires to assess psychological profile, as described afterward. We also asked the patients to fill in Headache Impact Test (HIT-6; Bayliss et al., 2003) and Migraine Disability Assessment (MIDAS; Stewart et al., 2001) scores.

The primary endpoint was to establish if MOH patients have an altered psychopathological profile as compared to HC.

The secondary endpoint was to establish whether a worst psychopathological profile correlates with the worsening of headache impact and disability measures in MOH patients.

This study was designed following the ethical principles of the Declaration of Helsinki and all participants were asked to sign an informed consent. The study was approved by Campus Bio-Medico University Ethics Committee, approval number 44-18, and registered at AIFA (Italian Drug Agency) with number Eudract 2017-004606-18.

Psychopathological Assessment

Patients, before starting bridge therapy protocol, and HC filled in a set of questionnaires to assess psychological profile, composed by:

1. Beck Depression Inventory-II Edition (BDI-2; Beck et al., 1996), a 21 multiple-choice questions self-report inventory to measure the severity of depression.
2. Trait subtest of State-Trait Anxiety Inventory (STAI-Y; Spielberger et al., 1983), a 20 multiple-choice items self-report questionnaire for measuring anxiety disorder.
3. Difficulties in Emotion Regulation Scale (DERS; Sighinolfi et al., 2010), a 36 items self-report questionnaire designed to measure multiple aspects of emotion dysregulation.

The scale provides both a total score and scores on six subscales: non-acceptance of emotional responses (NONACCEPTANCE), difficulties engaging in goal-directed behavior (GOALS), impulse control difficulties (IMPULSE), lack of emotional awareness (AWARENESS), limited access to emotion regulation strategies (STRATEGIES), and lack of emotional clarity (CLARITY).

4. Barratt Impulsiveness Scale (BIS-11; Fossati et al., 2001) a 30 multiple-choice items self-report questionnaire for measure impulsiveness. The questionnaire provides a total score and 3 s-order factors, attention, motor, and non-planning impulsiveness.
5. Toronto Alexithymia Scale (TAS-20; Bressi et al., 1996) a 20 multiple-choice items self-report inventory for evaluating difficulties to identify and describe emotions. The scale provides a total score and three subscores, related to Difficulty Identifying Feelings (DIF), Difficulty Describing Feelings (DDF), and Externally and Oriented Thinking (EOT).

Statistical Analysis

To better describe the psychopathological profile of patients and to highlight possible emotional dysregulation we decided to run a *post hoc* analysis partially based on previous data (Migliore et al., 2018). Chi-square test and Student's *t*-test were run to assess the statistical difference between MOH patients and HC for sex and age distribution. Baseline headache measures were expressed as mean (SD) or median (IQR) depending on the variable distribution.

For the primary endpoint, to examine differences in experimental groups test performances, all dependent variables, obtained from psychopathological assessment scores (BDI-2, DERS, STAI-Y, BIS-11, TAS-20), were submitted to one-way ANOVA directly comparing the scores of two different groups (MOH vs. HC).

For the secondary endpoint, to highlight possible relationships between clinical variables (headache impact and disability measures: headache frequency, drug consumption HIT-6, MIDAS total score) and MOH psychopathological questionnaire performance, we initially performed bivariate correlation analysis. Taken into account that data did not respect the assumption of linearity and normality, we used Spearman's correlation coefficient.

Alpha level was fixed to ≤ 0.05. All statistical analyses were performed using SPSS 25.

RESULTS

From November 2015 to May 2017 we enrolled 48 consecutive patients with MOH diagnosis (see **Table 1** for clinical and demographic characteristics). We then enrolled 48 matched HC (**Table 1**).

Patients showed a mean of 24.1 days (± 6.4) of headache per month and a median of 40 symptomatic medications taken per month (IQR: 36; minimum 12 and maximum 315). The mean HIT-6 score was 67.4 (± 5.6), the mean of MIDAS total score was 88.8 (± 71.3), MIDAS-A score was 61.2 (± 28.3) and MIDAS-B score was 8.2 (± 1.3). We found no significant difference between men and women.

The group comparison showed that MOH patients and HC groups differed significantly in terms of total score of emotion regulation difficulties (DERS total score; $F_{(1,94)} = 17.68$; $p < 0.00001$; $\eta_p^2 = 0.15$), depression (BDI-2; $F_{(1,94)} = 19.04$; $p < 0.0001$; $\eta_p^2 = 0.16$), alexithymia (TAS-20 total score; $F_{(1,94)} = 9.05$; $p = 0.003$; $\eta_p^2 = 0.08$), anxiety (STAI-Y; $F_{(1,94)} = 23.18$; $p < 0.00001$; $\eta_p^2 = 0.19$). No difference was highlighted between groups in term of impulsiveness (BIS-11 total score).

When comparing the subscales of DERS, significant differences were observed in the Nonaccept score ($F_{(1,94)} = 6.93$; $p = 0.01$; $\eta_p^2 = 0.06$), Impulse score ($F_{(1,94)} = 6.96$; $p = 0.01$; $\eta_p^2 = 0.06$), Aware score ($F_{(1,94)} = 6.55$; $p = 0.01$; $\eta_p^2 = 0.06$), Strategies score ($F_{(1,94)} = 16.28$; $p < 0.00001$; $\eta_p^2 = 0.14$), and Clarity score ($F_{(1,94)} = 7.31$; $p = 0.008$; $\eta_p^2 = 0.07$); no differences emerged in Goal score. Regarding to BIS subscales, significant differences were observed in the Attention score ($F_{(1,94)} = 7.7$; $p = 0.006$; $\eta_p^2 = 0.07$); no differences highlighted in motor and no planning. Regarding to TAS-20 subscales, we observed statistical difference in DIF subscales ($F_{(1,94)} = 16.47$; $p < 0.00001$; $\eta_p^2 = 0.15$); no differences emerged in DDF and EOT subscores. The full details of the comparison results are shown in **Table 2**.

We found a significant correlation between basal HIT-6 score and depression (BDI-2; rs = 0.58; $p < 0.0001$), impulsivity both Attention (BIS-11; rs = 0.43; $p \leq 0.002$) and total BIS-11 scores (rs = 0.33; $p = 0.02$), regulation of emotions (DERS nonaccept; rs = 0.4; $p = 0.006$; DERS goals; rs = 0.6; $p < 0.0001$; DERS strategies; rs = 0.53; $p < 0.0001$; DERS clarity rs = 0.45; $p = 0.001$; DERS total; rs = 0.58; $p < 0.0001$), trait anxiety (trait subtest of STAI-Y; rs = 0.6; $p < 0.0001$), and, finally, alexithymia (TAS-20 DIF; rs = 0.4; $p = 0.006$). Moreover, we found a significant correlation between headache frequency and regulation of emotions (DERS Aware; rs = 0.3; $p = 0.04$) and between number of medications and regulation of emotions (DERS Aware; rs = 0.3; $p = 0.03$). Finally, our analysis showed a significant correlation between basal total MIDAS Total score and depression (BDI-2; rs = 0.3; $p = 0.04$) and between MIDAS-B and trait anxiety (trait subtest of STAI-Y; rs = 0.28; $p = 0.04$). No correlation was found between psychopathological scores and disease duration.

DISCUSSION

Our study showed a significant difference in many psychopathological scales scores between MOH patients and HC subjects. Particularly, we demonstrated a high rate of depression, anxiety, and impulsiveness associated with a specific difficulty in recognizing and regulating emotions. Moreover, we found a positive correlation among psychopathological scales scores and both MIDAS and HIT-6 questionnaires, assessing the degree of migraine-related functional disability, showing that psychological comorbidities together with MOH negatively affect patients' activities of daily living. Finally, we found a positive correlation between the DERS Aware subscore and some clinical

TABLE 1 | Demographic and clinical characteristics of the study sample.

	MOH patients (n = 48)	Healthy controls (n = 48)	p
Sex	F:38–M:10	F:37–M:11	$p = 0.805$
Age in years (mean ± SD)	47.7 ± 12.1	46.8 ± 10.71	$p = 0.702$
Disease duration in years (mean ± SD)	26.1 ± 15.1	-	
Monthly days of headache (mean ± SD)	24.1 ± 6.4	-	
Monthly drugs intake Median (min-max)	40 (12–315)	-	
MIDAS-total (mean ± SD)	88.8 ± 71.3		
MIDAS-A (mean ± SD)	61.2 ± 28.3	-	
MIDAS-B (mean ± SD)	8.2 ± 1.3		
HIT-6 (mean ± SD)	67.4 ± 5.6	-	

Statistical comparisons refer to Chi-Square for the sex composition of the samples and Student's t-test for mean age.

TABLE 2 | Participants' scores across the outcome variables.

Psychological questionnaire	MOH patients *Mean ± SD*	Healthy controls *Mean ± SD*	p
DERS (total score)	91.64 ± 26.03	73.31 ± 18.34	$p < 0.001$
DERS (subscore nonaccept)	16.65 ± 7.09	13.1 ± 5.96	$p = 0.01$
DERS (subscore goals)	14.87 ± 4.91	12.95 ± 5.16	$p = 0.066$
DERS (subscore impulse)	13.22 ± 5.85	10.54 ± 3.94	$p = 0.01$
DERS (subscore aware)	15.62 ± 4.38	13.31 ± 4.46	$p = 0.01$
DERS (subscore strategies)	19.62 ± 8.06	14 ± 5.31	$p < 0.001$
DERS (subscore clarity)	11.66 ± 5.21	9.29 ± 3.13	$p = 0.008$
TAS-20 (total score)	53.9 ± 14.09	46.23 ± 10.7	$p = 0.003$
TAS-20 (subscore DIF)	20.87 ± 7.09	15.54 ± 5.7	$p < 0.001$
TAS-20 (subscore DDF)	13.81 ± 4.7	13.39 ± 4.31	$p = 0.65$
TAS-20 (subscore EOT)	19.23 ± 5.35	17.29 ± 5.05	$p = 0.072$
BIS-11 (total score)	61.85 ± 8.12	58.72 ± 10.08	$p = 0.098$
BIS-11 (subscore attention)	16.68 ± 2.52	14.93 ± 3.53	$p = 0.006$
BIS-11 (subscore no planning)	22.54 ± 4.17	23.62 ± 5.65	$p = 0.062$
BIS-11 (subscore motor)	19.62 ± 3.8	20.16 ± 4.27	$p = 0.514$
BDI-2	18.8 ± 11.4	9.9 ± 8.4	$p < 0.001$
Trait subset of STAI-Y	48.92 ± 12.11	36.79 ± 12.55	$p < 0.001$

Note: MOH, Medication Overuse Headache; DERS, Difficulties in Emotion Regulation Scale; NONACCEPT, non-acceptance of emotional responses; GOALS, difficulties engaging in goal-directed behavior; IMPULSE, impulse control difficulties; AWARE, lack of emotional awareness; STRATEGIES, limited access to emotion regulation strategies; CLARITY, lack of emotional clarity; TAS-20, Toronto Alexitimia Scale-20 item; DIF, Difficulty Identifying Feeling; DDF, difficulty describing feelings; EOT, externally oriented thinking; BIS, Barratt Impulsiveness Scale; BDI-2, Beck Depression Inventory 2; STAI-Y, State-Trait Anxiety Inventory.

variables, specifically headache frequency and the number of painkillers, but not with disease duration. This observation suggests that some of the psychological aspects evaluated are constitutional in patients with MOH and not the consequence of a long-standing pain condition. This relation between emotional dysregulation and pain intensity/analgesic consumption shows that the impairment in recognition/regulation of emotions producing an important dysfunctional behavior hugely impacts on disability from headache, regardless of the disease chronicity. To our knowledge, the present study is the first aiming to explore the emotions' regulation abilities in a population of MOH patients. Besides, this is the first attempt also to explore the relationship between emotion regulation abilities and depression and anxiety in a MOH patients' sample. Emotion regulation is the process of managing one's emotions, but at the same time regards the "when" and the "how" individuals experience or express the emotions (Ciarrochi et al., 2001). Such a process involves both negative and positive emotions and when it works successfully can guarantee good mental health, as recently shown (Eftekhari et al., 2009). Difficulties in recognizing and regulating emotions have emerged in other neurological diseases, i.e Huntington Disease (Zarotti et al., 2018) and Multiple Sclerosis (Migliore et al., 2019). In the last years, also great attention has been paid to the nighttime involvement of emotional experience during dreaming, that correlated with volumetric and ultrastructural brain measures (e.g., De Gennaro et al., 2011). These findings suggested that difficulties in emotional skills (recognizing and regulating) may represent a precursor of more general cognitive impairment that could negatively impact daily life activities. Different reviews and meta-analysis (Di Tella and Castelli, 2016; Koechlin et al., 2018; Aaron et al., 2019) highlight as a recent growing body of researches is interested to evaluate emotion regulation's role in different chronic pain (i.e., Complex Regional Pain Syndrome and Low Back Pain, Temporomandibular Disorders, Fibromyalgia, et cetera). These studies show significant emotion regulation difficulties in different types of chronic pain conditions. Emotion dysregulation may be an important risk factor in the development and maintenance of chronic pain and it is associated with many clinical (i.e., pain intensity) and psychological variables (anxiety and depression).

In MOH patients, it is possible to hypothesize that the chronic, almost daily, headache produces negative emotions. The MOH patient has difficulty coping with negative emotions (impairment

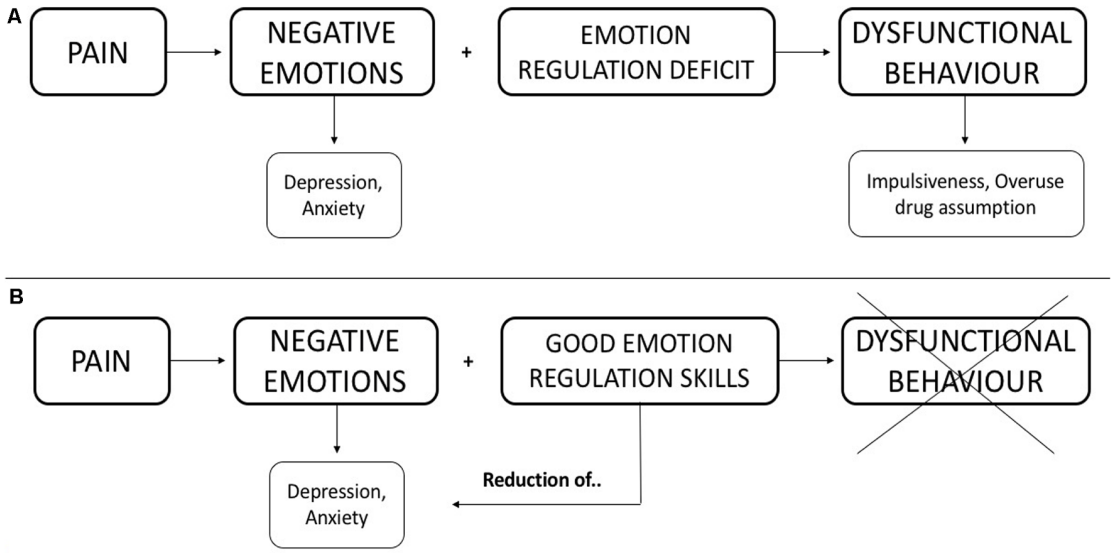

FIGURE 1 | Hypothesized interaction among the discussed constructs. **(A)** We hypothesize that negative emotions associate with deficits in emotional regulation produce dysfunctional behavior. **(B)** We illustrate how good emotion regulation skills can limit dysfunctional behavior and, consequently, reduce negative emotions.

in emotion regulation abilities) and this psychological feature can represent a specific condition that may generate dysfunctional behaviors (psychopathological symptoms). **Figure 1A** shows a schematization of the hypothesized interaction.

Furthermore, our study confirms the high rate of depression and anxiety symptoms in MOH patients, as highlighted by previous researches (Lampl et al., 2016; Sarchielli et al., 2016).

Several mechanisms have been proposed to explain the comorbidity of headache and psychopathological symptoms: (a) unidirectional or bidirectional causal models; (b) shared genetic factors; and (c) environmental risk factors. Overall, the lack of clear predictive relationships between psychopathological symptoms and headache raises the possibility either of a symmetrical causal link (i.e., each disorder would be a risk factor of the other), or of a common genetic or environmental risk factor (Radat and Swendsen, 2005). Indeed, the interactive effect between environmental risk factors and genetic factors could reasonably induce the development of both the considered diseases (Radat and Swendsen, 2005). On the contrary, the relationship between depression and migraine would appear to be bidirectional, i.e., each condition would increase the incidence of the other (Breslau et al., 2003).

We hypothesize that the altered ability, both to recognize and regulate emotions may play a central role in the behavior of patients with MOH. These altered behavioral abilities can contribute to the chronicization of head pain and to overuse of symptomatic drugs (as illustrated in **Figure 1A**), which is hardly treated only with a pharmacological approach.

The capability of recognizing emotions can allay a lot of negative emotions (moods) originating from headaches. In light of this, the evaluation of the psychopathological profile should be included in the general assessment of MOH patients. In this way, clinicians could plan an integrated treatment (both behavioral and pharmacological) to significantly improve MOH handling. Focusing early on the impairment of regulating emotions could have also a positive effect on anxiety-depressive symptoms and reduce dysfunctional behaviors (i.e., impulsiveness, overuse of drug assumption). We illustrated this hypothesis in **Figure 1B**.

Treating MOH patients, trying to reverse their compelling necessity to consume drugs, is a hard challenge for the headache specialist. Detoxification from MOH is a shared but not worldwide standardized practice used by headache units. Nevertheless, wash-out seems a useful protocol for treating medication overuse but only in the short term (Paolucci et al., 2017). There is a need for treating MOH comprehensively, including both a standardized pharmacological protocol and a psychological adequate approach. The battery of scales and questionnaires we used was useful in selecting patients with the highest degree of disability who might benefit from additional treatment approaches designed based on their individual profile of psychopathology.

The reason why some patients overuse acute treatments presenting MOH while others do not is not clearly understood. MOH might be related to some psychological states, such as fear and anticipatory anxiety of attacks, also defined as cephalalgophobia, The experience of recurrent severe pain may produce anticipatory anxiety for the forthcoming headaches and their consequence in terms of loss of daily activities which can be as dreadful as pain (Black et al., 2015). An alternative explanation relies on behavioral disorders, i.e., reward mechanism or compulsive disorder (Cupini et al., 2009). A drug-seeking behavior and the subsequent compulsive use of medications strongly complicate the drug withdrawal, which is the first step for treating MOH. So far, a direct link between

compulsive behavior and medication overuse has not been established. Understanding the underlying mechanisms of those behaviors might improve the management of MOH.

The main limitation of our work is the lack of comparison with headaches or other pain conditions other than MOH. Future research is needed to consider patients with other headaches (i.e., migraine headache, tension headache, or cluster headache) and without MOH for evaluating the potential difference in the psychopathological profile and assess whether emotional dysregulation can be transversal to different forms of headache or specific to MOH. Moreover, since the sample size in the present analysis is rather small, prospective confirmation is needed in larger cohorts. Finally, it is necessary to investigate whether specific behavioral treatment (i.e., cognitive-behavior psychotherapy, biofeedback, and so on) can be effective in reducing psychopathological symptoms, improve quality of life, and improving the management of MOH patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was designed following the ethical principles of the Declaration of Helsinki and all participants were asked to sign an informed consent. The study was approved by Campus Bio-Medico University Ethics Committee, approval number 44-18, and registered at AIFA (Italian Drug Agency) with number Eudract 2017-004606-18.

AUTHOR CONTRIBUTIONS

SiM was involved in the study design, clinical assessment, data collection, analysis, interpretation, and wrote the manuscript. MP was involved in the study design, clinical assessment, data collection, analysis, provided critical review and approval of the manuscript. LQ was involved in the analysis and interpretation of behavioral changes, provided critical review and approval of the manuscript. CA was involved in the study design, data collection, provided critical review and approval of the manuscript. SaM was involved in the interpretation of behavioral changes, provided critical review and approval of the manuscript. GD'A was involved in the study design, data analysis, provided critical review and approval of the manuscript. GC was involved in the study design, data analysis and interpretation, provided critical review and approval of the manuscript. FV was involved in the study design, data collection, data analysis and interpretation, provided critical review and approval of the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Correlation Between Migraine and Patent Foramen Ovale

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Background: Migraine is a widespread neurological disorder. The patent foramen ovale (PFO) is a remnant of the fetal circulation. Multiple studies suggest that migraine is more prevalent in subjects with PFO and vice versa. It is unclear if there is a causal relationship or simply a co-existence of these two conditions. Furthermore, the treatment of migraine with percutaneous closure PFO remains controversial.

Methods: We reviewed studies pertaining to the relationship between PFO and migraine as well as the effects of treatments on migraine attacks.

Results: We briefly summarized potential pathophysiological mechanisms of migraine, and elaborated on migraine type, frequency, and clinical symptoms of migraine with PFO and the clinical features of PFO with migraine. We also addressed the effects of PFO closure on migraine attacks.

Conclusion: The evidence supports a "dose-response" relationship between migraine and PFO although more work needs to be done in terms of patient selection as well as the inclusion of an antiplatelet control group for PFO closure interventions to uncover possible beneficial results in clinical trials.

Keywords: migraine, patent foramen ovale, prevalence, patent foramen ovale closure, systematic review

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INTRODUCTION

Migraine, one of the most common conditions of primary headache, often occurs in people aged 20-64 years old, with a high disability rate and heavy disease burden (1). According to the 2013 Global Burden of Disease survey from the World Health Organization (WHO), migraine was the 3rd most common disease and ranked 6th in causing major disability in humans, which was calculated based on the number of years of life lost to disability (2).

The foramen ovale is a channel between the left and right atria of the heart during the embryonic period. Under normal physiological conditions, the foramen ovale will close in the first year after birth. If, however, it is not closed after three years of age, it is termed as patent foramen ovale (PFO) (3). It has been reported that PFO is the most common congenital cardiac anomaly in adults (4). In fact, about 20-30% of adults have an incomplete fusion of the fossa, which is a permanent slit-like interatrial opening (5). Usually, the blood pressure of the left atrium is higher than that of the right atrium, which will not cause right-to-left shunt (RLS). RLS via the PFO may occur when the pressure in the right atrium exceeds the left to give rise to structural changes in the

heart, pulmonary hypertension, coughing, sneezing, and laughing. Although atrial septal defects and pulmonary arteriovenous malformations may also cause the right-to-left blood flow, they are relatively rare in migraine patients (6).

Del (7) first proposed the relationship between migraine and PFO in 1998, he found that the incidence of PFO in migraine patients was significantly higher than that in healthy controls. Later, a number of studies found that the incidence of PFO in migraine patients was 14.6-66.5% (8) while the incidence in the general population was 9-27.3% (5, 9, 10). In turn, in the population with PFO, the incidence of migraine was 9.13-51.7%, which was also higher than the incidence of migraine in the general population (11–13). However, until now, no consensus has been reached on the relationship between PFO and migraines. Therefore, this review aims to further investigate the association between migraine and PFO.

Pathophysiological Mechanisms

The idea that migraine and PFO is correlated has only been around for a few decades, and much of the underlying pathophysiology is still based on hypotheses. It is thought that many vasoactive substances are usually discharged or metabolized through the pulmonary circulation. Through the PFO channel, venous blood can enter arterial blood by shunting without circulating in the lungs. Some chemicals and hormones such as serotonin can bypass the pulmonary circulation and pass directly through the blood-brain barrier to cause migraine (5). Moreover, a tiny embolus in the systemic circulation can pass through the PFO and directly into the arterial system. These "paradoxical embolisms," which lead to tiny brain infarctions, triggering low perfusion or cortical spreading depression, may cause a migraine attack (5), and could be the most probable pathophysiological mechanism on how PFO could lead to a migraine attack. This hypothesis can also explain the use of antiplatelets or anticoagulants (14–16) and atrial fibrillation ablation (17) for relieving migraine attacks. Others have also found that a RLS is correlated with a higher frequency of multiple cortical lesions in DWI sequences, which distinguishes itself from atrial fibrillation-related ischemic stroke that is seen occurring in the cortical-subcortical territory (18). Incidentally, the posterior circulation is more likely to be involved (19). Blood flow of the posterior circulation significantly exceeds that of the anterior circulation in migraine patients with PFO when undergoing the Valsalva maneuver (20). During the aura phase, focal areas of hypoperfusion close to the ischemic threshold in occipital regions, which might be due to these cerebral microinfarcts, can cause visual symptoms (21). Meanwhile, a RLS results in decreased blood oxygen saturation and hypoxia, which increases the expression of plasminogen activator-1 and result in inhibition of fibrinolysis and thus increases the possibility of microembolization. On the other hand, a decrease in cerebral oxygen saturation will trigger cortical spreading depression as well, which can also lead to migraines (22, 23). Genetic factors may also cause these patients to develop both diseases. About 2-fold higher frequency of PFO is seen in migraineurs as compared with the general population, suggesting that a genetic influence could predispose some patients to a higher risk of developing both migraine and atrial septal abnormalities (4); hereditary associations with migraine have been found in autosomal dominant PFO (24). Taken together, the pathophysiological mechanisms are complex and migraine is possibly the result of these pathways working synergistically.

Methods for Diagnosing PFO

Clinical examination methods are commonly used for diagnosing PFO including transesophageal echocardiography (TEE), contrast transcranial doppler echocardiography (cTCD) and contrast transthoracic echocardiography (cTTE). Among these, TEE is considered the gold standard for PFO diagnosis (7). However, due to the invasive nature of the procedure, patients find it difficult to successfully complete the Valsalva maneuver during TEE examination. Thus, the detection rate of RLS is lower than that of cTTE (8, 9), and have been shown to normally have a 10% rate of false negatives (10). cTCD is used to predict RLS by observing the amount of air microemboli in the cranial circulation at the resting state and after Valsalva maneuver. Although cTCD is a non-traumatic procedure, about 5% of shunts detected by cTCD does not correspond with PFO (11). The sensitivity and specificity of cTCD for RLS are 68-100% and 65-100%, respectively (12). Likewise, cTTE is also noninvasive but can isolate the source of RLS with a specificity of 97-100% albeit with a slightly lower sensitivity of about 63-100% (13, 14). At present, the varying diagnostic methods contributes to the diversity in the relationship between PFO and migraine. Therefore, a comparison of these individual methods and how it affects the relationship in question may be helpful.

THE RELATIONSHIP BETWEEN MIGRAINE AND PATENT FORAMEN OVALE

The Relationship Between Migraine Type and Patent Foramen Ovale

The incidence of migraine with aura is 4.4%, comprising about 25-30% of migraineurs (25). Studies have found a stronger association between migraine with aura and PFO (26, 27). Among migraine patients, the incidence of PFO is 46.3-88% in migraine patients with aura (22, 23, 28, 29) compared with 16.2-34.9% in migraine patients without aura (30, 31). Interestingly, the incidence of PFO in migraine patients without aura is similar to that in the general population (6, 7, 9, 31). As PFO may be associated with migraine with aura, one study investigated the incidence of PFO in migraine patients with typical or atypical aura. The authors found that the PFO prevalence in the atypical aura group was 79.2% *vs.* 46.3% in the typical aura group (28). Therefore, it was suggested that PFO was more closely related to patients with atypical aura migraine but the specific mechanism remains unclear. Another report investigated the incidence of PFO in non-migraine patients with visual aura; 67% of the patients had PFO and 80% of those patients had improvement in symptoms after PFO closure, indicating that the presence of PFO could be one of the underlying mechanisms associated with aura pathology (32). Therefore, we consider the PFO having a closer relationship in migraine patients with aura, especially atypical

aura, although non-migraine with aura is also correlated with the presence of the PFO.

The Relationship Between Migraine Attack Frequency and Patent Foramen Ovale

Chronic migraine occur in about 2-3% of the population (33, 34). For one to be diagnosed with chronic migraine, the ICHD-3 criteria states that the patient would have "headache occurring on ≥15 days per month for >3 months, which has the features of migraine headache on ≥8 days per month" (35). Studies have shown that the incidence of PFO in chronic migraine, with aura or without aura, is higher. Of the 131 chronic migraine patients enrolled in a study, 66% had PFO, higher than PFO incidence in both the general population and episodic migraine patients (36). Another retrospective study focused on the relationship between visual aura frequency and PFO. A hundred and forty two migraine patients were divided into (i) frequent aura group (number of visual aura >50% of frequency of headaches) and (ii) accidental aura group (number of visual aura <50% of frequency of headaches). The results showed that migraine patients with frequent visual aura suffered a higher degree of RLS, and the symptoms improved after PFO closure (37). The high prevalence of PFO in chronic migraine patients do not indicate that PFO tend to stimulate chronic headaches, but still is associated with the number of migraine attacks, especially for large, high grade shunts.

The Relationship Between Clinical Symptoms of Migraine and Patent Foramen Ovale

The clinical presentation of migraine seems indistinguishable in migraine patients with or without PFO. There is little statistically significant evidence in the patient's personal history, including age, sex, smoking history or migraine onset, including the symptoms of headache, and concomitant symptoms of PFO. The SAM (Shunt-Associated Migraine) study was a prospective, multicenter, observational study, intended to illustrate the difference of the clinical features of migraine with or without blood flow shunt. A total of 460 patients were included in the study. Migraine patients with RLS and without RLS accounted for 58% and 42% of the total patients, respectively. Migraine features were not significantly correlated, except that patients with RLS were relatively young and had aura sensory symptoms with slightly higher frequency (38). In chronic migraine patients, PFO and non-PFO patients have similar headache characteristics and neurological symptoms (36). PFO seems to play a role in triggering migraines but have little relation to migraine symptoms. Recently, it was found that the attack frequency, HIT-6, and MIDAS scores among migraine patients with moderate or large PFO were significantly higher than those of the mild PFO and non-PFO groups. After PFO closure, the differences in VAS, HIT-6 and MIDAS scores as well as the headache duration were statistically significant (39). At this point in time, it cannot be concluded that the scale scores changed due to the attack frequency or severity, but the result does provide more evidence supporting the relationship between PFO presence and migraine presentation. Studies are now needed to explore the correlation and the analysis of the scale needs to be refined.

THE RELATIONSHIP BETWEEN PATENT FORAMEN OVALE AND MIGRAINE

The Relationship Between the State of Patent Foramen Ovale and Migraine

Under resting conditions, no RLS exists generally because the blood pressure in the left atrium is higher than in the right. After performing the Valsalva maneuver, the pressure of the right atrium will exceed that of the left atrium to give rise to transient RLS. During PFO examination, the RLS should be detected at rest and post-Valsalva. RLS occurring under normal respiration is called permanent PFO while RLS occurring only after the Valsalva maneuver is called latent PFO (23).

Persistent shunt accounts for 67-72% and latent shunt exist 28-33% in migraine with PFO patients (22, 23, 29). One study showed that 12 of the 159 migraine patients with aura experienced a migraine attack when they were undergoing the cTCD test. Surprisingly, all these patients had permanent PFO and the majority were massive shunts (22), indicating that permanent PFO is closely associated with migraines and triggers a migraine attack.

The Relationship Between the Size of Patent Foramen Ovale and Migraine

PFO is usually divided into three types: large PFO (≥4.0 mm), medium PFO (2.0-3.9 mm) and small PFO (≤1.9 mm) (40). However, this classification standard is only accurately measured by autopsy or estimated by TEE, which is not commonly used in clinical practice. RLS from PFO is considered when microvesicles are found within 3-5 cardiac cycles during a cTTE examination (41, 42). PFO size is usually graded according to the number of microbubbles in the left atrium on a single still image. cTCD is graded according to the number of microvesicles found in the bilateral cerebral circulation. The amount of RLS detected by cTCD is positively correlated with the size of PFO measured by TEE (43).

Approximately 75% of migraine patients with PFO have a large RLS and 25% have a small shunt (23). Among all PFO subjects, the proportion of large triage is higher in migraine patients than in healthy subjects. In migraine patients with aura especially, a greater proportion of permanent PFO and large PFO were found (44). Schwartzman (6) studied 93 migraine patients with aura and 93 healthy controls. All subjects underwent cTTE and they found that the number of people having small RLS among migraineurs and healthy controls were similar but a moderate or large RLS occurred more frequently in the migraine group. Similarly, among patients with cryptogenic stroke, Anzola (45) found that migraine patients had a larger shunt *vs.* non-migraine patients. The difference was even more pronounced when compared with the control group. PFO is also considered a probable risk factor in cryptogenic stroke of which micro-embolism may contribute to its pathogenesis. PFO is frequently found in older patients with stroke (46) as well as several other

TABLE 1 | The Effect of Patent Foramen Ovale Closure on Migraine in case series studies.

References	Type	Sample size	Age	Diagnostic mode	Residual shunt	Resolved	Improved	No change	Worsened	Follow-up (months)	Antiplatelet therapy time (months)	Adverse events
Wilmshurst et al. (65)	Retrospective	21	38.2	cTTE	0	10 (48%)	8 (38%)	3 (14%)	0	9-32	6	
Morandi et al. (66)	Prospective	17	48 ± 15	cTCD	4 (24%)	5 (29%)	10 (59%)	2 (12%)	0	6	6	AF in 2 subjects
Schwerzmann et al. (67)	Retrospective	MA 37	49 ± 11	TEE	3 (8%)	4 (11%)	26 (70%)	7 (19%)	0	20.4 ± 10.8	6	
		MO 11	42 ± 12			1 (9%)	9 (82%)	1 (9%)	0			
Reisman et al. (71)	Retrospective	MA 39	47 ± 12	cTCD and/or TEE	14 (72%)	21 (54%)	5 (14%)	12 (32%)	0	9.25 ± 5.75	6	
		MO 18				7 (62%)	2 (15%)	3 (23%)	0			
Azarbal et al. (68)	Retrospective	MA 24	49 ± 13	TEE	12 (18%)	18 (75%)	1 (4%)	-	-	12	-	
		MO 13				4 (31%)	5 (38%)	-	-			
Ferrarini et al. (69)	Retrospective	5	40.2 ± 11.3	cTCD, TEE	1 (20%)	4 (80%)	1 (20%)	0	0	6	-	
Mortelmans et al. (70)	Retrospective	MA 8	47 ± 13	-	-	4 (50%)	-	-	-	29	-	10 patients who did not have migraine before developed migraine
		MO 14	35 ± 14			6 (43%)	-	-	-			
Giardini et al. (72)	Prospective	MA 13	43 ± 13	TEE	6 (16%)	11 (84%)	1 (8%)	0	1 (8%)	58.5 ± 16.8	12	
Giardini et al. (73)	Retrospective	MA 35	41.1 ± 11.0	TEE	6 (17%)	29 (83%)	3 (8%)	2 (6%)	1 (3%)	20.8 ± 16.3	12	
Dubiel et al. (74)	Retrospective	MA 24	44 ± 13.5	TEE	1 (2.2%)	8 (33%)	14 (58%)	2 (8.3%)	0	39.6 ± 23.9	6	
		MO 22				3 (14%)	15 (68%)	4 (18.2%)	0			
Jesurum et al. (75)	Retrospective	MA 55	47 ± 12	cTCD and/or TTE	23 (34%)	36 (54%)	17 (25%)	11 (16%)	3 (5%)	18	6	
		MO 22	46 ± 10									
Luermans et al. (76)	Prospective	MA 10	51.6 ± 12.3	TEE	-	8 (80%)	-	-	-	6	6	1 TIA/1 ischemic stroke/1 inguinal hematoma/1 did not unfold
		MO 14				7 (50%)	-	-	-			
Chessa et al. (77)	Prospective	MA 28	40.2 ± 11.2	TEE	10 (23.8%)	7 (25%)	14 (50%)	-	-	6	6	
		MO 14	21 ± 11.2			4 (29%)	8 (57%)	-	-			
Wahl et al. (79)	Retrospective	MA 14	44 ± 12	TEE	1 (6%)	4 (29%)	4 (29%)	6 (43%)	0	32.4 ± 18	5	
		MO 3				0	2 (67%)	1 (33%)	0			
Papa et al. (79)	Prospective	76	43.2	TEE	2 (2.6%)	35 (46%)	27 (36%)	14 (18%)	0	13.7 ± 2.4	6	5 inguinal hematomas/1 AF
Wahl et al. (81)	Retrospective	MA 96	51 ± 11	TEE	14 (9%)	37 (39%)	44 (46%)	8 (8%)	7 (7%)	60.0 ± 22.8	-	1 TIA and 1 ischemic stroke
		MO 54	53 ± 11			14 (26%)	23 (42%)	15 (28%)	2 (4%)			
Rigatelli et al., (80)	Prospective	MA 34	40 ± 3.7	TEE, cTCD	2 (6%)	19 (56%)	6 (18%)	2 (6%)	-	9.0 ± 2.8 m	-	AF in 3 subjects

(Continued)

TABLE 1 | Continued

References	Type	Sample size	Age	Diagnostic mode	Residual shunt	Resolved	Improved	No change	Worsened	Follow-up (months)	Antiplatelet therapy time (months)	Adverse events
Trabattoni et al. (82)	Prospective	77	42.6 ± 12	TEE, cTCD and cTTE	-	26 (34%)	46 (60%)	5 (6%)	0	28 ± 27	-	Transient AF 15/vascular complications 2/Device malpositioning 1
Rigatelli et al. (83)	Prospective	80	42 ± 2.7	TEE, cTCD	7 (8.7%)	41 (51%)	21 (26%)	18 (23%)	0	50.1 ± 16.8	-	AF 3
Araszkiewicz et al. (84)	Prospective	MA 4	38 ± 18	TEE, cTTE	-	2 (50%)	-	-	-	28.6 ± 12.1	6	Supraventricular arrhythmias 3, groin hematoma 3, neurological events 5
		MO 17				8 (47%)	-	-	-			
Milev et al. (85)	-	22	40.7 ± 11.7 years	cTCD, TEE	15 (42.9%)	4 (18%)	18 (82%)	0	0	24	6	One femoral hematoma and hypotension; one chest pain

MA, migraine with aura; MO, migraine without aura; AF, atrial fibrillation; TIA, transient ischemic attack; "-": not mention.

stroke subtypes (47, 48), and the stroke attributable fraction for PFO can be defined through standardized scores (48, 49). Taken together, PFO may be associated with migraine and could increase the risk of stroke in migraine patients. The larger the PFO size indicates a larger RLS, which is more likely to cause a migraine.

The Relationship Between Patent Foramen Ovale Anatomical Structures and Migraine

Atrial septal aneurysm (ASA) is a kind of congenital atrial septal dilatation, which means that the atrial septal distention is >10 mm in one side of the atrial septal plane, and the basal width of the tumor is >15 mm, involving the fossa ovalis region (3). According to echocardiography studies and post-mortem epidemiological studies, the prevalence of ASA of the general population is about 1-2.5% (9, 50). PFO complicated with atrial septal tumor have been shown to be a risk factor for both cryptogenic (51, 52) and recurrent cryptogenic strokes, suggesting that medical treatment could be refined (53–55). Recent studies also showed that migraine has a high correlation with PFO and ASA (44, 56). In Snijder's study (44), the prevalence of PFO with ASA was significantly higher in migraine patients compared to patients without migraine. In addition, the shunt of patients with PFO combined with ASA was significantly larger than that of patients with PFO alone. Therefore, the combination of PFO and ASA may lead to increasing shunt flow and the occurrence of migraine.

The Eustachian valve (EV) and Chiari network (CN) are remnants of venous valves caused by incomplete absorption of these structures (52, 57). Embryologically, EV is a semicircular structure facing the anterior-inferior aspect of the inferior vena cava, directing blood flow from the inferior vena cava to the fossa ovale, which plays a vital role in the shunt of blood flow to the ovale (58, 59). The CN is a large multi-perforated EV with a reticular appearance found in approximately 2% of the population (60). Previous studies had reported that EV and CN were more common in patients with cryptogenic stroke (61, 62). Rigatelli (63) prospectively investigated the potential effects of EV/CN on migraine patients with PFO and found that the frequency of EV/CN was 100% and 60% in migraineurs with aura and migraineurs without aura, respectively. Meanwhile, patients with EV/CN had more "curtain pattern," larger RLS on TCD and higher preoperative MIDAS score. After PFO closure, the MIDAS score decreased significantly. Formation of an atrial septal aneurysm and persistent EV/CN may prevent spontaneous closure of PFO afterbirth, facilitating RLS, and indirectly inducing a migraine attack.

Treatment of Migraine With Foramen Ovale Closure

Migraine and PFO may be in a "dose-response" relationship. For example, the large size, persistency of PFO, and anatomic variations of PFO can intensify RLS, by which increased vasoactive substances or tiny emboli can pass through the blood-brain barrier and cause a higher number of hypoperfusion events to result in a migraine. These provide further evidence for

TABLE 2 | The Effect of Patent Foramen Ovale Closure on Migraine in case-control studies.

References	Type		Sample size	Age	Diagnostic mode	Occluder devices	Residual shunt	Resolved	Improved	No change	Worsened	Follow-up	Antiplatelet therapy time (months)	Adverse events
Kimmelstiel et al. (86)	R	Closure	24	63	TEE	Amplatzer	3 (13%)		20 (83%)	2 (8%)	2 (8%)	3	-	
		Open	26	62					0	25 (96%)	1 (4%)			
		Control	10	54					1 (10%)	9 (90%)	0			
Vigna et al. (87)	P	Closure	53		cTCD, TEE	Amplatzer/Cardia/ CardioSEAL/STARFlex	3 (6%)	18 (34%)	28 (53%)	7 (13%)	0	16 ± 7	6	-
		Control	29					2 (7%)	5 (17%)	19 (66%)	3 (10%)			
Rigatelli et al. (88)	P	Closure	MA 32	35 ± 6.7	cTCD, TEE	Amplatzer/Premere	2 (5%)	15 (47%)	12 (38%)	5 (16%)	0	29.2 ± 14.8	-	AF 2
			MO 8					2 (25%)	4 (50%)	2 (25%)	0			
		Control	MA 10					0	0	10 (100%)	0			
			MO 36					0	0	36 (100%)	0			
Khessali et al. (32)	-	Closure	MA72	48 ± 13	cTCD, TEE	CardioSEAL/Amplatzer/ Helex	-	39 (54%)	16 (22%)	1 (1%)	3 (4%)	12	-	-
			MO 8					6 (75%)	0	1 (13%)	0			
		Control	36	54 ± 17				-	-	-	-			
Biasco et al. (89)	R	Closure	MA 67	46.4 ± 12.7	TEE, cTCD	Amplatzer/Cardia/ Others	16 (24%)	36 (54%)	18 (27%)	10 (15%)	3 (5%)	46.6 ± 32.7	6	One endocarditis
			MO 22					10 (45%)	10 (45%)	0	2 (9%)			
		Medical	MA 82	47.1 ± 12.3				20 (24%)	19 (23%)	35 (43%)	8 (10%)			
			MO 46					11 (24%)	16 (35%)	14 (30%)	5 (11%)			
Xing et al. (90)	-	Closure	125	39.0 ± 12.9	cTCD, cTTE	Cardi-O-Fix	6 (5%)	67 (53.6%)	92 (76.3%)	31 (24.8%)	2 (1.6%)	12	6	One cardiac tamponade

MA, migraine with aura; MO, migraine without aura; AF, atrial fibrillation; "-": not mention; "r": retrospective; "p":prospective.

TABLE 3 | The Effect of Patent Foramen Ovale Closure on Migraine in randomized controlled studies.

	Subjects	Mean age	Diagnostic mode	Randomization	Follow-up		Result				Antiplatelet therapy
						Primary endpoint	Secondary endpoints			Exploratory analysis	
MIST trial	MA with frequent attacks, failed ≥2 prophylactic treatments, moderate or large RLS with PFO		cTTE, TEE		180 days	Cessation of migraine headache	Frequency of attack reduction (days/month)	Total MIDAS score	Total HIT-6 score	Reduction in total migraine headache days (excluding 2 outliers)	Aspirin and clopidogrel were given 300 mg in the 24 h before the procedure and 75 mg each daily for 90 days after the procedure
Intervention group	74	44.3 ± 10.6		STARFlex septal repair implant		3	3.26 ± 1.82	16 (0–270)	60 ± 10		
Control group	73	44.6 ± 10.4		Sham procedure (skin incision in the groin)		3	3.55 ± 2.14	18 (0–240)	59 ± 8.8		
P						1	0.13	0.89	0.79	0.027	
										Post-hoc analyses	
PRIMA	Unresponsive to 2 preventive medications MA with PFO		cTTE or cTEE and TEE		1 year	Reduction migraine (days/month)	The average attacks reduction	≥50% reduction of migraine days	MIDAS score improvement	Mean reduction in MA (days/month)	Aspirin 75–100 mg/day for 6 months, clopidogrel 75 mg/day for 3 months
Intervention group	53	44.1 ± 10.7		Amplatzer PFO Occluder		−2.9	−2.1	15 (38%)	−18.3	−2.4	
Control group	54	42.7 ± 11.0		Medical management		−1.7	−1.3	6 (15%)	−13.9	−0.6	
P						0.17	0.97	0.0189	0.53	0.0141	
PREMIUM	Failed ≥3 preventive medications, 6–14 days/month migraine with RLS		cTCD, cTTE		1 year	50% reduction in attacks	Number of migraine (days/month)	≥75% reduction in migraine attacks	Complete cessation of migraine attacks		Pre-treated with aspirin 325 mg and clopidogrel 600 mg
Intervention group	117	42 ± 10		Amplatzer PFO Occluder		45 (38.5%)	−3.4 ± 4.4	24 (20.5%)	10 (8.5)%		
Control group	103	41 ± 10		sham procedure		33 (32%)	−2.0 ± 5.0	17 (16.5%)	1 (1%)		
P						0.32	0.025	0.45	0.01		

MA, migraine with aura.

migraine treatment, not only more accurate treatment choices for different patients, but also help guide surgical treatment.

In 1992, percutaneous PFO closure was first performed (64), and the benefits of PFO closure in migraine patients were first reported in 2000 (65). Since then, there have been a series of studies about the effect of PFO closure in migraine. Among the case series studies, PFO closing resolved headaches in 14-85% of patients, among which 25-85% had migraine with aura and 14-50% were migraine without aura. 4-58% of patients had ameliorated migraine with aura and 20-68% migraine without aura. 6-43% of patients had no change in symptoms while 3-8% had worse symptoms (65–85) (see **Table 1**). In the case control studies, PFO closure is also associated with decreased migraine severity (32, 86–90) (see **Table 2**). In a study, PFO closure had statistically significant benefit with VAS, HIT-6 and MIDAS scores and the headache duration (39), especially for patients younger than 45 years (91). In addition, the closure of PFO resulted in a significant reduction in the use of abortive medications (86).

However, in randomized controlled studies, the results were unremarkable (see **Table 3**). Migraine Intervention With STARFlex Technology (MIST) is the first prospective, multicenter, double-blind, controlled study to evaluate the efficacy of PFO with STARFlex implants for refractory migraine. After follow-up at 6 months, there were no significant differences (implant *vs.* control group) in the main therapeutic endpoints and headache cessation at 91-180 days after the closure. The same results were seen at the secondary endpoint. Upon further exploratory analysis, after excluding two outliers, the implant group saw a significant reduction in number of migraine days. With respect to the results of MIST and observational studies, it was explained that, first of all, there were physiological differences between the study group and the group of patients treated in the observational study. In addition, the RLS might not be effectively closed by the device used, which resulted in differences in experimental results (92). Subsequently, the PRIMA (Percutaneous closure of patent foramen ovale in migraine with aura) study also aimed to evaluate the efficacy of percutaneous PFO closure in patients of migraine with aura who were refractory to medical treatment. The primary and secondary efficacy endpoints, the decrease number of migraine attacked in 3 months after treatment and the average decrease number of migraine attacked separately, including the total cessation of headache, all improved in the treatment group, though with no statistical significance (93). Recently, PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) studied patients with 6-14 days of migraine per month who had a large RLS and failed at least three preventive medications. For the primary efficacy end event endpoint, a 50% reduction in the number of headache episodes in the procedure group was seen though again, was not statistically significant. The secondary efficacy endpoint which was to reduce the number of headache days saw statistically significant differences in both groups. In the subgroup analysis, the proportion of frequent migraineurs with aura (more than 50% of migraine attacks with aura) reaching the primary efficacy end event was significantly higher than that of the control group, even 15.4% patients had headache cessation (94). These RCT results, although mostly insignificant, can still inform future clinical trials in terms of (i) patient selection e.g., patients with migraine with more frequent aura attacks and patients PFO with large RLS can be top priorities since these are affected by the "dose-response" relationship of migraine and PFO; and (ii) additional subgroup analyses e.g., excluding outliers. In fact, present ethical considerations stipulate that clinical studies can only recruit those with severe refractory migraine and not non-refractory migraine, which is an issue that needs to be addressed since a study design involving non-refractory migraine patients would be beneficial on many levels.

Considering the abnormal coagulation mechanism, the formation of "micro-embolisms" may also be one of the important causes of migraine. Some studies had reported the effects of antiplatelet agents on PFO associated with migraine (95, 96). A study of 136 patients with migraine and PFO who had a stroke previously, found that 90 patients (66%) had $\geq$50% decreased headache days per month compared to baseline after administration of clopidogrel or prasugrel. Fifty-five patients received PFO closure and discontinued antiplatelet medication 3 months after PFO surgery. Out of these, 52 patients (94%) had relief of headaches up until the follow-up of 6 years. Twenty-six patients without PFO closure who had been taking antiplatelet drugs also responded favorably up till 4 years of follow-up. However, 8 patients who did not take antiplatelet drugs or receive PFO closure, later experienced headache after 4-5 days, which was the anticipated washout period for the antiplatelet drugs. Antiplatelet medicine and PFO closure had a similar effect in migraine patients, so it was speculated that migraine pathogenesis involves venous platelet activation or aggregation, wherein tiny emboli causes the migraine (97). Subsequently, a prospective study found that the use of Tigarelor also reduced the frequency of migraine attacks in some PFO patients (98). Therefore, postoperative antiplatelet drug should be considered an important confounding factor in assessing the efficacy of PFO closure, and future research should consider setting the antiplatelet medication group as the control group for PFO closure. Of note, many studies of follow-up periods of less than 6 months possibly had their results confounded by the administration of antiplatelet drugs which they did not take into account during analyses.

SUMMARY

In this review, we attempted to specifically address the relationship between migraine and PFO, elucidate mechanisms and improve estimation of the risks and benefits of the different therapeutic strategies available. The incidence of PFO in migraine patients is higher than that in the general population, suggesting that PFO and migraine may be risk factors for each other, but more research is needed to confirm this speculation. An increasing number of studies have found that migraines with aura are more closely associated with PFO, and the presence

of RLS increased the likelihood of aura attacks, reducing the susceptibility to migraine attacks after exposure to other triggers. The frequency of headache onset, but not its clinical features, is also correlated with PFO, which seem to suggest that RLS may trigger the onset of migraine without directly affecting the migraine symptoms. In addition, the type and size of the foramen ovale are also associated with migraine. Persistent PFO, larger PFO, and complex tissue structures may cause more RLS of the blood to increase the incidence of migraine. Taken together, these support the "dose-response" relationship between RLS and migraine.

Based on the current findings, PFO occlusion was not satisfactory for the improvement of headaches in migraine patients. More accurate adequate patient recruitment may lead to greater postoperative benefit and more significant symptom improvement. Observational studies may further elaborate on the relationship between migraine and PFO type. Furthermore, randomized controlled studies should not be limited to patients with medication refractory migraineurs. Moving forward, investigation is needed to identify those migraineurs who are more likely to benefit or invalid from the closure of PFO, and in our opinion, migraines with more frequent aura attacks and PFO with larger RLS shunt should be research priorities. In addition, antiplatelet agents must be a control group for clinical trials of PFO closure. Lastly, researchers should consider that the closure of PFO may carry a small but relevant risk of serious adverse events including stroke, pericardial tamponade, atrial fibrillation and death (99).

AUTHOR CONTRIBUTIONS

KL conceived the idea for and edited the manuscript. BZW substantially revised the manuscript for readability and intellectual content. YH contributed to table design and manuscript revision. SS contributed expert medical advice and to manuscript revision. MP reviewed the literature and drafted and edited the manuscript. All authors read and approved the final submitted version.

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SYSTEMATIC REVIEW
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The Migraine-Anxiety Comorbidity Among Migraineurs: A Systematic Review

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Background: Migraine is recognized as a neurological condition that is often associated with comorbid psychiatric symptoms such as anxiety, depression, bipolar disorder and/or panic disorder. Though some studies have demonstrated the link between migraine and anxiety disorders, there are no systematic reviews that have been published in this area to summarize the evidence. The aim of the present study is to systematically review the literature associated with comorbidity of migraine and anxiety disorders among migraineurs compared to non-migraineurs.

Methods: The present systematic review included population-based, cohort and cross-sectional studies if they were reporting the frequency of migraine with either anxiety or depression as diagnosed by a medical practitioner according to the International Classification of Headache Disorders (ICHD-2/3).

Results: Eight eligible studies from 2060 relevant citations were included in the review. All participants were migraine patients from both primary care and outpatient settings, as well as tertiary headache and anxiety centers, and were compared to non-migraineurs. The results of the systematic review showed that there is a strong and consistent relationship between migraine and anxiety. The co-morbidity of co-occurrence for migraine and anxiety has an average OR of 2.33 (2.20–2.47) among the prevalence and cross sectional studies and an average RR of 1.63 (1.37–1.93) for two cohort studies; The major limitations of included studies were small sample sizes and a lack of adjusting of confounding factors.

Conclusion: The results highlight the need for inclusion of an anxiety screening tool during initial assessments of migraine patients by medical practitioners and/or physicians and may explain why some anxiolytic medications work better than others for migraine mitigation.

Keywords: migraine, anxiety, systematic (Literature) review, prevalence, comorbidity

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INTRODUCTION

Migraine and other headache disorders are among the most prevalent disorders worldwide (1). Migraine is a debilitating headache disorder that is usually diagnosed by medical practitioners based on clinical history and the exclusion of other headache types. There are broadly two main types of migraine; one with aura, and one without (2). The US statistics on the migraine prevalence rate show that one in every seven Americans suffer from migraine or severe headache annually (3). The findings of a review in Europe demonstrated migraine prevalence to be around 14.7% with almost twice as many females (17.6%) as males (8%) (4).

Migraine is a multifactorial neurological disorder, that is associated with genetic, hormonal, environmental, dietary and psychological factors (5). Most migraine is episodic (<15 headache days per month). Chronic migraine is less common but has a high personal, familial, and social impact. The diagnosis is made when there are at least 15 headache days monthly including 8 migraine days per month for at least 3 months. The prevalence is 1.4–2.2% in the population (6). Given the frequency of intensely painful headaches, it is not surprising that chronic migraine is often associated with common psychiatric disorders such as anxiety disorders (7). Generalized anxiety disorder is characterized by emotionally unpleasant developmentally inappropriate states of unfocused uneasiness and worry, usually about objectively unthreatening situations (8). Generalized anxiety disorder is associated with perturbed heart rate, blood pressure, inflammation, muscular tension (9), restlessness, fatigue and problems in concentration, somatic complaints, and rumination (10).

The association of migraine and anxiety has been elucidated in both clinical as well as community-based settings (11, 12). For example, individuals with migraine showed a higher prevalence of generalized anxiety disorder even after adjusting for demographic variables and pain conditions including arthritis and back pain (10, 12). The authors also reported that chronic condition such as arthritis and pain were also more prevalent in migraineurs than those who do not have migraine (12). The authors analyzed secondary data collected from a Canadian Community Health population based survey and found that people with generalized anxiety disorder were 2.5 times higher in migraineurs than those without migraine (10). In another study conducted by Antonaci et al., the authors reported that general anxiety and social phobia were the types of anxiety which demonstrated the strongest relationship with migraine amongst young adults (11).

Since the early epidemiological study of Breslau, Davis (13), the relationship between migraine in young adults and psychiatric disorders has been understood to be bidirectional with bipolar disorder, panic disorder, or generalized anxiety disorder and alcohol and drug abuse in the majority of migraine patients (13–15). Similarly, in a study by Swartz, Pratt (16), significant associations were found between migraine and depression, panic and phobia and suicide, even after adjusting for age and sex (16). Later, Breslau et al. (14) demonstrated that the comorbidity of migraine and psychiatric disorders further increased the likelihood of disability, complicated psychiatric and neurological care (14) and significantly heightened the risk of suicide (13, 14). Indeed, a recent review of the migraine-suicide link identified migraine as risk factors for suicide attempt, even after adjusting for psychiatric conditions (17). Such findings propose a role for migraine pain as a risk factor in suicide attempts (18). In another recent systematic review (19), a bidirectional relationship between migraine, major depression and panic disorder was also highlighted.

The neurological pathophysiology of comorbid migraine and anxiety disorders has been studied clinically, often when associated with balance disorders (20, 21). Such evidence on the neurophysiology of migraine has provided insight into its association with anxiety. For example, evidence suggests that altered brainstem signaling mechanisms play a vital role in the pathophysiology of migraine, particularly in relation to symptoms such as nausea, vertigo and other autonomic symptoms (22). These symptoms are also characteristics of heightened anxiety (23, 24). A role for trigeminovascular activation has been supported by the effect of serotonin agonists such as triptans and Calcitonin Gene Related Protein antagonists in managing migraines (25). CGRP as a potent vasodilator also functions in the transmission of nociception which is inevitably tied to the stress and anxiety occasioned by frequent migraine (25).

It is important to note that acute anxiety is an innate biologically adaptive response to real potential threats in the environment. Acute anxiety is mediated by the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic medullary axis (SMA) and together their interaction affects human behavior and cognition (26). By comparison, prolonged anxiety and over-activation of the HPA-axis is known to be maladaptive, leading to perturbation of the stress response (27, 28). Indeed, prolonged anxiety has been proposed as a causal factor influencing the role of neuropathologic processes and leading to increased risk of other psychiatric disorders, as well as the transformation of episodic migraines into chronic events (29, 30).

Currently, anxiety disorders are among the most common psychiatric disorders. The prevalence of anxiety disorders among migraineurs is double that associated with depression, (31, 32). It is generally acknowledged that depression and anxiety have overlapping but distinctive features that may have different neurobiological underpinnings. For instance, (33) influential tripartite model of anxiety and depression [developed by (34)] provided an extremely influential account of the similarities and differences between anxiety and depression. In terms of similarity, anxiety, and depression are both strongly associated with negative affectivity or the experience of distress and other negative emotional states. Clark and Watson also identified two other factors: (1) positive emotionality (involving energy and pleasurable engagement; it is orthogonal to negative emotionality; and (2) physiological hyperarousal. Depression (but not anxiety) is characterized by a relative absence of positive affect (or manifestation of anhedonia). In contrast, anxiety (but not depression) is characterized by hyperarousal. In contrast to the research into the relationship between depression and migraine, substantially less research is available on migraine

comorbidity with anxiety (6). Furthermore, there have been few, if any systematic reviews or meta-analyses on the migraine and anxiety relationship exclusively. Thus, the aims of this review were twofold: (a) to systematically evaluate the connection between anxiety and migraine, and (b) to determine using Odds Ratios (OR) and Relative Risk Ratio (RR) whether the comorbidity of migraine with anxiety is higher in migraineurs than non-migraineurs.

METHOD

The review was conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of etiology and risk (35).

Eligibility Criteria

The inclusion criteria were studies with (1) all types of quantitative study designs, (2) participants aged 16 years and above (3) a clear diagnosis of migraine by a medical practitioner or a recorded medical history or diagnosis based on ICHDS-II/III classifications, (4) patients who experienced at least one migraine episode monthly or more severe conditions as per Weatherall (31), and (5) a comparison group of non-migraineurs.

The outcomes of interest that were considered for this review were any measures of anxiety by a clinically validated tool such as the Goldberg Anxiety Disorder (GAD), Depression, Anxiety and Stress Score (DASS-21), Goldberg Anxiety Scale (GAS), Hamilton Anxiety Scale (HAS), self-reported anxious symptomology (RAS) & Hospital Anxiety Depression Scale (HADS). Studies were excluded from the review if (1) they were not written in English language, (2) if they included participants under 16 years of age, or (3) if they did not have a non-migraineur comparison group.

Data Sources

A systematic search was conducted on December 2019 through electronic database of Medline, PsycINFO, EMBASE (Ovid), Science Direct (Elsevier), Cochrane, and PubMed, for all available years of publication until December 2019. Reference lists of included studies were also hand searched. The following MeSH terms and Keywords were used: Migraine/or chronic or tension or intractable/or headache, Migraine disorders/or Tension type, headache/or Headache disorders and Anxiety/or Anxieties/or GAD, or Panic*/or Neurotic/or Neuro anxiety/or panic/or anxiety Disorders/or Panic disorders/or Neurotic Disorders.

Study Selection

Following the search citations were entered to EndNote X9 and duplicates were removed. citations were evaluated independently by two reviewers (LK and HK). The full text of identified citations was evaluated by the two reviewers (LK and HK). Two reviewers (LK and HK) independently evaluated the studies. Reasons for exclusion of full text studies were recorded. Any reference conflicts were resolved by consensus between the two reviewers.

Quality Assessment

The risk of bias within the citations were evaluated with the Joanna Briggs Institute (JBI) critical appraisal tools for prevalence, cross-sectional and cohort studies as shown in **Tables 2–4** (35, 36). The main criteria in assessing risk of bias included the appropriateness of study design, adequacy of sample size, methods and measurements, and data analysis.

Data Extraction

A template for data extraction was formed using the JBI Database of Systematic Reviews and Implementation Reports. Each reviewer extracted data on half of the included studies, while the other reviewer checked the extracted the data (LK and HK). The information extracted from each individual study included; study characteristics (country, author, date of study, setting of study), participant characteristics (total number, diagnosis), outcome measures (type of anxiety tool used), and results (association between migraine and anxiety, r (p) values or Odds Ratio (95% CI) where available).

Data Analysis

Data analysis including Odds Ratio (OR), relative risk ratio (RR) were produced using Meta-Essential (37). The meta-analysis graphs were not produced nor reported given large level of heterogenities among the studies and inadequate study size. We also undertook a sensitivity analysis by clacluating OR or RR on all the similar study types separately, (prevalence, cohort and cross-sectional studies). Based on Cochrane guideline "a sensitivity analysis is a repeat of the primary analysis or meta-analysis, substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear" (38). For this study, given different study types were used in the review, in addition to calculating overall OR or RR on all combined studies, a separate calculation was conducted on each sets of study types (i.e., prevalence, cohort, and cross-sectional studies) to find out if there is any variability in the results due to different study types.

The systematic review is registered with Prospero (#CRD42020153059).

RESULTS

The initial search generated a total of 2,132 citations. After removing the duplicates ($n = 72$), 2,060 unique citations were identified. After screening the citations ($n = 110$), 30 studies were identified as eligible for full-text review. Studies were removed if they were not written in English, participants within the study were aged under 16 years of age, incorrect study type, and/or the study did not meet risk of bias criteria. Following the full-text review, 22 more studies did not meet the eligibility criteria i.e., they did not include the minimum information required such as including a comparison group of non-migraineurs. A total of eight studies were eligible for inclusion in the review as shown in **Figure 1**.

Study Characteristics

The studies were conducted in Canada, Turkey, Brazil, USA, New Zealand, Korea, China, and the European Union. The study types were population-based, cohort and cross-sectional studies. Migraine was diagnosed in the majority of the studies based on ICHDS-II/III classifications. The studies used a variety of validated tools as the screening measure for anxiety,

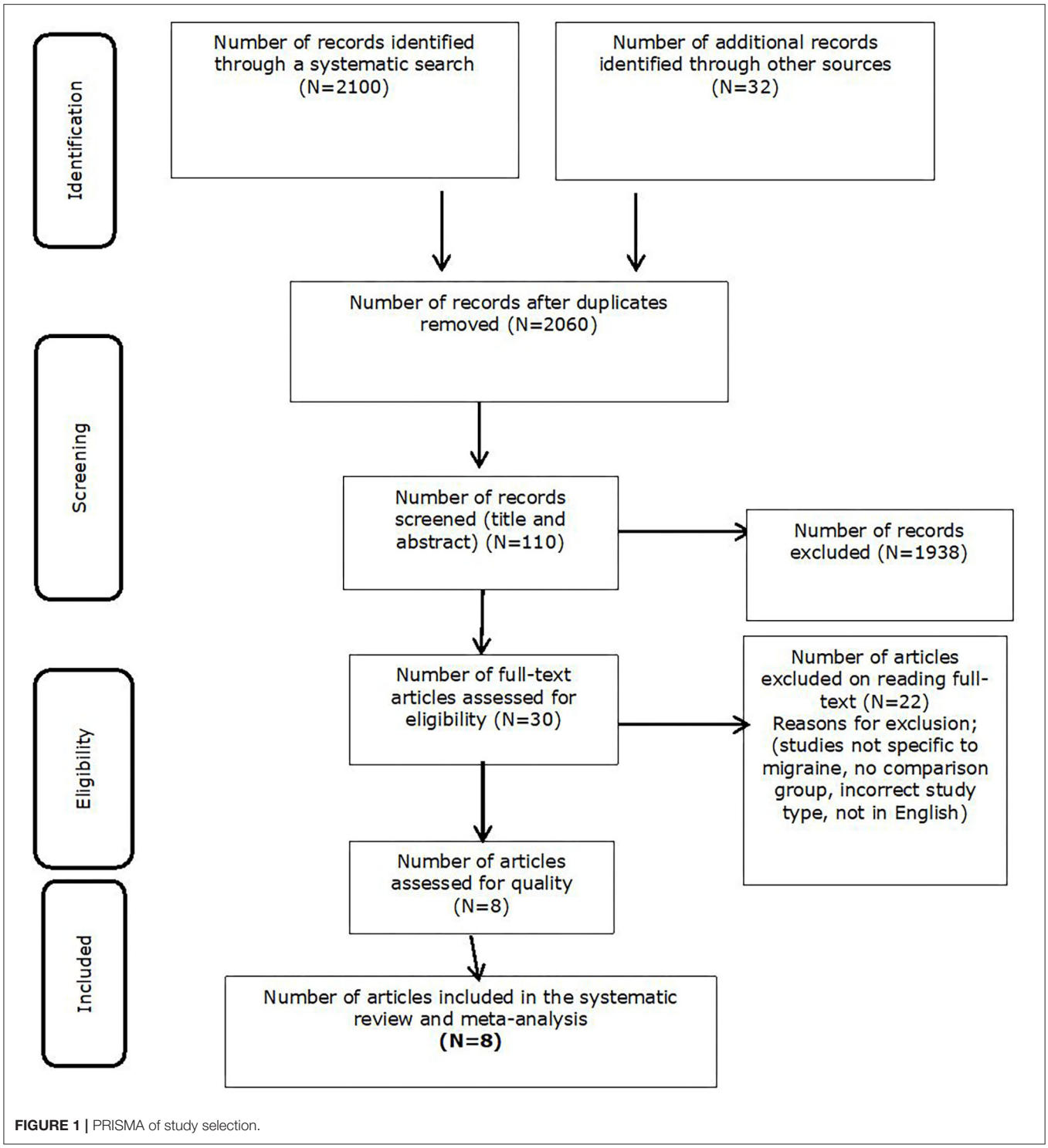

FIGURE 1 | PRISMA of study selection.

including the Goldberg Anxiety Disorder (GAD), Depression, Anxiety and Stress Score DASS-21, Goldberg Anxiety Scale (GAS), Hamilton Anxiety Scale (HAS/HAMA), and self-reported anxious symptomology (RAS). In all the studies the results demonstrated a strong relationship in terms of Odds Ratios (38) between anxiety and migraine compared to non-migraineurs. Both the Brazilian studies (29, 39) showed exceptionally high ORs (OR = 13 and 25 in order), with the other six studies showing ORs ranging from 1.77 to 4.5 (40, 41).

The same eight studies were included in the systematic review and were characterized by both primary care and outpatient settings, as well as tertiary centers. Participants included those

TABLE 1 | Characteristics of included studies—prevalence, cross-sectional, and cohort studies.

Country/References	Methods (data collection procedure)	Sample size	Age (years) Range/mean (SD)	Migraine assessment	Anxiety measure	Comorbidity of migraine with anxiety (vs. non-migraineurs) Odds ratio/Risk Ratio (95% CI)
Association of migraine with anxiety compared to non-migraineurs						
Brazil/Mercante et al. (39)	The Anxiety Disorders Program of the Institute of Psychiatry	60	19–70	ICHD-II	GAD	OR 13.00 (3.45–48.93)
Turkey/Karakurum et al. (42)	n/c	87	32.3 (10.05)	IHS	Hamilton Anxiety Scale (HAS)	RR 2.10 (1.38–3.19)
European union countries/Lampl et al. (43)	Primary care-population based surveys	6,624	42.1 (12.9)	ICHD-2	HADS	OR 1.77 (1.54–2.04)
Korea/Oh et al. (44)	Primary care -population based surveys	2,762	19-69	ICHD-2	Goldberg Anxiety Scale (GAS)	OR 4.5 (3.1–6.5)
North West Pacific areas (New Zealand)/Orta et al. (40)	Primary care -pregnant women	1,321	33.1 (4.3)	ICHD_II and the deCode Genetics migraine questionnaire (DMQ3)	DASS-21	RR 1.55 (1.21–1.99) mild—sever dass
Brazil/Peres et al. (29)	Primary care self-administered questionnaire	782	34.2 (6.3)	Self-reported ICHD-II	GAD-7 (anxiety)	OR 25.16 (16.50–38.39)[†]
Canada/Senaratne et al. (41)	Outpatient anxiety clinic-computer-assisted telephone interview (CATI)	206	37.8 (12.9)	IHS	GAD	OR 1.37 (0.72–2.61)
US/Victor et al. (45)	Epidemiological national survey	30,790	43.6	Self-reported medical diagnosis of migraine	Self-reported anxious symptomology (RAS)	OR 2.30 (2.15–2.45)

[†] *Calculation based on corresponding with the author.*

TABLE 2 | Risk of bias in prevalence studies.

References	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants	Was there appropriate statistical analysis?	Was the responses rate adequate, and if not, was the low response rate managed appropriately?
Oh et al. (44)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Senaratne et al. (41)	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Victor et al. (45)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

TABLE 3 | Risk of bias in cross sectional studies.

References	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?
Balaban et al. (51)	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes
Mercante et al. (39)	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Lampl et al. (43)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Peres et al. (29)	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes

with ICHDS-II/III classified migraine, compared against non-migraineurs. Please see **Table 1** for the study characteristics.

Eight studies did not meet the minimum number of studies as well as heterogneties criteria to be included in a meta-analysis (52). Given presence of large heterogenties of the combined studies ($p < 0.05$, $I^2 > 0.75$), a minimum of 40 studies are required to conduct a metanalysis (52). Therefore, only an average OR and RR for study subtypes are presented for this review. Based on the findings demonstrated in **Table 1**, an average OR of 2.33 (2.20–2.47) among the six studies are reported. For prevalence studies (41, 44), the OR was 2.54 (95% CI 1.48–4.35). The average OR for the cross-sectional studies (39, 46) was higher and reported to be 8.14 (95% CI 0.99–66.83). The high OR and CI for this group of studies were due to inclusion of the two Brazilian studies with very high OR. For two cohort studies an average of RR of 1.63 (1.37–1.93) reported. All the study types showed a significant association between migraine and anxiety.

Risk of Bias in Individual Studies

Prevalence Studies

There was a total of three prevalence studies as shown in **Table 2** (41, 43, 44). Only one study (43) fulfilled all the requirements for a high-quality study. The other two studies met the criteria for adequate sampling, valid methods for identifying the condition, and data analysis. Small sample size was the major limitation in one study (44).

Cross Sectional Studies

As presented at **Table 3**, there was a total of three cross sectional studies (29, 39, 45). All three studies had appropriate sampling, and the exposure and outcomes were assessed in a reliable way with suitable statistical analysis. None of the studies detailed any approaches to deal with confounding factors.

Cohort Studies

There were only two cohort studies (40, 42) eligible for inclusion in the cohort risk of bias consideration. Both studies measured exposure and the outcome in a valid and reliable way. Suitable statistical procedure was reported in both studies. Confounding factors and strategies to adjust or control for them were unclear in Karakurum et al. (42) (**Table 4**).

DISCUSSION

The aim of this review was to assess the link between anxiety and migraine, in order to determine whether (a) there is a usual comorbidity between migraine and anxiety and (b) if the incidence of anxiety is higher among migraineurs compared to non-migraineurs.

The results of the systematic review showed strong and consistent positive relationship between migraine and anxiety. The data analysis of included studies showed an average random effect of an average of RR of 1.63 (1.37–1.93) for two cohort studies and an average OR of 2.33 (2.20–2.47) for prevalence and cross-sectional studies of anxiety comorbidity among migraineurs compared to non-migraineurs or healthy participants. Clearly migraine and anxiety are comorbid, and the

TABLE 4 | Risk of bias in cohort studies.

References	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Were strategies to address incomplete follow up utilized?	Was appropriate statistical analysis used?
Orta et al. (40)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Karakurum et al. (42)	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes

incidence of occurrence is almost four times higher compared to non-migraineurs. Our results are consistent with previous studies (47–49).

Furthermore, (41) reported that more than a third of their participants who were diagnosed with migraine reported positive reduction in their migraine attacks as a result of receiving pharmacological treatment for their anxiety. This suggests a joint predisposition or some related biological underpinnings in both migraine and anxiety (41). These results are also in line with the findings of our systematic review demonstrating the link between anxiety and migraine.

The current systematic review have important implications for future clinical practice. Firstly, the results highlight the need for concurrent assessment of migraineurs for both neurological symptoms of migraine and psychiatric symptoms associated with potential anxiety and depression. Secondly, in order to understand the etiology better, future studies should seek more information regarding the apparent onset of biological symptoms associating migraine with physiological measures of anxiety. Currently there is little biological information regarding the onset of clinical anxiety with regard to the onset of the migrainous events or vice versa. Experimental studies on the chronological association of migraine and anxiety would be expected to lead to clinical trials regarding the effectiveness of known treatments for both migraine severity and debilitating anxiety. Indeed, this will increase the likelihood of earlier detection and development of preventative strategies among people with migraine.

Lastly, when comorbidity is detected for migraine patients, treatment options should be considered that lead to improvements in both conditions (50, 51). Moreover, exploring the comorbidity of migraine with anxiety from a neurological perspective is likely to lead to greater understanding of the early etiology and aid in development of more effective treatment options. As acknowledged by the researchers (51), the comorbid symptoms appear to be an outcome of sensorimotor, interoceptive and cognitive adaptations. As a result, the migraine and anxiety comorbidity can be observed within the contexts of neurological and psychopharmacological settings (51). Further studies are needed on these treatment options. The high comorbidity of migraine and anxiety highlights the need for more research on the neurobiological causes of migraine and how best to manage its risk factors in a more effective way. Furthermore, there is a need to continue research into the psychiatric comorbidities of migraine to ascertain if there is a greater prevalence of comorbidity for anxiety in migraineurs with aura.

Limitations

A limitation of the current systematic review is the small number of studies included in the review and not meeting the minimum required number of the studies for running a combined metanalysis. Furthermore, the nature of the observational studies included in this systematic review s limit the generalisability of the results. Finally, the diversity of the tools used to measure anxiety introduced a confounding factor to the statistical analysis.

CONCLUSION

In the reported systematic review two critical results were found: (a) the comorbidity of migraine and anxiety is strong and significant and (b) the comorbidity of anxiety with migraine is significantly higher among migraineurs vs. non-migraineurs. This study also highlighted a need for concurrent screening or assessing migraine patients with anxiety tools. Biological assessments of anxiety among migraineurs is missing in the clinical settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TW, SC, LK, and HK: substantial contributions to conception and design. LK, DE, and HK: acquisition of data or analysis and interpretation of data. LK, SC, TW, DE, HK, and AE: drafting the article or revising it critically for important intellectual content. All authors have agreed on the final version of the paper, contributed to the study, and development of the paper.

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BRIEF RESEARCH REPORT
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Genetics Influences Drug Consumption in Medication Overuse Headache, Not in Migraine: Evidence From Wolframin His611Arg Polymorphism Analysis

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Background: The Wolframin His611Arg polymorphism can influence drug consumption in psychiatric patients with impulsive addictive behavior. This cross-sectional study aims to assess the prevalence of the Wolframin His611Arg polymorphism in MOH, a secondary headache belonging to the spectrum of addictive disorders, episodic migraine (EM), and healthy subjects (HS), and its influence on drug consumption.

Methods: One-hundred and seventy-two EM, 107 MOH, and 83 HS were enrolled and genotyped for the Wolframin His611Arg polymorphism. Subjects were classified as homozygous for allele His (H/H subjects), homozygous for allele Arg (R/R subjects), and heterozygous (H/R subjects), regrouped as R/R and carriers of allele H (non-R/R), and matched for clinical data.

Results: There were no differences in allelic distributions between the three groups ($p = 0.19$). Drug consumption and other clinical characteristics were not influenced by the Wolframin His611Arg polymorphism ($p = 0.42$; $\beta = 0.04$) in the EM group. Among the MOH population, R/R subjects consumed more analgesics ($p < 0.0001$; $\beta = -0.38$), particularly combination drugs ($p = 0.0001$; $d = 2.32$).

Discussion: The Wolframin His611Arg polymorphism has a similar prevalence between the MOH, EM, and HS groups. The presence of the R/R genotype does not influence symptomatic drug consumption in EM, whereas it determines an increased use of symptomatic drugs in the MOH group, in particular combination drugs (i.e., drugs containing psychoactive compounds).

Conclusions: Our findings are consistent with the hypothesis that the Wolframin His611Arg polymorphism plays its effect only in the MOH population, influencing the impulsivity control underlying addictive behavior.

Keywords: wolframin (WFS1), migraine, medication overuse headache (MOH), pharmacogenomics, single nucleotide polymorphism (SNP)

Medication overuse headache (MOH) is a chronic form of secondary headache, usually developed by migraineurs in response to analgesic overuse (1), characterized by a relevant impact in clinical practice, with a prevalence of 0.5–2.6% in the adult population (2). The withdrawal of the symptomatic overuse usually, but not invariably, resolves MOH (1, 3); however, the recurrence into overuse after weaning from drugs is high and unrelated to the modality of detoxification (4) but is influenced by the presence of other forms of abuse (5). Additionally, MOH can be induced in susceptible patients by overuse of analgesics to treat other forms of pain (1) or drugs without a clear analgesic effect to treat another disease that somehow act on migraines (6).

MOH was thought by some authors to belong to the spectrum of addictive disorders (7, 8). According to this hypothesis, the withdrawal syndrome is represented by the chronic headache, the physical dependence is treated by detoxification, the psychological dependence accounts for the recurrences, and the genetic background influences the degree of disease severity by a pharmacogenomics effect (9). To support this theory, our group explored the influence of some genetic backgrounds, already related to substance dependence, on the clinical and physiological characteristics of patients with MOH (10–12). In particular, we analyzed the role of the His611Arg polymorphism of the wolframin gene (WFS1) in a sample of patients with MOH and found that patients homozygous for the rarer genotype (R/R subjects) experienced a more severe form of MOH in terms of doses of drugs consumed and depressive symptoms (10). At the time of our previous study, some authors regarded WFS1 as a promising gene in the development of abuse behavior (13), in particular, because related to two typical personality traits of addicted people: novelty seeking and impulsivity (14). Unfortunately, in the last decade, no other authors addressed studies on WFS1 to the topic, so our hypothesis of WFS1 gene polymorphism contributes to MOH by influencing the impulsivity control underlying addictive behavior, remained unproved.

This study aims to assess the influence of WFS1 His611Arg polymorphism on drug consumption in patients with EM and MOH and detect a possible difference in the prevalence of the analyzed polymorphism among patients and HS. We hypothesized that only in MOH patients the WFS1 His611Arg polymorphism can contribute to the propensity to high symptomatic drug consumption.

METHODS

Patients

Patients with diagnoses of EM and MOH were screened, between January 2012 and December 2014, at the outpatient Headache-Unit of our Hospital, according to the accepted International Classification of headache disorders (ICHD)-2 criteria. After the release of the ICHD-3 criteria, all patients' files were reanalyzed, and the diagnoses were also confirmed according to these revised criteria. Socio-demographic and clinical data were obtained after an accurate anamnesis performed by a headache-skilled neurologist. At the time of their first visit to the outpatient Headache-Unit, patients were instructed to complete a headache diary to record clinical data (consumption of analgesic drugs per month, days with headache per month, days with drug consumption per month). Inclusion criteria were: (a) the patient's written informed consent; (b) absence of other major medical conditions that potentially could worsen headache or requires a regular pharmacologic treatment (only hormonal treatments, namely pill, patch, and ring, for contraceptive purposes were allowed); (c) absence of psychiatric disorders that could sustain a chronic pain condition (psychotic and/or somatoform disorders); (d) accurate completion of the last 3-month headache diary; (e) diagnostic confirmation of EM or MOH by diary analysis and. Moreover, subjects were screened with the Snellen visual acuity test and with the pure tone audiometry test in order to exclude the visual and auditory deficits related to the Wolfram Syndrome (15, 16). The absence of optic atrophy was assessed by an ophthalmological evaluation including best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, and indirect ophthalmoscopy.

Consecutive outpatients that matched the inclusion criteria were enrolled in the current study at the end of a routine visit. Episodic migraine patients had no history of medication overuse The MOH had $\geq$15 headache days per month but improved (headache reverts to episodic pattern, $<$15 headache days per month) after detox and were thus included. Consistent with our previous study (11), the drug types were grouped in four classes: triptans, non-steroidal anti-inflammatory drugs (NSAIDs), associations (i.e., consumption of different types of drugs), combinations (i.e., drugs containing more than one active principle, including psychoactive compounds). The control group was composed by HS of comparable gender distribution as the headache groups, recruited among hospital employees and patients' spouse, that has no headache, neurological, psychiatric and other major medical conditions. All the recruited subjects were independent from those enrolled in the previous study (10). Our Institutional Ethical Committees approved the study.

Detoxification Protocols

The detoxification protocol depends on each patient. All patients received the advice to stop the use of analgesics for at least 5 weeks (3) and underwent educational training to manage their attacks by antiemetics in case of nausea, myorelaxants in case of neck muscle contraction, and benzodiazepines in case of pain-induced anxiety. Moreover, it was suggested the use of an ice bag to treat the pain if unsupportable. In case of headache worsening, it was allowed the intramuscular injection (IM) of dexamethasone 4 mg, maximum twice per week. Patients with a previous story of multiple medication overuse relapsing received a prescription of prednisone p.o. during the first 10 days (60 mg/day, 2 days; 40 mg/day, 2 days; 20 mg/day, 6 days). The latter group of patients was not allowed to use dexamethasone as rescue medication but was prescribed ketorolac 30 mg IM, maximum twice per week. Finally, patients who overuse drugs containing opiates or butalbital were also treated with decremental therapy with benzodiazepines.

Molecular Analysis

After obtaining the patients' written informed consent, 10 ml of peripheral blood were collected, total genomic DNA was purified, and patients were genotyped for the WFS1 His611Arg polymorphism by a PCR-RFLP (restriction fragment length polymorphism) method. Briefly, PCR was performed in a total volume of 20 μl consisting of: 40–100 ng of DNA; 200 μM each of dATP, dGTP, dCTP, and dTTP; 10 pmol of the specific primers; and 0.2 U of Taq (GE Healthcare, Cologno Monzese, Italy). A PCR product of 139 bp was obtained using specific primers (Primm, Milan, Italy, www.primm.it): WFS1-F 5′-GAGCTCACCAAGATCGCAGT-3′, and WFS1-R 5′-ACACC AGGATGAGCTTGACC-3′. The PCR reaction consisted of an initial denaturation at 94°C for 5 min, followed by 40 cycles of 30 s of denaturation at 94°C, 30 s of annealing at 59°C, and 30 s of extension at 72°C. A final extension step was performed for 5 min at 72°C. Seven microliters of PCR product were cleaved overnight at 37°C with the endonuclease BsrI (New England Biolabs, Pero, Italy) in a total volume of 10 μl. The cleaved fragments were separated after electrophoresis on a 2.5% agarose gel and stained with ethidium bromide (10).

By these procedures, we detected the presence of the G to A substitution in position 2002 within exon 8 of the gene, accounting for the aminoacidic polymorphism His611Arg (rs734312) (17). According to the results of genetic analysis, patients were classified as homozygous for allele His (H/H subjects), homozygous for allele Arg (R/R subjects), or heterozygous (H/R subjects).

Power Calculation and Statistical Analysis

Since our primary endpoint was to detect differences among the WFS1 genotype subgroups, the sample size analysis was based on our previous study about the difference in the number of analgesics consumed per month by MOH patients between R/R and carriers of allele H (non-R/R) (10). The monthly drug number consumed by the overall MOH population was 41.82 ± 25.07. The monthly drug number consumed in R/R and non-R/R MOH subgroups was 59.59 ± 31.13 and 37.17 ± 21.15, respectively. To fulfill a desired power of 90% with a significance level at 5% (18), the required sample size was 82 subjects (17 R/R and 65 non-R/R) in the MOH subgroup. Due to the lack of studies about the WFS1 genotype in migraineurs, we decided, as conservative approach, to double the number of subjects (164) required for the migraine sample to detect the difference in number of analgesics consumed per month between R/R and non-R/R with an acceptable power.

All data obtained in the three phases of the study (socio-demographic and clinical recordings and genetic determinations) were merged in a comprehensive database by an independent data-manager, which opened the blind and performed the statistical analyses on definitive data.

Statistics has two levels of analyses: in the first one, there were univariate analyses; in the second one, we carried out two types of multivariate regression models, the multinomial logistic regressions for the categorical dependent variables and the general regression models for continuous dependent variables.

TABLE 1 | Genetic results of polymorphism analysis are reported as frequencies (and percentages) of WFS1 genotypes in HS, EM, and MOH.

	HS ($n = 83$)	EM ($n = 172$)	MOH ($n = 107$)
H/H ($n = 70$)	13 (16%)	28 (16%)	29 (27%)
H/R ($n = 189$)	45 (54%)	91 (53%)	53 (49%)
R/R ($n = 103$)	25 (30%)	53 (31%)	25 (24%)

Descriptive statistics to compare WFS1 genotypes were performed among and within diagnostic groups using parametric or, when appropriate, non-parametric tests. *Post hoc* tests were performed with Bonferroni's confidence interval adjustment for multiple comparisons. The Likelihood Ratio Chi-Square test, based on Maximum Likelihood Estimation, was used in both univariate and multivariate models (multinomial logistic regression) with dependent and independent categorical variables. A General Regression Model (GRM) was employed to identify significant predictors of the monthly drug number in the whole headache group and, due to different clinical features of the headache disorders (particularly for the number of analgesics consumed per month), separately in the EM and MOH groups. In addition to well-known indices of null hypothesis significance testing, effect size measures were also reported to recognize the value of the degree of association among variables (19, 20). Effect sizes were calculated with the phi (ϕ) coefficient [or, when appropriate, Cramér's V (ϕ_c)] for the χ^2 test and with Cohen's d (d) for Student's *t*-test, with partial Eta squared (η_p^2) for analysis of variance (ANOVA). Standardized coefficients (Beta coefficient, β), partial correlations (r_p), and semi-partial correlations (r_{sp}), and GRM effect size estimates were also reported. Statistical significance was set at $p < 0.05$.

RESULTS

Three-hundred and sixty-two subjects (261 women and 101 men; age, mean ± SD: 42.54 ± 11.52 years) were enrolled in the study: 83 HS (52 women and 31 men; age, 44.57 ± 10.55), 172 EM (125 women and 47 men; age, 39.16 ± 11.14), and 107 MOH patients (84 women and 23 men; age, 46.41 ± 11.36). The three groups and gender were not statistically associated (-2LL = 26.626, $\chi_2^2 = 5.804$, $p = 0.06$). Age was different among three groups ($F_{2,359} = 15.960$, $p = 0.0001$, $\eta_p^2 = 0.08$): migraineurs were younger than controls [$p = 0.001$, d = 0.50 (95% Confidence Interval, CI_{95}:−1.77–2.61)] and MOH patients [$p < 0.0001$, d = 0.65 (CI_{95}:−1.50–2.31)] whereas controls and MOH did not differ [$p = 0.77$, d = −0.17 (CI_{95}: -2.44–1.98)].

The results of the genetic analysis are shown in **Table 1**. Both the general sample ($\chi_1^2 = 1.015$; $p = 0.31$) and the three groups separately (HS: $\chi_1^2 = 0.959$, $p = 0.33$; EM: $\chi_1^2 = 1.128$, $p = 0.29$; MOH: $\chi_1^2 = 0.007$, $p = 0.93$) were in Hardy-Weinberg equilibrium.

A preliminary analysis was performed to investigate associations between the three genotypes and the three groups and differences in monthly drug numbers between H/H, H/R, and R/R separately in the EM and MOH groups. The Likelihood

Ratio Chi-square test (-2LL = 28.907, $\chi_4^2 = 6.136$, $p = 0.19$) showed that the genotypes were not associated with one of three groups. In the EM patients, the three genotypes did not differ statistically (among them) in the number of monthly used drug ($F_{2,169} = 1.493$, $p = 0.23$, $\eta_p^2 = 0.02$). On the contrary, in MOH patients, there was a difference among the genotypes in the number of monthly used drug ($F_{2,104} = 10.012$, $p = 0.0001$, $\eta_p^2 = 0.16$); R/R patients showed statistically higher values than the H allele carriers (*post hoc* pairwise comparisons: R/R *vs*. H/H, $p = 0.02$; R/R *vs*. H/R, $p < 0.0001$; H/H vs. H/R, $p = 0.44$). These results further confirmed our previous decision (10) to consider together the carriers of allele H in the non-R/R group. To perform further statistical analyses, the general sample was divided into two groups: those with the R/R genotype (103 subjects), homozygotes for allele R, and those with the non-R/R genotype (259 subjects), carriers of allele H, either in heterozygosity or in homozygosity.

A three-way ANOVA (grouping factor: "gender", "diagnosis", and "genotype") showed that age was significantly different among the three diagnostic groups ($F_{2,350} = 13.544$, $p < 0.0001$, $\eta_p^2 = 0.07$). No further effects ("gender" and "genotype") or interaction effects ("gender" × "diagnosis", "gender" × "genotype", "diagnosis" × "genotype", and "gender" × "diagnosis" × "genotype") were significant.

Clinical characteristics and descriptive statistics for the migraine and MOH groups are illustrated in detail in **Table 2**. In migraineurs, R/R patients had shorter headache durations than non-R/R patients ($p = 0.002$, d = −0.53). In MOH patients, R/R subjects consumed a high number of drugs monthly than the non-R/R patients ($p < 0.0001$, d = 0.97).

Multivariate Regressions

A full factorial multinomial logistic regression model showed no association between R/R and non-R/R genotypes and the HS, EM, and MOH groups, even after controlling for the "gender" effect and the "genotype" × "gender" interaction effect (-2LL = 35.231, $\chi_6^2 = 10.374$, $p = 0.11$). When age was inserted in the multinomial logistic regression, the model was significant (-2LL = 441.376, $\chi_8^2 = 40.270$, $p < 0.0001$). Only age resulted as a predictor of diagnosis (-2LL = 471.273, $\chi_2^2 = 29.897$, $p < 0.0001$) and particularly predicted the migraine group (B = −0.042, Wald = 11.118, df = 1, $p = 0.001$). This result confirmed no association between genotype and diagnostic group even after controlling for "gender" and age effects.

In the whole headache group, the independent variables entered into the GRM to identify the predictors of monthly drug number (dependent variable) were: age, illness duration, and monthly headache days as continuous variables, and "diagnosis" (EM *vs*. MOH) and "WFS1 genotype" (non-R/R *vs*. R/R) as grouping variables. The model was significant ($F_{6,272} = 106.384$, $p < 0.0001$) and explained 69.5% (adjusted R^2) of the variance of the monthly drug number. "Diagnosis" (β = −0.49), monthly headache days (β = 0.45), the "diagnosis" × "WFS1 genotype" interaction (β = 0.22), and "WFS1 genotype" (β = −0.20) emerged as significant, independent predictors of pre-detoxification the monthly drug consumption in whole headache group. No further variables considered as possible predictors were entered in the GRM. Detailed results of GRM in whole headache group are reported in upper side of **Table 3**. The presence of a significant interaction effect between "diagnosis" and "WFS1 genotype" grouping variables on the number of analgesics consumed per month in the whole headache group supported our statistical plan of analyzing headache patients as separated subgroups (EM and MOH) in order to investigate independent predictors of monthly drug number by two different GRMs, one for EM group and one MOH group.

In the EM, the independent variables entered into the GRM to identify the predictors of monthly drug number (dependent variable) were: age, illness duration, headache attack frequency, and monthly headache days as continuous variables, and "WFS1 genotype" (non-R/R *vs*. R/R) and "drug type" (triptans vs. NSAIDs vs. associations vs. combinations) as grouping variables. The model was significant ($F_{11,160} = 57.211$, $p < 0.0001$) and explained 78.3% (adjusted R^2) of the variance of the monthly drug number. Monthly headache days (β = 0.69), illness duration (β = −0.26), headache attack frequency (β = 0.23), and age (β = 0.23) emerged as significant, independent predictors of the pre-detoxification monthly drug consumption in migraineurs. No further variables considered as possible predictors were entered in the GRM. Detailed results of GRM in EM group are reported in middle of **Table 3**. The graph in the left panel of the **Figure 1** illustrates the number of analgesics consumed per month in EM, separately for the four analgesic classes in both WFS1 genotypes.

In the MOH group, the independent variables entered into the GRM to identify the predictors of monthly drug number (dependent variable) were: age, illness duration, MOH duration, and monthly headache days as continuous variables, and "WFS1 genotype" (non-R/R vs. R/R) and "drug type" (triptans vs. NSAIDs vs. associations vs. combinations) as grouping variables. The model was significant ($F_{11,95} = 4.303$, $p < 0.0001$) and explained 25.5% (adjusted R^2) of the variance of the monthly drug number. The "WFS1 genotype" (β = −0.38), "drug type" × "WFS1 genotype" interaction (β = 0.29), and monthly headache days (β = 0.27) emerged as significant, independent predictors of pre-detoxification monthly drug consumption in MOH patients. No further variables considered as possible predictors were entered in the GRM. Detailed results of GRM in MOH group are reported in lower side of **Table 3**. The graph in the right panel of the **Figure 1** illustrates the number of analgesics consumed per month in MOH, separately for the four analgesic classes in both WFS1 genotypes. In the *post hoc* analysis, pairwise comparisons of MOH patients that consumed drugs of combination revealed a statistically higher consumption of drug in the R/R group than the non-R/R group [82 ± 33.01 vs. 33.95 ± 18.45; $p = 0.0001$; d = 2.32 (CI_{95}:−26.62–10.21)]. Among those that used an association of drugs, the monthly consumption was higher in the R/R group than the non-R/R group; however, this difference did not reach the statistical threshold [63.25 ± 32.80 vs. 38.81 ± 16.84; $p = 0.09$; d = 1.18 (CI_{95}:−21.55–7.65)]. Using a less conservative approach with the Fisher's Least Square Difference (LSD) test and a significance threshold adjustment for multiple comparison tests with Bonferroni's correction (0.05/8 = 0.00625), the significance threshold was reached ($p = 0.003$)].

TABLE 2 | Detailed results of comparisons between WFS1 genotypes in EM group and MOH group.

	EM group ($n = 172$)				**MOH group ($n = 107$)**			
	R/R ($n = 53$)	**non-R/R ($n = 119$)**	**Statistics**	**es**	**R/R ($n = 25$)**	**non-R/R ($n = 82$)**	**Statistics**	**es**
Gender								
Women	38 (72%)	87 (73%)	$\chi^2 = 0.04$ $p = 0.85$	$\varphi = 0.02$	18 (72%)	66 (80%)	$\chi^2 = 0.82$ $p = 0.41$	$\varphi = 0.09$
Men	15 (28%)	32 (27%)			7 (28%)	16 (20%)		
Age	36.94 ± 11.98	40.14 ± 10.65	$t = -1.75$ $p = 0.8$	$d = -0.29$	46.48 ± 10.2	46.39 ± 11.74	$t = 0.03$ $p = 0.97$	$d = 0.01$
Attack frequency[a]	3.53 ± 1.88	3.78 ± 1.43	$t = -0.88$ $p = 0.38$	$d = -0.16$	-	-	-	-
Monthly headache days	6.09 ± 3.43	5.89 ± 3.15	$t = 0.38$ $p = 0.7$	$d = 0.06$	25.32 ± 5.97	25.28 ± 5.93	$t = 0.03$ $p = 0.98$	$d = 0.01$
Headache duration	**20.6 ± 12.21**	**26.71 ± 11.47**	**$t = -3.16$ $p = 0.002$**	**$d = -0.53$**	31.04 ± 10.09	31.44 ± 13.81	$t = -0.13$ $p = 0.89$	$d = -0.03$
MOH duration	-	-	-	-	5.96 ± 9.3	4.66 ± 5.41	$t = 0.86$ $p = 0.38$	$d = 0.2$
Monthly drug number	6.04 ± 3.04	5.66 ± 2.33	$t = 0.88$ $p = 0.38$	$d = 0.15$	**58.56 ± 27.35**	**37.93 ± 19.39**	**$t = 4.21$ $p < 0.0001$**	**$d = 0.97$**
Drug type								
Triptans	36 (68%)	71 (60%)	$\chi^2 = 1.16$ $p = 0.79$	$\varphi_c = 0.09$	7 (28%)	22 (27%)	$\chi^2 = 0.57$ $p = 0.91$	$\varphi_c = 0.07$
Nsaids	7 (13%)	22 (18%)			5 (20%)	13 (16%)		
Associations	4 (8%)	12 (10%)			8 (32%)	26 (32%)		
Combinations	6 (11%)	14 (12%)			5 (20%)	21 (25%)		

Descriptive statistics [expressed as mean ± SD and frequencies (and percentages)], statistics tests and effect size (es) indices are reported. In bold significant comparisons.
[a]The attack frequency was not reported in MOH group by genotype because MOH is a chronic headache condition often characterized by a continuous of headache days. It makes very difficult to group the headache days in separate attacks.

DISCUSSION

The findings of this study confirm, in a larger sample, our previous result that, within the MOH population, R/R patients have an increased use of symptomatic drugs. In particular, herein we showed that the drug consumption was higher in R/R patients who overuse combination drugs (i.e., drugs containing psychoactive compounds such as caffeine, opiates, or butalbital). According to the study hypothesis, we did not observe the same effect in patients with EM. Moreover, the prevalence of the R/R genotype did not differ among the three examined groups (HS, EM, and MOH).

Wolframin is a membrane calmodulin-binding glycoprotein that resides in the endoplasmic reticulum and regulates cellular Ca^{++} homeostasis (21). In the brain, wolframin is mainly expressed by the limbic system and structures closely related to it (22) and the visual system (retina, optic nerve, brain) (23). Its localization could explain the presence of psychiatric features in Wolfram Syndrome (early-onset diabetes mellitus, progressive optic atrophy, diabetes insipidus, deafness, and psychiatric disorders) and the modulation of WFS1 gene expression in psychiatric, behavioral, and emotional features. As an example, there is evidence that wolframin is synthesized in the amygdala as a consequence of exposure to danger and could be involved in bioactive peptide production (24). A deregulation of these mechanisms is also involved in impaired function of the dopaminergic system (25) and a reduced expression of the alpha1 and alpha2 subunits of GABA(A) receptors (26). As consequence, carriers of dysfunctional WFS1 gene expression could express increased anxiety (26), impaired behavioral adaptation in stressful environments (27), post-traumatic stress disorder (28), and mood disorders (29).

Consistent with our prior papers, we considered the number of analgesic doses consumed monthly by patients as one of the most useful markers of MOH severity in order to stratify patients according to the degree of their likelihood of abuse behavior. In fact, in MOH, the headache frequency ranged from 15 to 30 days per month; on the contrary, the variability of monthly drug consumption ranged from 10 to a not existing hypothetical upper limit. Therefore, according to their drug consumption, patients could be distributed on a wider range that better reflects their disease severity.

In patients with MOH, higher drug consumption would reflect the higher severity of headache or the higher proneness to abuse (i.e., to have poor impulse control). In the previous study, we supposed that the influence of wolframin on MOH is mainly due to an impulsivity-related increased need for drugs, and not to a worsening influence on pain or other primary headache symptoms (10). Interestingly, in the present study all MOH patients reverted to an episodic headache pattern after the detoxification. This point is especially important because it implies that patients' chronic headache was due to medication

TABLE 3 | Detailed results of three General Regression Models (GRMs).

	F	df	*p*	η_p^2	op	β (CI_{95})	r_p	r_{sp}
Whole headache group								
Diagnosis	**36.19**	**1.272**	**<0.0001**	**0.12**	**1.00**	**-0.49 (-0.65-−0.33)[a]**	**−0.34[a]**	**−0.20[a]**
Monthly headache days	**32.62**	**1.272**	**<0.0001**	**0.11**	**1.00**	**0.45 (0.29–0.60)**	**0.33**	**0.19**
Diagnosis × WFS1 genotype	**31.43**	**1.272**	**<0.0001**	**0.10**	**1.00**	**0.22 (0.14–0.30)[a]**	**0.32[a]**	**0.19[a]**
WFS1 genotype	**33.43**	**1.272**	**<0.0001**	**0.11**	**1.00**	**-0.20 (-0.27-−0.14)[a]**	**−0.33[a]**	**−0.19[a]**
Headache duration	0.04	1.272	0.84	0.00	0.06	0.01 (-0.11–0.14)	0.01	0.01
Age	0.01	1.272	0.93	0.00	0.05	0.01 (-0.12–0.13)	0.01	0.00
EM group								
Monthly headache days	**159.73**	**1.160**	**<0.0001**	**0.50**	**1.00**	**0.69 (0.58–0.80)**	**0.71**	**0.45**
Headache duration	**8.65**	**1.160**	**0.004**	**0.05**	**0.83**	**-0.26 (-0.44-−0.09)**	**-0.23**	**-0.11**
Attack frequency	**19.58**	**1.160**	**<0.0001**	**0.11**	**0.99**	**0.23 (0.13–0.34)**	**0.33**	**0.16**
Age	**7.22**	**1.160**	**0.008**	**0.04**	**0.76**	**0.23 (0.06–0.41)**	**0.21**	**0.10**
Drug type × WFS1 genotype	1.81	3.160	0.15	0.03	0.46	−0.11 (-0.22–0.00)[b]	−0.16[b]	−0.07[b]
Drug type	0.69	3.160	0.56	0.01	0.19	0.06 (-0.03–0.15)[b]	0.10[b]	0.05[b]
WFS1 genotype	0.65	1.160	0.42	0.00	0.13	0.04 (-0.06–0.14)[b]	0.06[b]	0.03[b]
MOH group								
WFS1 genotype	**19.71**	**1.95**	**<0.0001**	**0.17**	**0.99**	**-0.38 (-0.56-−0.21)[c]**	**-0.42[c]**	**-0.37[c]**
Drug type × WFS1 genotype	**3.94**	**3.95**	**0.01**	**0.11**	**0.82**	**0.29 (0.05–0.53)[c]**	**0.24[c]**	**0.20[c]**
Monthly headache days	**9.41**	**1.95**	**0.003**	**0.09**	**0.86**	**0.27 (0.10–0.45)**	**0.30**	**0.26**
Drug type	2.54	3.95	*0.06*	0.07	0.61	−0.27 (-0.52-−0.03)[c]	−0.20[c]	−0.19[c]
MOH duration	1.07	1.95	0.30	0.01	0.18	0.09 (-0.09–0.27)	0.11	0.09
Age	0.08	1.95	0.78	0.00	0.06	0.04 (-0.22–0.29)	0.03	0.02
Headache duration	0.02	1.95	0.89	0.00	0.05	0.02 (-0.23–0.27)	0.01	0.01

In bold the parameters of three GRM equations are significant independent predictors of monthly drug number, respectively in whole headache group (EM and MOH), EM group and MOH group. Parameters are sorted based on descending β values. df = degree of freedom; η_p^2 = partial eta-squared; op = observed power (alpha = 0.05); β (CI_{95}) = Beta (95% Confidence Interval); r_p = partial correlation; r_{sp} = semi-partial correlation.

[a]Effect level with the lowest p value among parameter estimates of whole headache group GRM: "diagnosis", EM vs. MOH; "WFS1 genotype", non-R/R vs. R/R; "diagnosis" × "WFS1 genotype", EM × non-R/R vs. MOH—R/R.

[b]Effect level with the lowest p value among parameter estimates of EM group GRM: "drug type", triptans vs. combinations; "WFS1 genotype", non-R/R vs. R/R; "drug type" × "WFS1 genotype", triptans—non-R/R vs. combinations — R/R.

[c]Effect level with the lowest p value among parameter estimates of MOH group GRM: "drug type", triptans vs. combinations; "WFS1 genotype", non-R/R vs. R/R; "drug type" × "WFS1 genotype", triptans—non-R/R vs. combinations—R/R.

overuse. So that, we were not dealing with patients affected by a pure chronic migraine (CM). The actual results seem to confirm our earlier hypothesis (10): the MOH clinical picture observed in our sample is an abuse-related disorder and not a simply chronic picture of migraine.

Even if the current headache classification takes together under the diagnosis of MOH (1) both patients who improve and those who do not improve with the detoxification protocols, we are probably facing two different clinical pictures (30). It would be interesting, in the future, to evaluate the role of WFS1 in MOH patients who remain chronic even after detoxification.

In patients with EM, only age and some headache characteristics related to the burden of disease (illness duration, headache attack frequency, and monthly headache days), not the WFS1 genotype, influenced drug consumption. We read this data as the proof of the lack of any effect of the examined polymorphism on headache characteristics and drug consumption behavior in EM. Thereby, the worsening effect of WFS1 genotype we observed only in MOH patients should be interpreted only in terms of influence not on migraine clinical features but on the severity of abuse behavior, exclusively expressed in MOH.

Consistently with our previous hypothesis (10), although no studies analyzed addictive behavior development and drug dependence related to WFS1 gene expression, we suppose that a partial dysfunction of wolframin is predictable in R/R subjects and could sustain the mechanism of addiction observed in our patients. In fact, wolframin could account for the substance dependence because of the limbic structures in which it is expressed, its aminergic and calcium modulation, and its influence on psychiatric, behavioral, and emotional features (31–35). Since it is already known that gene polymorphisms modulate neural plasticity (12, 36, 37), we hypothesize that WFS1 polymorphism could induce synaptic plastic modifications underpinning the development of medication overuse behavior by its modulation of the dopaminergic striatal pathway and intracellular calcium signaling (38–41). Interestingly, alterations of synaptic plasticity were observed in MOH patients, but not in patients with CM, even if they have similar clinical features, excluded the medication overuse that is absent in CM (30, 42).

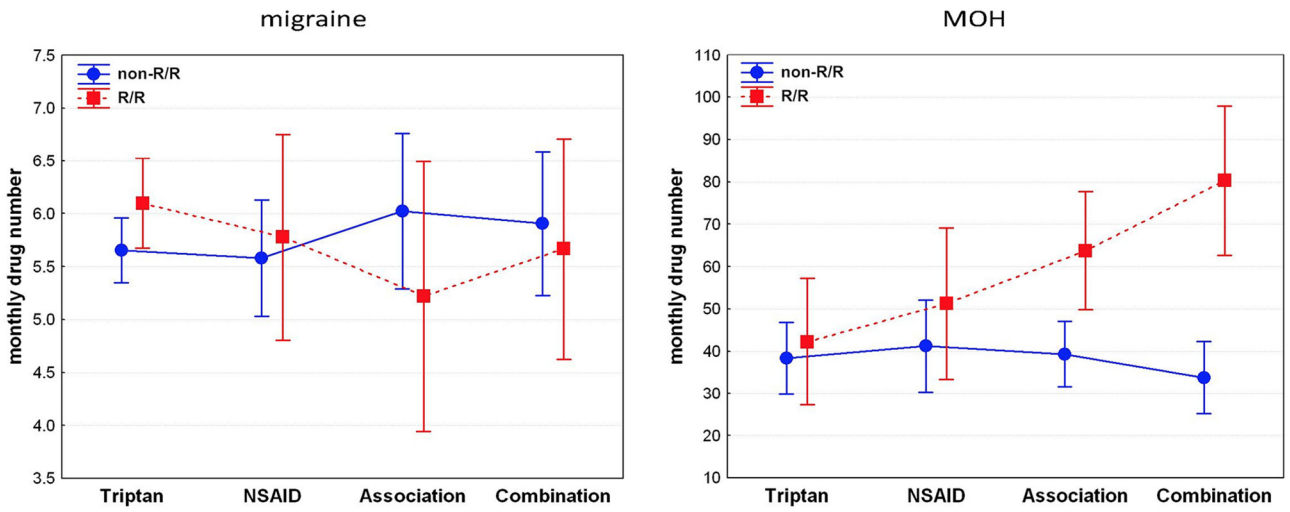

FIGURE 1 | R/R genotype is related to higher consumption of analgesics and preference for combination drugs in patients with MOH, not in migraineurs. NSAIDs: non-steroidal anti-inflammatory drug; associations (i.e., consumption of different types of drugs); combinations (i.e., drugs containing more than one active principle, including psychoactive compounds).

We argue that the examined WFS1 polymorphism may induce a more severe picture of abnormal synaptic plasticity, related to a more severe clinical picture in terms of higher number of symptomatic drug consumption, as we observed in our patients.

Since the effect we observed is higher in patients with MOH who overuse combination drugs, an alternative explanation is that the WFS1 His611Arg polymorphism somehow influences the drug-induced cortical anomalies observed in patients with MOH that are related to the class of symptomatic drugs. In fact, it is well known that the different classes of overused drugs influence the cortical activity of patients with MOH in different ways (43, 44); in patients with MOH, the higher these abnormalities, the higher the drug consumption (44). It is possible to speculate that WFS1 His611Arg could induce the anomalies of cortical activity related to medication overuse and that it results in patients' increased need for drug consumption.

Moreover, we found that the allelic distribution was similar among groups, allowing us to speculate about the possible mechanisms with which WFS1 His611Arg acts in MOH patients. Our results suggest that the polymorphism is not a predisposing factor to development of EM or MOH, i.e., the worsening effect observed among patients with MOH seems to be exerted only after the development of the secondary form of chronic headache due to the medication overuse. It is plausible that, in terms of headache worsening, the genetic polymorphism is silent in EM. When medication overuse leads to the development of MOH, the polymorphism starts to express its worsening effect only because of its potential to affect the abuse behavior (that worsens MOH but does not worsen EM), plausibly by a pharmacogenomics effect (9). Although the genomic aspects of headache have been widely studied for many years (45), pharmacogenomics is poorly explored in headache medicine, even if it is regarded as a promising field of research in various diseases (46). Our view on these results about the entity of medication overuse as a genetically influenced marker of MOH gravity is consistent to another study on abuse behavior in which a genetic background did not lead to the development of the heroin addiction, but only to its higher severity (47).

Finally, certain limitations of the present study should be acknowledged. First, we lack a measure of gene expression to assess if the type of overused drug, detoxification, or His611Arg polymorphism influence WFS1 expression. The eventuality of a drug (or detoxification)-induced epigenetic modification of the observed pharmacogenomics phenomena would result in a very interesting "epipharmacogenomics" effect. Another shortcoming of our study is the absence of a follow-up phase for the analysis of the recurrence of MOH, to assess if the examined polymorphism would result in a higher MOH relapse rate. Unfortunately, the perspective design of the study, the use of different kinds of prophylactic treatments after detoxification, and the long time required to have a recurrence of MOH do not allow the possibility of including the relapse rate in the present study. We plan to pursue this type of observation in further studies.

In summary, because the WFS1 His611Arg polymorphism seems to be unable to influence the development and clinical features of migraine, we suppose that the observed worsening of MOH due to the polymorphism is likely driven by the R/R genotype-related proneness to abuse and, in turn, that the monthly drug consumption in MOH patients is not necessarily the only expression of headache severity. In fact, proneness to abuse is non-influential on EM clinical picture (development and severity) but can worsen MOH. In other terms, since drug consumption is the hallmark of MOH, this form of chronic headache is not a simple worsening of a preexisting migraine but a complex syndrome in which the development of an addictive behavior disorder in a headache

patient induces a new clinical picture, sustained by a specific background not shared with EM. We can suppose that drug-induced effects, in joint to a specific genetic background, neuroadaptation, and environmental factors, contribute to the complex mechanisms leading to the development of MOH, despite the WFS1 genotype that, though it may seem strange, stops to be silent only after the start of medication overuse.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CDL designed the study and participated to the manuscript draft. GDL performed the statistical analysis and participated to the manuscript draft. GC performed the clinical data recruitment and participated to the manuscript draft. VP performed the ophthalmologic evaluations, aided in interpreting the results, and worked on the manuscript. GG performed the molecular analysis of samples. FS performed the molecular analysis of samples. EP performed the molecular analysis of samples. FP supervised the work and revised the final version of the manuscript. All authors discussed the results and commented on the manuscript.

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Pathophysiological Bases of Comorbidity in Migraine

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Despite that it is commonly accepted that migraine is a disorder of the nervous system with a prominent genetic basis, it is comorbid with a plethora of medical conditions. Several studies have found bidirectional comorbidity between migraine and different disorders including neurological, psychiatric, cardio- and cerebrovascular, gastrointestinal, metaboloendocrine, and immunological conditions. Each of these has its own genetic load and shares some common characteristics with migraine. The bidirectional mechanisms that are likely to underlie this extensive comorbidity between migraine and other diseases are manifold. Comorbid pathologies can induce and promote thalamocortical network dysexcitability, multi-organ transient or persistent pro-inflammatory state, and disproportionate energetic needs in a variable combination, which in turn may be causative mechanisms of the activation of an ample defensive system with includes the trigeminovascular system in conjunction with the neuroendocrine hypothalamic system. This strategy is designed to maintain brain homeostasis by regulating homeostatic needs, such as normal subcortico-cortical excitability, energy balance, osmoregulation, and emotional response. In this light, the treatment of migraine should always involves a multidisciplinary approach, aimed at identifying and, if necessary, eliminating possible risk and comorbidity factors.

Keywords: CNS disorders, thalamocortical network dysexcitability, trigeminovascular system, migraine threshold, energetic balance

INTRODUCTION

It is commonly accepted that migraine is a pathology of the nervous system. For many years, attention has been focused on the predominant role of the brainstem in the genesis of migraine attacks and, probably, in its recurrence (Weiller et al., 1995; Bahra et al., 2001; Stankewitz et al., 2011). This role of the brainstem is closely linked to its physiological actions such as its ability to set the signal-to-noise ratio of cortical activity directly or indirectly through the thalamus (Mesulam, 1990), to control the neuro-vascular coupling at the cortical level (Raichle et al., 1975; Goadsby et al., 1982; Edvinsson et al., 1983), probably playing a role in the unleashing of the migraine aura, and its contribution in the development of the central sensitization processes (Zambreanu et al., 2005; Lee et al., 2008). The latter action is likely to be mediated both by the caudal trigeminal nucleus and by other brainstem nuclei and is at the basis of some clinical manifestations of episodic migraine (EM) and chronic migraine (CM), such as phono/photo-phobia and osmophobia (Okamoto et al., 2009; Stankewitz et al., 2011; Joffily et al., 2016). More recently, however, functional neuroimaging studies renewed the interest in the hypothalamus as the possible generator of migraine. They showed that the hypothalamus activates shortly before the beginning of migraine attack, during the period in which some patients experience premonitory symptoms, and during the attack, it displays altered connection with the spinal trigeminal nucleus (Schulte and May, 2016; Schulte et al., 2020). The hypothalamus and the brainstem are not the only brain structures involved in the pathophysiology of migraine. There is various evidence of functional and structural abnormalities of the thalamus and thalamus–cortical fiber bundles in migraineurs, especially between attacks when the patient has no pain but is in the potency of its recurrence (Coppola et al., 2005, 2014; DaSilva et al., 2007; Rocca et al., 2008). As for the brainstem, also the thalamus may contribute to the clinical manifestation of migraine (Burstein et al., 2010; Noseda et al., 2010; Russo et al., 2014). Both functional and structural abnormalities have been consistently detected also at the cortical level, predominantly in the visual areas (Puledda et al., 2019), but no cortex has been spared, not even the cerebellar one (Coppola et al., 2020).

The peripheral nervous system is also evidently involved. This is the case of the sensory afferences of the first branch of the trigeminal nerve that innervate the small meningeal arteries to form the trigeminal–vascular system. Various scientific evidence suggests that the migraine attack begins at that level, i.e., with the release of the vasoactive polypeptide calcitonin gene-related peptide (CGRP) and the consequent triggering of the so-called peripheral sensitization (Burstein et al., 2000a). The latter consists in the release at a peripheral level of pro-inflammatory substances that sensitize the meningeal nociceptors and constitute a neurogenic pro-inflammatory state, which, if it persists long enough, triggers the aforementioned central sensitization and, therefore, the procession of symptoms and neurological signs that accompany migraine pain (Edvinsson, 2019). The animal model shows that the activation of first-order neurons of the trigeminal–vascular system can be evoked by cortical spreading depression (CSD), an electrocortical phenomenon thought to be at the base of the migraine aura (Bolay et al., 2002).

This important and widespread involvement of the central and peripheral nervous system is sustained by genetics. Unfortunately, the genetics of rare, familiar forms of migraine with hemiplegic aura does not seem to be the same as the most common forms of migraine with and without aura (Hovatta et al., 1994; Monari et al., 1997; Kim et al., 1998; Jones et al., 2001; Brugnoni et al., 2002; Noble-Topham et al., 2002; Wieser et al., 2003). But more recent genome-wide association studies carried out on a large cohort of migraine patients have identified a number of loci associated with the risk of migraine. These loci show enrichment for genes expressed in vascular and muscular tissues (Gormley et al., 2016), as well as for genes involved in glutamate homeostasis, synaptic plasticity, and pain-related pathway (Chasman et al., 2011), However, metabolic aspects should not be overlooked. In fact, evidence from neuroimaging (Sándor P. et al., 2005; Lodi et al., 2006; Lisicki et al., 2018) and genetic (Sparaco et al., 2006; Di Lorenzo et al., 2009) studies, as well as controlled pharmacological trials (Schoenen et al., 1998; Sândor P. S. et al., 2005), shows how mitochondrial energy metabolism can be altered in migraine and can predispose to the recurrence of attacks.

The simultaneous presence of multiple comorbidities can further complicate the clinical and prognostic presentation of migraine. Various disorders can occur as comorbidities with migraine and include neurological, psychiatric, cardio- and cerebrovascular, gastrointestinal, metaboloendocrine, painful, and immunological conditions. Each of these has its own genetic load and shares some common characteristics with migraine. In fact, all the aforementioned pathologies are associated with migraine in both adults and children (Scher et al., 2003b, 2005, 2008; El-Metwally et al., 2004; Buse et al., 2019). For these reasons, some researchers believe that there may be a common genetic background that predisposes some people to migraines and other comorbidities (Burch et al., 2019).

In this article, we review, narratively, published data describing these migraine comorbidities, and then we further discuss available evidence for their shared pathophysiological mechanisms.

CEREBROVASCULAR DYSFUNCTION AND MIGRAINE

Scientific Evidence of Comorbidity and Pathophysiological Links

A meta-analysis including over a million subjects concluded that migraineurs present an increased long-term risk of cardiovascular and cerebrovascular events (Mahmoud et al., 2018). The relative risk varies from 1.56 to 2.41 in migraine with aura (MA) to 1.11–1.83 in migraine without aura (MO) (Øie et al., 2020).

The physiopathological link between stroke and migraine is multifaceted: different aspects from thromboembolism,

hemodynamic dysfunction, to energetic failure. They each act as part of a puzzle piece.

Thrombosis and Embolism

Clinical atherosclerosis has been cleared as being responsible for the increased vascular risk in migraine patients, but some studies reported that subclinical atherosclerosis (i.e., intima-media thickening) could be a marker of endothelial dysfunction, linking vascular disease to migraine (Stam et al., 2013; Van Os et al., 2017; Magalhães and Sampaio Rocha-Filho, 2018; Magalhães et al., 2019; Yilmaz Avci et al., 2019). Nitric oxide (NO), endothelin-1, von Willebrand factor, plasminogen activator inhibitor-1, angiotensin II, prostacyclin, and platelet-activating factor are among the substances secreted by the endothelium in reaction to local environment changes, which can result in local inflammation and thrombosis. This phenomenon is defined as endothelial activation (Boulanger, 2018).

The endothelial activation was found guilty of predisposing patients with migraine to vascular diseases.

A pro-inflammatory and pro-coagulative milieu was consistently demonstrated in migraineurs, particularly in MA, CM, and women, predominantly in the premenopausal period (Liman et al., 2015; Ferroni et al., 2017; Tietjen and Collins, 2018). Nevertheless, genetic studies on polymorphism for thrombophilic mutations were not consistent; although some reported an increased prevalence of pro-thrombotic polymorphisms (Lippi et al., 2015; Cecchi et al., 2018), a definitive conclusion is difficult to draw (Malik et al., 2016). High estrogen state is probably the most significant factor associated with stroke occurrence in migraine, especially if accompanied by cigarette smoking, particularly in MA patients (Kurth et al., 2012). Finally, platelet activation has been suggested as another possible intermediary to explain the increased vascular risk via augmented aggregation and interaction with leucocytes (Borgdorff and Tangelder, 2012; Danese et al., 2014). Supporting this evidence, antiplatelet therapy seems to relieve MA (Turk et al., 2017), also in patients without patent foramen ovale (PFO) (Altamura et al., 2019b).

It is not completely understood if migraine attacks determine endothelial activation as the results of neural activation and oxidative stress or the other way around: transient hypoperfusion due to the pro-inflammatory and pro-thrombotic states may favor neural distress, inducing migraine (Dalkara et al., 2010). In this scenario, the high prevalence of PFO observed in MA patients offers the pathway through which micro-emboli can reach the cerebral circulation (Del Sette et al., 1998). Interestingly, in the Oxford Vascular Study cohort, migraine was the factor most strongly associated with cryptogenic TIA and ischemic stroke, suggesting a causative role for migraine or a shared etiopathogenesis (PFO?) (Li et al., 2015). As a further complication, migraine with visual aura is a risk factor for atrial fibrillation (Sen et al., 2018), while the relation between migraine and carotid artery dissection is still elusive, although they may share a common genetic substrate (Malik et al., 2016; De Giuli et al., 2017; Kok et al., 2018).

Hemodynamic Dysfunction

In addition to monogenic diseases with cerebral arteriopathy and migraine typical features [i.e., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)], a meta-analysis of susceptibility genes for migraine identified enrichment for genes expressed in vascular and smooth muscle tissues, consistent with a vascular involvement (Gormley et al., 2016).

Cerebral hemodynamics is a complex system that allows adequate brain perfusion also in conditions that pose cerebral blood supply at risk. It relies on the orchestral action of neurogenic, myogenic, endothelial, and metabolic responses.

The neurogenic control is achieved by neurotransmitters with vasoactive properties [CGRP, serotonin, pituitary adenylate cyclase-activating polypeptide (PACAP), and NO] released by sympathetic, parasympathetic, and sensory neurons and in smaller arterioles in response to the neuronal firing (Frederiksen et al., 2019). These neurotransmitters have a key role also in migraine attacks. Similarly, the endothelium plays a significant role in vessel caliper regulation via the paracrine secretion of substances such as NO, adrenomedullin, and endothelin-1 that have been largely involved in migraine physiopathology (Kis et al., 2003; Tietjen and Collins, 2018). The myogenic control regulates vessel caliper in response to change in transmural pressure (i.e., autoregulation), while the metabolic response allows vasodilation following the local increase in H+ concentration [vasomotor reactivity (VMR)].

Cerebral VMR is a marker of hemodynamic efficiency and correlates with stroke risk (Reinhard et al., 2014). During migraine attacks, particularly in the aura phase of MA, VMR, and neurovascular coupling are impaired as demonstrated by experimental studies on CSD (Harer and von Kummer, 1991; Ayata and Lauritzen, 2015). Conversely, in the interictal period, most studies reported a preserved or higher VMR in migraineurs compared with controls, especially in MA patients (Thomsen et al., 1995; Silvestrini et al., 1996, 2004; Valikovics et al., 1996; Kastrup et al., 1998; Fiermonte et al., 1999; Dora and Balkan, 2002; Vernieri et al., 2008; Chan et al., 2009; Altamura et al., 2019a, 2020), with some exceptions suggesting an impaired VMR mainly in the posterior circulation (Totaro et al., 1997; Silvestrini et al., 2004; Perko et al., 2011b; Rajan et al., 2014). To note, cerebral VMR seems to be less effective in CM (Akgün et al., 2015; González-Quintanilla et al., 2015). Moreover, estrogen use was associated with lower VMR in MA patients, curtailing their hemodynamic resources (Altamura et al., 2019b).

Cerebral autoregulation was investigated by obtaining controversial results for the anterior circulation (Müller and Marziniak, 2005; Reinhard et al., 2007), while it resulted in impairment in the posterior circulation only in MA patients (Reinhard et al., 2012).

How and whether the endothelium activation is implicated in this abnormal hemodynamics are a matter of several investigations (Yetkin et al., 2006; Vanmolkot et al., 2007; Napoli et al., 2009; Butt et al., 2015; Heshmat-Ghahdarijani et al., 2015). The endothelial reactivity can be studied peripherally by brachial artery flow-mediated dilation (FMD), which reflects the arterial

tone self-regulation mediated by the endothelium in response to changes in the local environment (Tremblay and Pyke, 2018). An altered FMD is associated with a higher vascular risk (Shechter et al., 2014). Most studies suggest that FMD is preserved or increased in episodic MO and MA (Vanmolkot and de Hoon, 2010; Vernieri et al., 2010; Perko et al., 2011a; Larsen et al., 2016; Altamura et al., 2018, 2020) and reduced in CM (González-Quintanilla et al., 2015).

In summary, cerebral hemodynamics in the anterior circulation is preserved or hyper-reactive in migraine patients and especially in MA, supporting mostly a protective rather than impaired hemodynamics. Moreover, the hemodynamic efficiency seems to improve over time in MA patients (Gollion et al., 2019), possibly as the result of frequent ischemic threats (i.e., ischemic preconditioning). On the other hand, VMR may be impaired during attacks, and both cerebral and peripheral hemodynamics seem to be altered in the chronic condition. Finally, the frequent use of triptans or ergots can disrupt the hemodynamic balance toward vasoconstriction (Roberto et al., 2014).

Energetic Failure

The migraine brain seems to be easy prey for vascular insults. Phylogenetically, CSD can be interpreted as a metabolic reset of cerebral activity occurring when energetic demands overcome the resources, aiming at restoring homeostasis and reducing harmful oxidative stress levels (Meldrum Robertson et al., 2020). However, the criticality is not the scarce energy supply but its excessive requirement, due to the transient or persistent sensory hypersensitivity and its inefficient use. Several evidence supports this hypothesis: from the genetic link where mitochondrial disturbances and migraine coexist [e.g., mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)] to the common observation that being starved is an important trigger for migraine attacks. The energetic frailty of the migraine brain makes it particularly vulnerable to ischemic damage. Familial hemiplegic migraine (FHM)1 transgenic mouse models present a more rapid expansion of infarct volumes and larger perfusion deficits (Eikermann-Haerter et al., 2012). The same observation was clinically made in humans: among stroke patients, migraineurs, and in particular those with MA, displaying a reduced ratio between infarcted and hypo-perfused tissue (Mawet et al., 2015; Pezzini et al., 2018). Besides, patients with migraine present more often with cortical infarcts (Øygarden et al., 2014).

These findings strongly support the susceptibility of the migraine brain (mainly with aura) to milder ischemic conditions.

In summary, when investigating the case of the migraine–stroke connection, we should look for a criminal conspiracy where all the suspects of the neuro-vascular-endothelial unit have a guilty role.

METABOLIC AND ENDOCRINE COMORBIDITIES OF MIGRAINE

Metabolic diseases, like diabetes and obesity, as well as endocrine diseases are highly prevalent conditions in the general population. Recently, several studies showed the presence of a complex and intriguing comorbidity between migraine and these disorders, suggesting new pathogenetic mechanisms for migraine.

Scientific Evidence of Comorbidity

Insulin Resistance, Metabolic Syndrome, and Migraine

Insulin resistance (IR) is a condition characterized by a subnormal physiological response to normal insulin concentrations, with increased quantities of insulin produced to maintain adequate intracellular glucose concentrations. Metabolic syndrome (MetS) is a syndrome characterized by a cluster of metabolic abnormalities including hyperglycemia, hypertension, dyslipidemia, abdominal obesity, and a pro-inflammatory state. These two medical conditions are interrelated and share common underlying mediators and pathways.

Since the first description in 2005 (Rainero et al., 2005), several studies showed the presence of an association among migraine, IR, and MetS (Cavestro et al., 2007; Bhoi et al., 2012; Fava et al., 2014). Glucose plasma concentrations are significantly increased during spontaneous migraine attacks (McCarthy et al., 2001). Hyperinsulinemia is associated with a 5.7-fold higher risk for migraine (Netzer et al., 2008). Patients with CM are more insulin resistant than patients with EM and controls (Zhang et al., 2020). In comparison with healthy controls, patients with MA are at higher risk of MetS [odds ratio (OR) = 3.45; 95% CI: 1.63–7.29], while MO individuals are not (Gruber et al., 2010). A recent study showed that MetS is significantly associated with CM (OR = 5.342, $p = 0.032$), and the risk for MetS increases significantly in patients with CM and medication-overuse headache (OR = 12.68, $p = 0.007$; Fava et al., 2014). Furthermore, genetic studies provided evidence that polymorphisms of the insulin-receptor gene (INSR) are associated with migraine (He et al., 2015; Streel et al., 2017). A recent systematic review of the observational studies linking the MetS with migraine has identified several weaknesses in the available research and suggested the need for future investigations using more rigorous methodology (Andreeva et al., 2019). However, a modulation of the metabolic pathway linked to insulin metabolism might be of relevance in migraine prophylaxis.

Diabetes and Migraine

Several studies investigated the relationship between diabetes and migraine. Epidemiological data showed that migraine patients are not at increased risk of developing and type 2 diabetes mellitus (T2DM) (López-De-Andrés et al., 2018). Data from the Nord-Trøndelag Health Surveys showed that patients with type 1 diabetes showed a lower prevalence of migraine (OR = 0.47, 95% CI: 0.26–0.96) than did subjects without DM (Hagen et al., 2018).

A recent study showed a lower risk of T2DM in women with active migraine compared with women with no migraine history [univariate hazard ratio, 0.80 (95% CI: 0.67–0.96)]. Furthermore, the authors found a linear decrease in the prevalence of active migraine during the 24 years before a diagnosis of T2DM (Fagherazzi et al., 2019).

Biological mechanisms underlying the protective effect of diabetes on the risk of developing migraine attacks are, at present, unclear.

Obesity and Migraine

Overweight and obesity are both highly prevalent medical conditions, associated with substantial personal and societal impact. Population studies have consistently identified an association between obesity, headache, and particularly migraine (Peterlin et al., 2010; Pavlovic et al., 2017; Kristoffersen et al., 2020). A recent meta-analysis, encompassing 288,981 participants in 12 different studies, showed that the age- and sex-adjusted pooled risk for migraine in obese patients is increased by 27% in comparison with those of normal weight (OR = 1.27; 95% CI: 1.16–1.37, $p < 0.001$). In underweight individuals, the pooled risk of migraine was marginally increased by 13% (OR = 1.13; 95% CI: 1.02–1.24, $p < 0.001$; Gelaye et al., 2017). Plasma concentrations of adipokines, like leptin, adiponectin, and resistin, are significantly increased in both EM and CM, suggesting a role for these pro-inflammatory mediators in the comorbidity between obesity and migraine (Peterlin et al., 2016; Rubino et al., 2017).

Comorbidity between migraine and obesity as well as the role of several dietary factors in headache attacks prompted the investigations of different dietary regimens for migraine prevention (Gazerani, 2020; Hindiyeh et al., 2020). Finally, the ketogenic diet, a diet that leads to the elevation of ketone bodies, has shown great promise in the prevention of migraines (Di Lorenzo et al., 2015, 2019b).

Hypothyroidism and Migraine

Hypothyroidism is a frequent medical condition with a lifetime prevalence of 2%. Several studies showed an association between migraine and hypothyroidism, in both adolescents and adults, with hypothyroidism being significantly more prevalent in subjects with CM compared with those with EM (Fallah et al., 2012; Spanou et al., 2019). Data from the Fernald Medical Monitoring Program in the USA demonstrated that headache disorders are risk factors for the development of new-onset hypothyroidism, with migraine patients showing an increased risk of 41% of developing this disorder (Martin et al., 2017). A recent, case–control study showed that patients with subclinical hypothyroidism have an increased risk of developing migraine (Rubino et al., 2019). Taken together, these studies suggest that migraine and hypothyroidism are linked by a bidirectional relationship. Genetic and immune mechanisms may explain this association.

Endometriosis and Migraine

Observational studies indicated that migraine and endometriosis co-occur within individuals more than expected by chance (Yang et al., 2012). A recent systematic review found a significant association between endometriosis and the risk of migraine (OR = 1.56; 95% CI: 1.21–1.90) (Jenabi and Khazaei, 2020). The analysis of endometriosis phenotypes showed that ovarian endometrioma and deeply infiltrating endometriosis were significantly more frequent in migraine female patients than in controls (OR = 2.78; 95% CI: 1.11–6.98 and OR = 2.51; 95% CI: 1.25–5.07, respectively) (Maitrot-Mantelet et al., 2020). The biological mechanisms underlying this comorbidity remain unknown. Interestingly, a recent genome-wide association study found a positive and highly significant genetic correlation ($p = 2.30 \times 10^{-25}$) between endometriosis and migraine and suggested a role for genes involved in interleukin-1 receptor binding, focal adhesion-PI3K-Akt-mTOR-signaling, mitogen-activated protein kinase (MAPK), and tumor necrosis factor-alpha (TNF-α) signaling in the association between these two traits (Adewuyi et al., 2020).

Supposed Pathophysiological Mechanisms

The pathophysiological mechanisms underlying the complex association between migraine, metabolic, and endocrine disease are still under investigation; and additional, rigorous studies are needed. However, some suggestions are of particular interest.

Investigations of metaboloendocrine comorbidities of migraine further support the role of shared molecular genetic mechanisms between all these highly prevalent medical conditions. Migraine and diabetes, obesity, and endometriosis are complex genetic traits sharing common genes as well as common metabolic pathways (McCarthy et al., 2001; Netzer et al., 2008; Adewuyi et al., 2020). Further investigating these pathways will allow us to disentangle the biochemical mechanisms of migraine.

An increasing amount of evidence suggests that migraine patients have a reduced cerebral energy reserve, facilitating the onset of headache attacks under stress. The study investigating the level of metabolism with fluorodeoxyglucose (FDG)-PET and the level of functional cortical activity with evoked potentials showed a low metabolism of the cortical areas and high functional activity in migraineurs compared with healthy subjects (Lisicki et al., 2018). This abnormal functional activity in migraineurs, defined as cortical hyperresponsivity (Coppola et al., 2007), can be normalized through non-pharmacological therapies as a ketogenic dietary regimen (Di Lorenzo et al., 2016, 2019a). This is consistent with the ability of ketogenic feeding of potentiating mitochondrial energy metabolism (Bough et al., 2006; Maalouf et al., 2007).

Migraineurs have altered mitochondrial functioning (Sparaco et al., 2006; Di Lorenzo et al., 2009), and drugs like riboflavin and Co-Enzyme Q10, both physiologically implicated in the mitochondrial respiratory chain, are efficacious in disease prophylaxis (Schoenen et al., 1998; Sândor P. S. et al., 2005). In this context, the study of the metaboloendocrine comorbidity of migraine supports the notion that a reduction of cerebral metabolism is a key factor in the disease pathogenesis (Lisicki and Schoenen, 2020). Binding of insulin to its receptor induces structural changes leading to auto-phosphorylation of various tyrosine residues. The final effect of insulin receptor stimulation includes translocation of the glucose transporter proteins (GLUT1 and GLUT4), promoting glucose influx in different cells. Besides, insulin receptors regulate several complex physiological actions like the synthesis and storage of carbohydrates, lipids, and protein. Dysfunction in the insulin signaling pathway may,

therefore, explain the reduced metabolism observed in patients with migraine.

Insulin sensitivity is clearly impaired in migraine, even in young, non-obese, non-diabetic, normotensive patients. Plasma glucose and insulin levels increase during spontaneous migraine attacks, leading to impairment in complex metabolic patterns. Furthermore, studies with FDG-PET in migraine patients showed glucose hypometabolism in several brain areas, like the occipital, orbitofrontal, and rostral anterior cingulate cortices (Magis et al., 2017; Lisicki et al., 2018). However, the precise mechanisms of glucose metabolism impairment in migraine need to be further elucidated.

EPILEPSY AND MIGRAINE

Scientific Evidence of Comorbidity

Epilepsy and migraine may mimic each other, and occipital lobe seizures may be easily misinterpreted as migraine with visual aura (Panayiotopoulos, 1999). The frequency of epilepsy among people with migraine (range 1–17%) is higher than in the general population (0.5–1%), just as the prevalence of migraine among patients with epilepsy is also higher than that reported in individuals without epilepsy (Lipton et al., 1994).

A cross-sectional study (Gameleira et al., 2013) conducted in adults with epilepsy showed a greater tendency of comorbidity with headaches (OR = 1.6, $p = 0.077$), which occurred in 66.1% of the cases; the highest occurrence was of migraine (32.9% of the patients), followed by tension-type headaches (TTHs) (9.2%). Yet other studies have reported a significant association with headaches, particularly migraine-type headaches, being linked to the frequency of seizures (Wang et al., 2014a,b; Mainieri et al., 2015; Mameniškienė et al., 2016; Çilliler et al., 2017). In a more recent adult large sample (15,133 subjects), migraine was also confirmed to be associated more likely with epilepsy (Buse et al., 2020). As further evidence in favor of a non-random association, a more recent systematic review (Duko et al., 2020), conducted on 5,564 study participants, reported a higher prevalence (48.4%, ranging from 46 to 52.2%) of headache among epileptic patients.

Yamane et al. (2004) found that among epileptic children, 46% of patients suffer also from headaches, of which 43.5% are classified as migraine type. In some specific childhood epilepsy syndromes (such as benign occipital epilepsy of childhood with occipital paroxysms and benign rolandic epilepsy), migraine/headaches appear to be more prevalent (Andermann and Zifkin, 1998; Clarke et al., 2009). Piccinelli et al. (2006) found electroencephalography (EEG) interictal abnormalities in 16 (12.8%) out of 137 children and adolescents with headache, particularly in those with MA. In a large, consecutive, pediatric headache population, Toldo et al. (2010) found a strong association with epilepsy; this significant strong correlation was confirmed in children (Baca et al., 2011) and adolescents (Lateef et al., 2012).

The literature shows somewhat conflicting data regarding the epidemiological aspects in the various age groups (Lipton et al., 1994; Tonini et al., 2012). This may be attributed to the co-occurrence (synergistic and/or divergent) of confounding variables adopted in the different sampling methods and study designs. These conflicting results may partly be explained by differences in the target populations, study design, age range, and methods, by inclusion criteria that are limited to referral patients with epilepsy or tertiary headache centers, by the lack of appropriate control groups, and/or by different or ill-defined diagnostic criteria (Belcastro et al., 2012; Tonini et al., 2012).

Children are more likely to have an autonomic symptomatology in both epilepsy and headache attacks (Kasteleijn-Nolst Trenité and Parisi, 2012; Parisi et al., 2012a). Moreover, they may have isolated, long-lasting ictal autonomic manifestations, while ictal autonomic manifestations (in both epilepsy and headache) in adults are usually associated, whether simultaneously or sequentially, with other motor or sensory ictal signs and symptoms (Kasteleijn-Nolst Trenité and Parisi, 2012).

So despite the limited number of studies (Yamane et al., 2004; Piccinelli et al., 2006; Toldo et al., 2010), the framework assumes markedly different shapes in the pediatric population, as stressed above, and this is, probably, why the ictal epileptic headache (IEH) (Parisi et al., 2012b) is a phenomenon that occurs with much higher probability among the infantile epileptic population (Belcastro et al., 2012).

Supposed Pathophysiological Mechanisms

Glutamatergic (Jen et al., 2005), serotoninergic (Johnson and Griffiths, 2005), dopaminergic metabolism (Chen, 2006), and ion channel (sodium, potassium, and chloride) function might be impaired in both epilepsy and migraine (Pietrobon, 2010). In particular, it is likely that voltage-gated ion channels play a critical role in the pathways associated with migraine and epilepsy (Di Stefano et al., 2020). After blockade of either the P-/Q-type Ca^{2+} channels or the NMDA receptors, CSD cannot be induced in wild-type mouse cortical slices. By contrast, the blockade of N- or R-type Ca^{2} channels only has a slight inhibitory effect on the CSD threshold and velocity of propagation. These findings support a model according to which the initiation and propagation of the CSD involved in migraine require the influx of Ca^{2+} through pre-synaptic P-/Q-type Ca^{2+} channels, which in turn releases glutamate from the recurrent cortical pyramidal cell synapses and activates NMDA receptors (Hamberger and van Gelder, 1993; Lönnqvist et al., 2009).

CSD may be considered one of the links between headache and epilepsy (Parisi, 2009; Parisi et al., 2012a, 2013, 2015) and is characterized by a slowly propagating wave of sustained strong neuronal depolarization that generates transient intense spike activity, followed by neural suppression, which may last for minutes. As mentioned before, in animal models, CSD seems to be able to activate the trigeminovascular system, inducing the cascade release of numerous inflammatory molecules and neurotransmitters, which in humans may result in the ignition of a migraine attack (Parisi, 2009; Belcastro et al., 2011; Parisi et al., 2012a).

Both basic and clinical neurosciences support that CSD and an epileptic focus may facilitate each other, though with different extents. The required threshold is suggested to be lower for CSD than for a seizure, which would explain why it is far more likely that an epileptic patient presents a peri-ictal headache than vice versa (Parisi et al., 2008, 2012a, 2015, 2019; Parisi, 2009; Belcastro

et al., 2011). The triggering causes, which may be environmental or individual (whether genetically determined or not), result in a flow of ions that mediate CSD through neuronal and glial cytoplasmic bridges rather than through interstitial spaces, as instead usually occurs in the spreading of epileptic seizures (Parisi et al., 2008, 2012a; Parisi, 2009; Belcastro et al., 2011).

Migraine and epilepsy have an important genetic component, with strong evidence pointing to a shared genetic basis between headache and epilepsy emerging from clinical/EEG and genetic studies on FHM (Di Stefano et al., 2020). Genetic variants in the same gene may be associated with migraine in some cases and with epilepsy in others. Accordingly, the genetic role as link to explain the comorbidity between headache and epilepsy and other paroxysmal disorders have also been recently underlined (Crompton and Berkovic, 2009; Ebrahimi-Fakhari et al., 2015; Galizia et al., 2015; Barbieri et al., 2019; Di Stefano et al., 2020).

Lastly, it is intriguing to stress that IEH cannot just be classified with a unique mode of pain transmission because different afferent/efferent nociceptive types of receptors and central (afferent and efferent) pathways are involved. Moreover, given the complexity of the networks involved, it is likely that the cortical projections of headache pain are widespread, also involving the areas belonging to neurolimbic network (insula, cingulate cortex, pre-frontal cortex, amygdala, and other parts of the limbic system) and not just the primary sensory-sensitive areas. This is the reason why we could consider most cases of IEH as autonomic seizures (Belcastro et al., 2011; Parisi et al., 2012a, 2019) and not just "a rare form of painful seizure," as conversely suggested, recently, by others (Hwang et al., 2019).

PSYCHIATRIC COMORBIDITY

Scientific Evidence of Comorbidity

Migraine condition, especially when chronic, represents a huge burden, as it affects different aspects of daily living, ranging from occupation and academic to familial and social scenarios (Leonardi et al., 2005). Patients suffering from migraine might experience a higher prevalence of psychiatric comorbidities than do non-migraineurs (Burch et al., 2019). Indeed, a large body of literature shows that psychiatric disorders are highly associated with migraine, e.g., major depressive disorder (MDD), bipolar disorder (BD), post-traumatic stress disorder (PTSD), and anxiety disorders. Moreover, such comorbidities increase with the frequency of migraine episodes. Indeed, people with a 14-day or more occurrence of migraine have an adjusted OR of 6.4 for depression and 6.9 for anxiety disorders (Zwart et al., 2003). Being affected by psychiatric disorders is considered an independent modifiable factor of progression toward chronification of migraine and a tendency to medication overuse (Scher et al., 2008; Sances et al., 2010). Nonetheless, emotional distress is commonly recognized as migraine trigger (Kelman, 2007).

Depressive Disorders and Migraine

Depression is up to 2.5 times more prevalent in patients with migraine than in the general population, with 40% of them reporting depressive episodes during their lifetime (Lipton et al., 2000; Jette et al., 2008). As these two conditions are often comorbid, they can both lead to a higher degree of social life, family life, and career disability (Rossi et al., 2005; Bigal and Lipton, 2009). Indeed, evidence shows a consistent amount of underlying pathophysiological mechanisms shared by both disorders (Amoozegar, 2017). Currently, no international society has issued guidelines on the treatment of migraine comorbid with depression yet. Few medications are proven to target both disorders, and therefore, they might be used in their clinical management. Among these, venlafaxine and amitriptyline (Peck et al., 2015) provided the best evidence. Notwithstanding, new promising approaches, such as repetitive transcranial magnetic stimulation (rTMS), are reporting encouraging results in either condition (Leung et al., 2020).

Bipolar Disorders and Migraine

Up to 55% of migraineurs are also diagnosed with BD (Dresler et al., 2019). Such prevalence is particularly relevant in patients with type II BD (Low et al., 2003), with headache usually preceding the onset of manic episodes (Ortiz et al., 2010). This association seems to be bidirectional, as one third of patients with BD suffer from migraine (Leo and Singh, 2016). Treatment-wise, evidence has shown multiple therapeutic choices to be effective in either disorder, such as valproate and topiramate when stabilizing manic episodes and lamotrigine when targeting both bipolar depression and migraine (Vikelis and Rapoport, 2010).

Anxiety Disorders and Migraine

It is well-known that migraine has an up to 10-fold likelihood to be comorbid with anxiety disorders, especially generalized anxiety disorder (GAD) and panic disorder (PD) (Dresler et al., 2019). Indeed, it is not surprising that the prevalence of anxiety increases as headache episodes increase (Zwart et al., 2003). This is also true from a time perspective, as people with PD and migraine are proven to experience panic attacks earlier than non-migraineurs (Yamada et al., 2011).

The management of anxiety disorders comorbid with migraine mostly relies on antiepileptics, with topiramate, lamotrigine, and pregabalin being the best therapeutic options (Van Ameringen et al., 2004; Calandre et al., 2010; Casucci et al., 2010).

Obsessive-Compulsive Disorders and Migraine

Evidence shows a correlation between CM and obsessive-compulsive disorder (OCD), whose presence might influence migraine response to treatment, in both the short and long run (Buse et al., 2013). A previous study highlights how obsessive fearful thoughts about headache pain may fill patients' life more than migraine attacks (Curone et al., 2014). Furthermore, a consistently worse response to treatment was found to be more prevalent in chronic migraineurs with obsessive-compulsive traits as well as the tendency to undergo an early relapse (Curone et al., 2012).

Post-traumatic Stress Disorders and Migraine

In the last decades, evidence about the comorbidity of PTSD and migraine is grown. Up to 25% of migraineurs has PTSD, with higher rates than the general population (up to 10%). PTSD

occurs with a higher prevalence in people suffering from CM (43%) than those with EM (9%) (Peterlin et al., 2008). This comorbidity is up to three times more common among women than men (Peterlin et al., 2011). Shared pathophysiological aspects, as the different hormonal maturation trajectory and the exposure to major psychological trauma, may explain the difference in comorbidity distribution among genders.

Recently, the 11th revision of the International Classification of Diseases (ICD-11) [World Health Organization (WHO), https://icd.who.int/en] has introduced the diagnosis of complex PTSD (cPTSD). It develops from prolonged interpersonal traumatic experiences without the opportunity to avoid them. Along with typical PTSD clinical dimensions, cPTSD has "disturbances in self-organization" (DSO; affect dysregulation, negative self-concept, and disturbances in relationships). This syndrome has a higher level of depression and dissociation and is more associated with medical diseases (Longo et al., 2019; Ho et al., 2021). Because, to date, data on the association between cPTSD and migraine are scarce, future studies will need to clarify the prevalence of this comorbidity.

Substance Use Disorders and Migraine

Data on the co-presence of migraine and substance use disorder (SUD) are slightly controversial. For instance, previous evidence suggests a lower prevalence of alcohol consumption/addiction among patients with migraine. This is possible since wine, beers, or spirits are commonly perceived as easy triggers for headache attacks (Zlotnik et al., 2014; Pellegrino et al., 2018). On the other hand, evidence on caffeine addiction points out how patients with CM were more likely to be frequent caffeine consumers than healthy individuals (Scher et al., 2004).

The literature shows that the association between migraine and substance abuse is no longer significant when controlling for PTSD and depression variables (Buse et al., 2013). For these reasons, substance abuse has to be considered as secondary to additional psychiatric comorbidities rather than migraine (Radat and Swendsen, 2005).

Somatic Symptom Disorders and Migraine

Conflicting results are also reported on the association of migraine and somatic symptom disorder. Previous studies have emphasized an equal prevalence of somatic symptoms among episodic migraineurs when compared with non-migraineurs (Lake et al., 2005). On the other hand, a higher prevalence of somatoform disorders was found among patients diagnosed with CM, with a direct association between somatic symptom severity and migraine frequency (Maizels and Burchette, 2004). Consistent with these results, children with migraine are found to display a higher set of somatic complaints (Bruijn et al., 2010), with a heavier sense of shame and fear than their healthy counterparts (Tarantino et al., 2015).

Supposed Pathophysiological Mechanisms

The elevated rates of comorbidity between psychiatric disorders and migraine indicate that pathophysiology of these disorders may share several, common mechanisms. Some of these commonalities are listed below. Although they have been reported separately, some authors speculate that different pathophysiological mechanisms, which would explain the comorbidity between psychiatric disorders and migraine, may overlap and intersect with each other.

Neurotransmitters and Psychiatric Comorbidity

As previously reported in the literature, migraineurs, like depressed patients, show altered serotonin blood levels, i.e., higher during migraine attacks and significantly lower between them. These neurochemical alterations would favor an unbalance activity of the brainstem nuclei, a condition that may predispose to the activation of the trigeminovascular nociceptive pathway and may favor the abnormal neuro-vascular coupling accompanying CSD as well (Hamel, 2007). In addition, migraine might be treated with drugs acting on the serotonin system, such as triptans as painkillers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (Silberstein et al., 2012). Other monoamines may be involved in the mechanisms of psychiatric bidirectional comorbidity with migraine. A study showed how a specific dopamine D2 receptor allele is present in migraineurs comorbid with aura, anxiety, and depression (Peroutka et al., 1998). Moreover, depressed chronic migraineurs have significantly lower GABA cerebrospinal fluid levels than non-depressed patients. This may suggest that also this neurotransmitter may play a key role in the pathophysiology of such comorbidity (Vieira et al., 2006).

Neuroinflammation and Psychiatric Comorbidity

The neuro-inflammation hypothesis has always been considered in the etiology of MDD and migraine. Indeed, evidence of altered hypothalamic–pituitary adrenal (HPA) axis was found in both disorders (Peres et al., 2001; Gonda et al., 2019). Obese patients with CM and depression showed significative higher pro-inflammatory cytokine blood levels, suggesting a link between these conditions (Bigal et al., 2007). Similarly, a common neuro-inflammatory diathesis might be seen both in migraineurs and in patients with BD. Pro-inflammatory cytokines like TNF-α and IL-1, in fact, may take part in the comorbidity process (Brietzke et al., 2012).

Genetics and Psychiatric Comorbidity

Previous studies have shown that migraine and MDD are bound by a bidirectional red thread, meaning that migraine might cause or be the cause of MDD (Moschiano et al., 2011). Indeed, some authors have suggested how these two conditions show a shared set of genes, especially when they are comorbid together (Schur et al., 2009; Ligthart et al., 2014).

As for MDD, also for BD, a common inheritance with migraine might be assumed. Genome-wide association studies, in fact, have highlighted a shared set of single-nucleotide polymorphisms (SNPs) encompassing a region of the gene KIAA0564 (Oedegaard et al., 2010). The gene KIAA0564 has putative ATPase activity expressed in the brain, as seen in patients with FHM2, and one transcript of this gene shows a pattern of expression in the whole brain, substantia nigra, amygdala, and hypothalamus, all regions known to be involved in both migraine and BD (Oedegaard et al., 2010). Evidence

has shown that many neurotransmitters seems to be involved in the comorbidity of both disorders, such as serotonin (Mahmood and Silverstone, 2001; Hamel, 2007), glutamate (Vaccaro et al., 2007; Chen et al., 2010), and dopamine (Akerman and Goadsby, 2007; Ashok et al., 2017). It was also reported in literature that patients with migraine and BD share mutations on calcium and sodium channels, explaining why they both may respond to anticonvulsants like sodium valproate (Askland et al., 2009; de Vries et al., 2009).

Stress and Psychiatric Comorbidity

Stressful events predispose, trigger, or worsen psychiatric disorders. For example, PTSD is a consequence of major psychological trauma, and traditionally, MDD could be classified as reactive or endogenous if a significant life stressor is present before the onset of the symptoms or not. Similarly, stressful events characterize the clinical presentation of migraine and mark migraineurs' life. Stress and migraine share mutual characteristics, as the first might be considered as a trigger for migraine episodes and, conversely, the second is a well-established source of stress (Dresler et al., 2019). The process of central sensitization, commonly claimed to be at the base of migraine evolution to a chronic form, postulates disrupted processing taking place in the trigeminal nucleus caudalis for pain and in limbic structures, such as the amygdala and insula, for stress- and anxiety-related disorders (Grassini and Nordin, 2017). Some researchers differently postulate that patients in which a failure of limbic structures in adjusting to pain may occur, therefore resulting in an abnormal endocrine response that in turn leads to an altered response to stress, may belong to a "limbically augmented pain syndrome" (Rome and Rome, 2000).

Neurocircuits and Psychiatric Comorbidity

From a neurophysiological point of view, a dysfunctional neurolimbic network (Schwedt et al., 2013) might explain this aberrant interaction of pain and mood and therefore can support the clinical connection between migraine and depressive and anxiety disorders (Maizels et al., 2012).

Indirect evidence of this shared pathophysiological mechanism in the neurolimbic network is provided by a recent retrospective study in patients with comorbid migraine and unipolar depression treated with a therapeutic paradigm of high-frequency rTMS (HF-rTMS) over the left dorsolateral pre-frontal cortex (l-DLPFC) (Kumar et al., 2018). In addition to the clinical improvement of depression, a decrease in frequency, severity, and functional disability of migraine was reported. These findings may be explained with a sustained modulation effect, generated by the HF-rTMS therapeutic paradigm, of l-DLPFC, an area involved in cognitive control of pain.

COMORBIDITY WITH OTHER PAIN SYNDROMES

Scientific Evidence of Comorbidity

Migraine patients often experience pain outside the territories primarily involved, as those innervated by the trigeminal nerve. The first cervical roots, C1–C3, have an anatomical and functional contingencies with the trigeminal nucleus caudalis, so migraine attack is usually diffused into the neck (Vincent, 2011). Besides, migraine pain allows the spread of allodynia phenomenon in the shoulder and even upper limbs (Burstein et al., 2000b). Central sensitization occurs during single attacks, so migraine patients are prone to comorbidities with other pain syndromes sharing this phenomenon as the main causal factor (de Tommaso et al., 2016; Arendt-Nielsen et al., 2018).

A bidirectional association has been observed between migraine and other, often chronic pains such as chronic low-back pain (Ashina et al., 2018), which accompanies dysmenorrhea (Miller et al., 2018; Gagnon and Elgendy, 2020), and temporomandibular disorder (Grossi et al., 2009). Results of the German Headache Consortium study showed that the OR of having frequent low-back pain was between 2.1 (95% CI: 1.7–2.6) and 2.7 (95% CI: 2.3–3.2) times higher in all episodic headache, including migraine, and between 13.7 (95% CI: 7.4–25.3) and 18.3 (95% CI: 11.9–28.0) times higher in all patients with chronic headache subtypes when compared with non-affected subjects (Yoon et al., 2013). But in recent years, much attention has been given to fibromyalgia (FM), as it seems to be strongly associated with migraine, especially if chronic. FM is a chronic and disabling disease dominated by diffuse pain and several associated symptoms, such as sleep disorder, cognitive impairment, and fatigue (Wolfe et al., 2010).

In the last 10 years, many studies confirmed a high prevalence of FM among patients with migraine, varying from 5% to more than 30%, depending upon the type of population considered (de Tommaso, 2012; Küçükşen et al., 2013). A high prevalence of FM was found in tertiary headache centers, where patients with severe migraine are prevalently followed up. FM comorbidity seems to be a hallmark for severe migraine, characterized by frequent headache, general disability, allodynia, and sleep disturbances (de Tommaso, 2012; de Tommaso et al., 2016).

Patients with FM suffer from CM and chronic TTH, while EM, and especially migraine forms with very sporadic attacks, like migraine with pure visual aura, rarely shares this comorbidity (de Tommaso, 2012). Factors favoring evolution into CM, such as sleep disturbances, prevail among CM with FM comorbidity (de Tommaso et al., 2014a).

FM comorbidity would not be a feature of a long history of migraine, as cases of FM are present even among migraine child cohorts (Kashikar-Zuck et al., 2013; de Tommaso et al., 2017). In child cohorts, the comorbidity with FM defines a clinical phenotype with more severe migraine, higher anxiety and depressive symptoms, and lower quality of life in all domains (Kashikar-Zuck et al., 2013).

Detecting FM in migraine patients could help in individuating patients with a profile of severe illness and poor quality of life. Clinical trials in FM patients displayed a low efficacy profile, with several adverse events and a prominent nocebo effect (Häuser et al., 2012). The correct therapeutic approach to single causes of comorbidity in such complicated patients could improve their global clinical picture (Affaitati et al., 2020). A recent observational study on the effects of preventive treatments after 3 months of therapy showed that patients with FM have a profile of resistance to first-line preventive drugs (Delussi et al.,

2020). Tricyclic antidepressant amitriptyline was actually the most frequently prescribed drug for the treatment of migraine patients comorbid with FM (Delussi et al., 2020). However, researchers did not report the possible effect of amitriptyline on specific symptoms of FM and how the mild improvement of migraine could impact the disability linked to diffuse pain (Affaitati et al., 2020). Another important topic could be the assessment of the effects of therapeutic approaches to severe migraine, like botulinum toxin (Diener et al., 2010) and CGRP monoclonal antibodies (Edvinsson, 2019), to the global clinical impairment of FM.

Pathophysiological Basis of Comorbidity

FM is one of the most diffuse and disabling conditions sharing with primary headaches central sensitization as the main pathophysiological mechanism (Arendt-Nielsen et al., 2018). Migraine and TTH are included into the central sensitization-related syndromes, which often coexist in a complex modality. The recent classification of chronic pain has included the category of "nociplastic pain" specifically referring to pain that "arises from altered nociception despite no clear evidence of actual or threatened tissue damage" (IASP Terminology, 2020). Central sensitization implies hyper-function of neurons and circuits in nociceptive pathways with increased neurons excitability and synaptic efficacy as well as reduced inhibition. It is mainly based on the remarkable plasticity of the somatosensory nervous system in response to different causes, neural-inflammation, or neuronal damage (Latremoliere and Woolf, 2009). In migraine, the inflammation occurring at the perivascular and meningeal level is followed by sensitization of second-order nociceptive neurons and wide dynamic range neurons within the trigeminal caudal nuclei, and third-order nociceptive neurons within the thalamus, with hyperalgesia and allodynia involving the skin and the muscles in the head, neck, and other somatic sides (Burstein et al., 2000b). In FM, the initial causes of pain are sometimes unknown and sometimes are due to inflammation or trauma. Moreover, a hyperactivity of cortical regions devoted to pain processing has been demonstrated by neuroimaging studies in FM (López-Solà et al., 2017) and migraine (Moulton et al., 2011). Neurophysiological studies based on bioelectrical correlates of nociceptive and multimodal stimuli stated that phenomena of reduced habituation to repetitive stimuli, especially the painful ones, accompany central sensitization phenomena in both FM and migraine (Coppola et al., 2013; Choi et al., 2016).

More recent studies underlined the presence of small fiber pathology in patients with FM (Oaklander and Nolano, 2019). In more than 50% of FM patients, a proximal partial loss of skin sensitive terminals has been detected. These FM cohorts with small fibers involvement include patients with migraine (Vecchio et al., 2020). The FM subgroup with migraine comorbidity did not show different neurophysiological and skin biopsy features except for a trend toward a more expressed lack of habituation to repetitive painful stimuli (de Tommaso et al., 2014b).

In FM patients, including those with associated migraine, proximal skin denervation corresponded to reduced habituation of laser-evoked responses (Vecchio et al., 2020). The occurrence of this phenomenon is in agreement with the hypothesis that the loss of cortical adaptation to peripheral inputs could be related to an initial condition of hypo-activation followed by a delayed response potentiation (Coppola et al., 2013).

The evidence of a mild small fiber pathology in migraine patients with FM comorbidity opens a new scenario about the causes of the coexistence of peripheral and central nervous system (CNS) dysfunction, like genetic abnormalities of voltage-gated sodium channels (Eijkelkamp et al., 2012).

Very pertinent to the pathophysiology migraine is the observation that a mechanism involving the release of CGRP was also described for pain in musculoskeletal disorders and may be a direct cause of pain in other conditions. Musculoskeletal tissues are rich in CGRP-immunoreactive nerves and are associated with altered CGRP expression pain. These observations paved the way for randomized controlled trials of monoclonal antibodies for the treatment of pain conditions other than migraine (Walsh and McWilliams, 2019).

SLEEP-RELATED DISORDERS AND MIGRAINE

Scientific Evidence of Comorbidity

The relationship between sleep and migraine has always been known, but current knowledge on the exact nature of the link between migraine and sleep remains incomplete and unclear. A large amount of epidemiological data shows a high comorbidity between migraine and sleep disorders (Drake et al., 1990; Sahota and Dexter, 1990; Dodick et al., 2003; Olesen et al., 2006).

Migraine and Insomnia

The association between migraine and insomnia is statistically significant, since one presents a risk of incidence, if the other condition is present, equal to about twice (OR = 1.4–2.6) the risk of incidence of only one of the two conditions (Uhlig et al., 2014). This relationship is bidirectional, and the association is stronger in more frequent, severe, or comorbid headache (Ødegård et al., 2013). Considering migraine sufferers only, a reduced sleep duration (<6 h per day) is independently associated with an increase headache attack frequency (Song et al., 2018). Although migraineurs suffer more frequently from disorders, the average sleep duration does not differ between migraineurs and non-migraineurs (Song et al., 2018). On the contrary, a reduced "sleep quality" (a satisfaction index based on the evaluation of how restful sleep is) is significantly more frequent in migraine sufferers (Song et al., 2018). The prevalence of insufficient sleep is statistically higher in migraine sufferers than in subjects with other forms of headache and then in subjects without headaches. Multivariate analysis confirms an OR (corrected for sociodemographic variables, anxiety, and depression) of 1.8 for migraine in subjects with insufficient sleep (Kim et al., 2017). Neurophysiological data support the hypothesis that relative sleep deprivation and varying robustness of the neurobiological arousal system may be among several causal factors for a migraine attack (Engstrøm et al., 2014; Rains, 2018).

Migraine and Sleep-Disordered Breathing

Since the first systematic descriptions, it was not clear whether morning headache and sleep apnea headache were two distinct nosological entities. Similarly, it was debated if the awakening headache was the recurrent manifestation of a primary headache, such as migraine. The first study of 304 patients concludes that morning headache is not an integral part of obstructive sleep apnea syndrome (OSAS) (Aldrich and Chauncey, 1990). Based on the results of many studies, morning headache does not have strictly specific characteristics (Loh et al., 1999; Neau et al., 2002; Alberti et al., 2005). Overall, there are also conflicting literature data on the association between morning headache and OSAS severity (Aldrich and Chauncey, 1990; Loh et al., 1999; Greenough et al., 2002; Neau et al., 2002; Göder et al., 2003; Alberti et al., 2005), but comorbidity between OSAS and migraine was not considered in most studies. Treatment of the respiratory disorder results in an improvement of the morning headache. Other studies say that such improvement, as well as headache, is likely to be non-specific (Aldrich and Chauncey, 1990; Poceta and Dalessio, 1995; Paiva et al., 1997; Loh et al., 1999; Göder et al., 2003; Ohayon, 2004). Considering specific forms of primary headache, the cumulative incidence of migraine was significantly higher in a large sleep-disordered breathing (SBD) cohort than in the comparison cohort (Harnod et al., 2015). The prevalence of primary headache in OSAS varies from 11 to 25% up to more than 40% (Loh et al., 1999). Habitual snoring was more frequent in chronic daily headache subjects (24%) than in controls (14%) (Scher et al., 2003a). However, the wide discrepancy in reported headache prevalence may reflect differences in study design (retrospective or prospective), in the definition of the headache itself and in considering patients who are undergoing polysomnography with suspicion of OSAS. Several studies have shown the effectiveness of continuous positive airway pressure (CPAP) treatment in improving all types of headache. These studies highlight that even patients with a mild form of OSAS improve with non-invasive ventilation. These data suggest treating headache patients with OSA symptoms, with any degree of severity (Johnson et al., 2013).

Migraine and Restless Legs Syndrome

Both clinic-based (Young et al., 2003; Rhode et al., 2007; d'Onofrio et al., 2008; Chen P. K. et al., 2010; Suzuki et al., 2011; Lucchesi et al., 2012; Lin et al., 2016; Valente et al., 2017) and large-scale population-based studies suggest an association between migraine and restless legs syndrome (RLS) (Schürks et al., 2012; Winter et al., 2013). The association was confirmed also after adjustment for confounding factors such as age, sex, major depression, anxiety, and sleep quality (Zanigni et al., 2014). RLS also accounts for poorer sleep quality in those patients with comorbidity (Valente et al., 2017). The frequency of migraine attacks correlates positively with the prevalence of RLS, and the MA had a stronger trend of association with RLS (Lin et al., 2016). The authors suggest that, at least in part, this relationship might be explained by a pharmacological overload of serotoninergic drugs, which might interfere with the physiological balance between dopaminergic and serotoninergic pathways (Valente et al., 2017).

Migraine and Narcolepsy

Some studies showed an increased frequency of migraine (37–54%) in patients with narcolepsy (Dahmen et al., 1999, 2003). However, a large multicenter observational study found an increased frequency of TTH (60.3 vs. 40.7%) but not migraine (21.9 vs. 19.8%) in narcolepsy patients compared with controls (Evers, 2003). More recent data confirm that patients with narcolepsy and idiopathic hypersomnia more frequently experienced headache than the healthy controls and that the patients with both conditions more commonly experienced excessive daytime sleepiness and had reduced total sleep time than the patients with narcolepsy without headache (Suzuki et al., 2015).

Migraine and Advanced Sleep Phase

Although there is no robust epidemiological evidence, the description of a family with a genetic mutation related to a condition characterized by the so-called advancement of the familial advanced sleep phase (FASP) (Xu et al., 2005) inspired the hypothesis of a close physiological correlation between migraine and this sleep disorder as well as a brilliant editorial (Ahn and Goadsby, 2013). These data give the opportunity to assume the important role of the hypothalamus in migraine pathophysiological mechanisms and hypothesize any new therapeutic targets (Ahn and Goadsby, 2013).

Migraine and Parasomnias

Numerous old studies have shown the association between migraine and sleepwalking (Barabas et al., 1983; Giroud et al., 1986; Pradalier et al., 1987). Other studies have shown the high prevalence of various parasomnias (pavor, sleepwalking, and enuresis) even in adults (in the first two decades of life) (Messina A. et al., 2018). In several studies, subjects with bruxism seem to have a high prevalence of primary headaches and especially CM (Dexter, 1979; De Luca Canto et al., 2014). The serotonergic circuits of the median raphe nucleus have been involved as a common key structure between migraine and parasomnias, as they play a central role in pain processing and in the determination of sleep/wake rhythms (Messina A. et al., 2018).

Sleep-Related Migraine

The International Classification of Headache Disorders, 3rd edition (ICHD, 2018) does not include forms of sleep-related headache or sleep-related migraine; however, some migraine patients have >50 or >75% of sleep-onset migraine attacks (Della Marca et al., 2006b; Rains, 2018). The chronobiological mechanisms are likely more involved in specific forms of headache. In this view, some authors suggest that data on this form of migraine should be collected (Rains, 2018).

Migraine, Sleep, and Chronification

All types of sleep dysregulation are involved in the chronicity mechanisms of primary headaches.

Every year, up to 3% of patients (Scher et al., 2003b) may experience the progression of EM into a chronic form (Rains, 2008). The potential mechanisms of chronification are manifold,

and sleep disturbances have been identified among the risk factors associated with chronic headaches. Others are overuse of drugs, stress, psychiatric disorders, and obesity (Rains, 2008). Consequently, screening and treatment of sleep disorders are recommended in the clinical management of migraine (Poceta and Dalessio, 1995; Ong and Park, 2012).

Supposed Pathophysiological Mechanisms

Migraine and sleep disorders have a high prevalence in the general population but are extremely and so overlapped that it is difficult to believe that their comorbidity is only incidental.

In addition to the pure epidemiological evidence, other physiological aspects strongly suggest close pathophysiological links between migraine and sleep fluctuations: circadian oscillations in the sleep/wake rhythm (cyclic biological changes that occur in the 24-h interval) (Ahn and Goadsby, 2013), changes in the ultradian rhythm [shorter than a day, the alternation of non-rapid eye movement (NREM)/REM phases in sleep cycles] (Jennum and Jensen, 2002), and modifications of the arousal mechanisms (Bruni et al., 2004; Della Marca et al., 2006a).

Moreover, key structures have an unequivocal modulatory involvement in both migraine and sleep, namely, the hypothalamus, brainstem (Goadsby, 2005), and thalamus–cortical circuits (Coppola et al., 2016).

Finally, orexinergic (Hoffmann et al., 2015), serotoninergic (Goadsby et al., 2017), and dopaminergic (Charbit et al., 2010) neurotransmissions have a crucial and common role in migraine and sleep. Interestingly, premonitory symptoms of migraine such as yawning, craving for food, and gastrointestinal disturbances, supposed to be dopamine-mediated (Akerman and Goadsby, 2007), were more frequently reported in migraine patients with RLS compared with those without RLS (Cologno et al., 2008). It is well-known that migraine is characterized by a hypersensitivity to dopamine (Sicuteri, 1976; D'Andrea et al., 2006) and that dopaminergic projections play an important role in the processing of trigeminovascular information (Charbit et al., 2010). Some authors have suggested that a dysfunction of the hypothalamic dopaminergic nucleus A11 may be part of the complex pathophysiology of migraine and RLS and that both disorders have a common genetic basis, also involving dopaminergic transmission (Bonati et al., 2003; Charbit et al., 2010).

Patients with migraine do not differ from non-migraineurs in sleep macrostructure but have a marked reduction in the polysomnographic parameters of arousal in NREM sleep and a lower incidence of "cortical" arousals in REM sleep (hypo-arousability) than do non-migraineurs (Della Marca et al., 2006b). On the other hand, migraineurs showed an increased instability of the autonomic balance during sleep (Vollono et al., 2013).

In conclusion, since the most reproducible hypnological marker in migraine is hypo-arousability (Bruni et al., 2004; Della Marca et al., 2006b; Vollono et al., 2013; Engstrøm et al., 2014; Rains, 2018), it is possible to hypothesize that the dysfunction of arousal system is the expression of the modified brain's ability to process exogenous and endogenous stimuli during sleep.

GASTROINTESTINAL DISORDERS AND MIGRAINE

Due to an overly complex multifactorial pathway, gastrointestinal disorders are quite common among migraine patients. In fact, on the one hand, it is well-known that there is a higher prevalence of migraine in people with much reflux symptoms, diarrhea, constipation, or nausea than in those without them (Aamodt et al., 2008). On the other hand, nausea and vomit are common symptoms of the migraine attack, according to classifying criteria (ICHD, 2018); and alterations of the intestinal transit (leading to constipation or diarrhea) are part of the autonomic symptoms accompanying pre- and post-dromal phases of the attack (Gazerani and Cairns, 2018). The gastrointestinal comorbidities in patients with migraine involve disorders in different organs of gastrointestinal (GI) tract, from the mouth to the bowel.

Scientific Evidence of Comorbidity

A recent multicenter study evidenced that the presence of periodontitis (a serious gum inflammatory condition due to bacterial infections) is independently related to CM, with a higher prevalence than patients with EM (53.9 vs. 44.6%) (Leira et al., 2020).

In a large questionnaire-based cross-sectional study (the Head-HUNT Study), researchers observed that the more severe the gastroesophageal reflux disease (GERD), the more prevalent is migraineur and non-migraineur headache (Aamodt et al., 2008). A similar association between the presence of GERD and its severity and headache was also evidenced in other two large studies (Saberi-Firoozi, 2007; Katić et al., 2009). More recently, a more detailed analysis was performed among patients with dyspepsia. Fifty-four percent of patients with epigastric pain syndrome also suffered from migraine, but headache seems to be not induced by meal ingestion. Besides, migraine prevalence in patients with postprandial distress syndrome was 76%, and almost all patients reported a meal-related headache with a correlation between the entity of the gastric discomfort threshold and migraine severity (Di Stefano et al., 2019).

Helicobacter pylori is the bacteria responsible for gastric ulcer and its neoplastic degeneration, and its infection seems to negatively influence migraine symptoms, according to the patient's ethnicity, the place of residence, and the bacterial strains (Cámara-Lemarroy et al., 2016). It was also observed that its infection is more prevalent in patients with migraine than in controls (Su et al., 2014), and the bacterial eradication is related to relief of migraine symptoms (Faraji et al., 2012; Savi et al., 2014).

Abdominal discomfort ascribable to the liver is almost double in patients with migraine than in controls (Kurth et al., 2006). Particularly, the clinical presentation of hepatobiliary disorders seems to be severer in patients with migraine (Aggarwal and Bielefeldt, 2013) and related to it by a common genetic background, as suggested by a large study on twins (Nilsson et al., 2010). Also, non-alcoholic fatty liver disease was related to headache in general (with a borderline value for the significance in patients with migraine) (Martami et al., 2018) and MA in particular (Celikbilek et al., 2014).

Celiac disease (CD) is a genetically based autoimmune systemic disorder triggered by gluten (a cereal grain group of protein) ingestion and characterized by GI and non-GI symptoms, including migraine (Taylor et al., 2016). A recent meta-analysis reported that CD and headache (mainly migraine) have a bidirectional relationship, and it was suggested to screen headache patients for CD since they may benefit from a gluten-free diet (GFD) (Zis et al., 2018). The GFD improves migraine in patients with CD (Ameghino et al., 2019), but among migraineurs, the CD is present only in 2.4% of subjects (Zis et al., 2018), so only a limited number of patients deserves screening for CD. It should be advised only to patients with an important presence of GI symptoms and/or several non-GI symptoms (Taylor et al., 2016), also because the beneficial effect of GFD in non-celiac patients with migraine is not clear (Beuthin et al., 2020).

Irritable bowel syndrome (IBS) and migraine are often comorbid, and researchers observed that the longer the history and severity of migraine, the higher the risk of being affected by IBS (Li et al., 2017); moreover, in case of co-occurrence of both disorders, patients are more prone to develop more complicated clinical pictures (Georgescu et al., 2018). IBS and migraine share several features: both are chronic disorders, diagnosed only by symptomatic criteria (standardized diagnostic biomarkers are not available), characterized by recurrent pain attacks, more prevalent among females, and comorbid with somatic (interstitial cystitis, FM, and chronic fatigue syndrome) and psychiatric (abuse behavior, insomnia, anxiety, and depression) diseases (Georgescu et al., 2018).

Compared with that in the general population, migraine is more prevalent also in patients with inflammatory bowel disease (IBD), in both adults (Moisset et al., 2017) and children (Ben-Or et al., 2015), being their most prevalent neurological disorders (Oliveira et al., 2008). IBD includes Crohn's disease and ulcerative colitis, both characterized by relapsing/remitting acute inflammations.

Migraine seems to be more prevalent among patients with constipation (Aamodt et al., 2008), and it has been proposed that the dietary treatment for this GI complaint leads to migraine improvement (Prakash and Mullen, 2010). Also, laxative treatments seem to be useful to improve migraine-related disability and severity in children with migraine and constipation (Rezaeiashtiani et al., 2019). On the other hand, constipation is more prevalent in patients with migraine than in those with TTH and non-headache subjects (Martami et al., 2018).

Supposed Pathophysiological Mechanisms

Attempting to speculate about the pathophysiological bases of GI comorbidities in patients with migraine, we can invoke three main different mechanisms of action: the involvement of the enteric and autonomic nervous system (ENS and ANS), the production of inflammatory cytokines, and dysbiosis, that is, a microbial imbalance or maladaptation.

During embryogenesis, the ENS develops simultaneously with the CNS, and they are connected by the modulation of the vagal nerve. Therefore, although it is unclear if the correlation between migraine and gastric digestive symptoms is due to a primary neurologic or gastric issue, gastric symptoms can be regarded as part of the spectrum of dysautonomia dysfunctions related to a migraine attack. To support this hypothesis, the entity of gastroparesis is related to the severity of migraine intensity (Boyle et al., 1990), and negative gastroscopic results are observed in 90% of patients with migraine who complained of gastric symptoms (Meucci et al., 2005). On the other hand, a bidirectional connection between CNS and ANS/ENS is suggested by some reports of migraine improvement after the pharmacological treatment of gastric symptoms (Mavromichalis et al., 1995; Spierings, 2002; Hwang et al., 2016). Nevertheless, the widely used proton-pump inhibitors are regarded as a worsening factor for migraine (Makunts et al., 2019), meaning that not the drugs' mechanism of action but the relief of GI symptoms leads to migraine improvement. The involvement of ENS/ANS was also called into question IBS comorbidity. Although sexual hormones, genetics, and biopsychosocial background seem to underpin the comorbidity, ANS was theorized as the link with the shared central sensitization and allodynia during the acute attack onset (Chang and Lu, 2013). Lastly, ANS/ENS dysfunctions, together with the use of anticholinergic drugs to prevent migraine, dehydration, and an inadequate dietetic regimen, were supposed to be at the base of constipation comorbidity (Diaz et al., 2020).

Inflammatory cytokines seem to be potentially involved in the inflammation-accompanied IBD and other GI comorbidities. The increase in pro-inflammatory substances such as serum pentraxin 3, soluble TNF-like weak inducer of apoptosis (Leira et al., 2018), and serum procalcitonin (Gonzalez et al., 2016) was found in case of periodontitis. The release of different inflammatory cytokines by Helicobacter Pylori (HBP) infection may contribute to explain its comorbidity with migraine (Arzani et al., 2020). It is also possible to hypothesize a role for the cholecystokinin (CCK), a duodenal endocrine peptide that is involved in gallbladder movement, lipid digestion, and hunger suppression, which also has vasoactive activity and coexists with CGRP in trigeminal ganglion (O'Connor and Van der Kooy, 1988; Ruiz-Gayo et al., 2006). In turn, the CGRP, by modulation of vagal parasympathetic outflow (Li et al., 1998), is involved in the pathophysiology of gallstone disease (Mulvihill and Yan, 1995). Nonetheless, CGRP is a key peptide in response to GI inflammation (Holzer, 2007), and its secretion from peripheral sensory nerves could have CNS consequences by sustaining a pro-inflammatory permissive state, which in turn may lower the threshold to the onset of migraine attacks. Finally, we can hypothesize that also constipation can induce gut inflammation and permeability, with reabsorption of molecules that can trigger migraine attacks. This is the case of the lipopolysaccharide that, in animal models, can induce neuroinflammation in trigeminal ganglia (Kemper et al., 1998) and was adopted as an experimental model of migraine attack (Fiebich et al., 2002).

It is well-known that the microbiota and brain functions are related by a reciprocal modulation: several neuropsychiatric disorders have been associated with impaired microbiota (Tremblay et al., 2021). Interestingly, in animal models, gut microbiota dysbiosis contributes to chronicity of migraine-like pain by upregulating TNF-α level in the trigeminal nociceptive

system, while probiotic administration significantly inhibited the antibiotic-produced migraine-like pain prolongation (Tang et al., 2020). Despite this preclinical evidence, clinical studies in humans do not clearly support the efficacy of probiotics in treating patients with migraine (Dai et al., 2017).

IMMUNOLOGICAL DISORDERS AND MIGRAINE

Scientific Evidence of Comorbidity

The relationship between migraine and immunological/autoimmune diseases is overly complex and not completely defined, but several epidemiological, clinical, and laboratory evidence supports this association.

From an epidemiological point of view, it is widely accepted that migraine more commonly affect women than men (Lipton et al., 2001), and this is consistent with the high prevalence of autoimmune diseases in women (Pennell et al., 2012).

Sometimes, headache and specifically migraine can be a clinical manifestation of many autoimmune disorders, either for those primarily involving the CNS, like multiple sclerosis (MS), or systemic disorders, like systemic lupus erythematosus (SLE). It is not clear whether the headache, and specifically migraine, is a direct, specific manifestation of disease and its activity or it is only a concomitant disorder; and, most importantly, it is a matter of debate if headache and in particular migraine can predispose some patients to the subsequent development of an autoimmune disorder.

Several studies assessed migraine prevalence in MS patients, which varies consistently among studies, ranging from 19.8 to 78% (Abb and Schaltenbrand, 1956; Poser et al., 1966; Clifford and Trotter, 1984; Freedman and Gray, 1989; D'Amico et al., 2004; Vacca et al., 2007; Boneschi et al., 2008; Nicoletti et al., 2008; Villani et al., 2008; Putzki et al., 2009; Kister et al., 2010; Möhrke et al., 2013). This variability can in part be attributed to the difference in the study design, populations included, and MS and migraine criteria adopted. A meta-analysis including eight studies (1,864 MS patients and 261,563 controls) found a significant association between migraine and MS with an OR = 2.60 (95% CI: 1.12–6.04); for MO with MS, OR was 2.29 (95% CI: 1.14–4.58), without a significant heterogeneity (Pakpoor et al., 2012). Interestingly, in a large population-based cohort (Nurses' Health Study II), a history of migraine was associated with an increased risk of developing MS (1.39 times higher), but the difference in absolute MS risk between migraineurs and non-migraineurs was small (Kister et al., 2012). When migraine occurrence was considered in relation to clinical characteristics and subtypes, MS patients with headaches and in particular with migraine are significantly younger, are more often female, and more frequently have a diagnosis of clinically isolated syndrome (CIS) or relapsing/remitting MS (RRMS) and lower Expanded Disability Status Scale score (EDSS) than MS patients without headaches (Möhrke et al., 2013). In contrast, headache with tension-type characteristics was more often reported by MS patients with a progressive form of the disease (D'Amico et al., 2004).

The relationship between migraine and the disease activity was investigated by a study of Tabby et al. (2013), who showed that MS patients with migraine presented more relapses than patients without migraine and that 85% of patients whose attacks were often or always of severe intensity reported a headache worsening during MS exacerbations. Furthermore, Kister et al. (2010) observed that migraine in MS patients was significantly associated with a more symptomatic course of the disease, but not with disability or T2 lesion burden on brain magnetic resonance imaging (MRI). Headache is indeed the most common indication for performing MRI in cohorts with radiologically isolated syndrome (RIS). Accordingly, headache was the reason for neuroimaging in about half of subjects from a case series collected by Granberg et al. (2013), but only a few of them showed a progression of MRI lesions during the next 2 to 5 years.

As far as the influence of disease-modifying treatment for MS on migraine course is concerned, it is widely recognized that IFN-beta exacerbates attacks in MS patients already suffering from migraine or induce a *de novo* migraine in patients who did not suffer from headache before (Nikfar et al., 2010; Patti et al., 2012; De Jong et al., 2017). Conversely, a significant reduction of migraine frequency in the MS patients switching from IFN-beta to natalizumab, irrespective of clinical variables such as fatigue, anxiety, depression, and MIDAS scores, was observed (Villani et al., 2012).

Altogether, the above evidence suggests that migraine is a relevant symptom in MS especially in the early stages of the disease. In some cases, a previous personal history of migraine can be recorded; in other cases, headache developed *de novo* in temporal relationship to the neurological symptoms leading to the diagnosis of CIS or MS or in the course of the disease particularly during a relapse or in relationship to IFN treatment.

Much research investigated headache occurrence in SLE patients because headache was indicated as a typical although not specific manifestation of CNS involvement in SLE. In particular, the SLE Disease Activity Index (SLEDAI) included lupus headache as a descriptor, defined as a severe, persistent headache with often migraine-like features and unresponsive to analgesic treatment (Bombardier et al., 1992). However, in a recent study conducted by Hanly et al. (2013), only 1.5% of patients specifically meet the criteria of lupus headache, as defined in SLEDAI. In addition, if present, headache was associated with other neuropsychiatric manifestations. Not surprisingly therefore, lupus headache was not included in the American College of Rheumatology definition of neuropsychiatric syndrome in SLE. When SLE was considered without a specific mention to an SLE CNS involvement, no difference in headache prevalence emerged between controls and SLE patients in a meta-analysis carried out by Mitsikostas et al. (2004). Several studies more specifically focusing on the prevalence of migraine in SLE patients found, like for MS patients, a large variability of results with percentages ranging from 7.9 to 52% (Isenberg et al., 1982; Markus and Hopkinson, 1992; Sfikakis et al., 1998; Fernández-Nebro et al., 1999; Ainiala et al., 2001; Glanz et al., 2001; Whitelaw et al., 2004; Lessa et al., 2006). Some authors also found a higher prevalence of MA in patients with SLE (Brandt and Lessell, 1978; Glanz et al., 2001),

but these data were not confirmed by others (Vázquez-Cruz et al., 1990; Fernández-Nebro et al., 1999; Glanz et al., 2001; Lessa et al., 2006; Katsiari et al., 2011).

Headache and migraine were associated with antiphospholipid antibodies (aPLs) and beta2GPI antibody positivity other than Raynaud's phenomenon in two (Weder-Cisneros et al., 2004; Lessa et al., 2006) out of three studies (Sfikakis et al., 1998).

Finally, based on the available evidence, the possible link between SLE and migraine has not been clarified, and therefore, the occurrence of headache in SLE patients in most cases does not itself require further investigation. Migraine in these patients should be classified according to International Headache Society (IHS) criteria and, in general, managed according to the available treatment guidelines.

A variety of dated studies investigated the association between antiphospholipid syndrome (APS) and migraine, reporting a migraine prevalence ranging from 0 to 30% (Hogan et al., 1988; Hering et al., 1991; Iniguez et al., 1991; Robbins, 1991; Tietjen, 1992). More recently, the Euro-Phospholipid Project revealed a prevalence rate of migraine of 20% in APS patients (Cervera et al., 2009), with the onset of headache preceding one or two decades before the APS diagnosis (Hughes, 2010). Some authors recommended screening for aPL in patients known to have migraine or recurrent headaches since there may be a link between migraine and stroke in APS patients (Cuadrado and Sanna, 2003). However, although some research reported higher prevalence of aPL in migraineurs patients as compared with healthy controls (Briley et al., 1989; Iniguez et al., 1991), others failed to find an association (Verrotti et al., 2000; Williams et al., 2008; Meroni et al., 2014). Conflicting results were obtained about anticardiolipin antibody (aCL) positivity in migraine (Levine et al., 1987; Iniguez et al., 1991; Robbins, 1991; Hinse et al., 1993; Gallo et al., 1994; Tietjen et al., 1998; Verrotti et al., 2000).

Antibodies to PT have been reported to occur in 50–90% of patients with APS (Vlagea et al., 2013). Furthermore, in a recent study, migraine headaches have also been observed more frequently in patients with both aPS antibodies and Raynaud phenomenon (Kopytek et al., 2018). According to Sanna et al. (2006), headache associated with APS is often untreatable, poorly responding to analgesics and typically starts several years before the diagnosis of APS. In spite of that, heparin followed by long-term anticoagulation with warfarin, which is the cornerstone of APS treatment, induces a clear improvement or resolution of migraine in many cases (Asherson et al., 2007; King and Odette, 2012; Erkan et al., 2014).

Some studies demonstrated a significantly higher prevalence of migraine in patients with primary Sjögren's syndrome (pSS) than in normal subjects (Pal et al., 1989; Gökçay et al., 2008). Therefore, it was claimed that both migraine and dry eye could be a part of a common inflammatory process. However, further evidence denied this association (Tjensvoll et al., 2013). Interestingly, in a study by Morreale et al. (2014) involving 120 pSS patients, headache was the most common neurological complaint referred by the patients (46.9%) followed by cognitive (44.4%) and mood disorders (38.3%). The most frequently observed headache was MO. Interestingly, cutaneous allodynia, a sign of central sensitization, was referred by 31% of patients with headache, and particularly in migraine. Migraine occurrence was also significantly related to SSA antibodies, MR spectroscopy (MRS) alterations (reduction of NAA levels or decrease in NAA/Cr ratio), and hemodynamic dysfunction at ultrasonographic evaluations, but not to the presence of vasculitis brain lesions and/or macrovascular damage [such as white matter (WM) lesions and MS-like lesions]. In addition, the frequency of headache and alterations to MRS appeared to be higher in patients with Raynaud's phenomenon.

Among the other systemic autoimmune disorders, rheumatoid arthritis (RA) seems to be more prevalent in migraineurs than in non-migraineurs (Kalaydjian and Merikangas, 2008; Le et al., 2011). Moreover, one recent study showed also that patients with migraine were more likely to develop RA later in life. This temporal relationship may imply a causal link between migraine and RA.

Several studies have investigated this association between migraine and atopic diseases in both adult and child populations. In particular, a relationship between asthma and migraine-type headaches has been reported especially in females as well as a greater prevalence of hay fever, rhinitis, and dermatitis in migraineurs than in healthy non-atopic controls (Mortimer et al., 1993; Wilkinson et al., 1994; Davey et al., 2002; Ku et al., 2006; Özge et al., 2006; Aamodt et al., 2007; Tollefsen et al., 2008). Asthma has also been indicated as a risk factor for new-onset CM (Lee et al., 2013; Gryglas, 2016; Martin et al., 2016). In most of these studies, however, diagnosis of allergic disorders is not definitive and is solely based on medical history and to the presence of allergic or respiratory symptoms. The most recent findings on this topic concern the greater risk of migraine in atopic children (Wang et al., 2016). Furthermore, the risk shows a cumulative effect of more allergic diseases and more allergy-related health care (Wei et al., 2018). Children and adolescents with migraine were more likely to complain of persistent asthma, the latter being associated with higher frequency and more disabling migraine attacks. Interestingly, the history of anti-asthmatic or anti-allergic therapies was associated with a decreased risk of migraine, suggesting their potential role on the prevention of migraine occurrence in these patients (Aupiais et al., 2017). Concurrent with the above results, a lower "degree of atopy" has been related with less frequent and milder migraine headaches in younger patients while a higher degree with more frequent and disabling attacks. In these patients, the administration of immunotherapy induced a decrease in the frequency of migraine headache and associated disability (Martin et al., 2011).

Supposed Pathophysiological Mechanisms

Dysfunction of the immunological system can be the common pathophysiological link between migraine and immunological diseases. Indeed, some immunological dysfunction has been suggested to play a role in migraine pathogenesis (Kemper et al., 2001; Bruno et al., 2007). Compared with that in healthy subjects, a significant increase in CD4+ and a decrease in CD8+ populations has been found in migraine patients, which was

associated with a reduction in immunoregulatory CD4+CD25+ cell levels. These findings suggest a possible failure of self-recognition mechanisms in migraine patients, which could predispose them to immunological and specifically autoimmune disorders (Arumugam and Parthasarathy, 2016).

In pSS patients, pro-inflammation-mediated mechanisms and endothelial dysfunctions of the cerebral microcirculation could account for the comorbidity with migraine and Raynaud's phenomenon (Morreale et al., 2014). For this reason, headache with migraine features and Raynaud's phenomenon may be attributed to a sort of "autoimmune endotheliitis" directly inducing perivascular inflammation and a vasomotor dysfunction.

One of the possible explanations of the occurrence of migraine *de novo* or an exacerbation of a preexisting migraine is the location of MS lesions in strategic sites of the nociceptive pathways involved in the processing of head pain in migraine, such as midbrain/periaqueductal gray matter areas (Gee et al., 2005).

The association between RA and SLE and migraine has been related to a shared dysfunction of the serotonergic system (Zeller et al., 1983; Hamel, 2007; Wang et al., 2017). Platelet serotonin levels are significantly decreased in RA patients and are inversely related to clinical RA activity (Zeller et al., 1983). Nonetheless, the production of inflammatory cytokines, such as TNF-α, was inhibited by the serotonin (Cloëz-Tayarani et al., 2003) and during treatment with serotonin reuptake inhibitors (Sacre et al., 2010).

An increased production of platelet-activating factor and the release of vasoactive neuropeptides can play a role both in asthma pathogenesis (Wasserman, 1994) and in the induction of migraine attacks (Sarchielli et al., 2004). Interestingly, transient receptor potential cation channel subfamily V member1 channels, which co-localize with vasoactive peptide CGRP and are implicated in migraine pathophysiology, were found to be overexpressed in asthmatic mice, and their antagonists effectively suppressed inflammation (Li et al., 2019). Nonetheless, a common genetic denominator is not negligible since children have been demonstrated to be at higher risk of asthma if their parents have a history of migraine (Gürkan et al., 2000).

MIGRAINE COMORBIDITY AS JUDGED BY NEUROIMAGING TECHNIQUES

A good clinical history and neurological examination are sufficient to make a diagnosis of migraine and to evaluate the association with other medical conditions (Evans, 2019). Nowadays, diagnostic tests are recommended only if an abnormal neurological examination, red flags for secondary headaches, atypical features of migraine, or changes in migraine characteristics are present. However, diagnostic tests are often performed in clinical practice to reduce diagnostic uncertainty, to address the concerns of patients, or for medicolegal reasons (Evans et al., 2020).

Since the late 1980s, MRI studies have disclosed the presence of small, punctuate, regions of high-signal intensity involving the deep or periventricular WM in patients with migraine (Hougaard et al., 2014). Infarct-like lesions involving the cerebellum and deep brain structures have also been described in migraine patients with and without aura (Kruit et al., 2005; Bashir et al., 2013). An increased risk of WM hyperintensities (WMHs) is present even in pediatric patients with migraine (Mar et al., 2013; Rocca et al., 2014). Whether these findings are migraine-specific and what factors might influence their presence are still a matter of debate. The prevalence of WM alterations in migraine patients varies widely among the studies (Kruit et al., 2004; Hamedani et al., 2013; Hougaard et al., 2014). Discordant findings have been found regarding the association between the occurrence of WMHs and a higher migraine attack frequency, longer disease duration, the female gender, and presence of migraine aura (Kruit et al., 2010; Palm-Meinders et al., 2012; Bashir et al., 2013; Gaist et al., 2016). Results of longitudinal studies investigating the progression of WMHs in migraine patients are also inconsistent, probably due to the use of different methods of WMH evaluation and the inclusion of patients of different ages (Kurth et al., 2011; Hamedani et al., 2013; Mar et al., 2013). WM alterations are common in people aged 50 or over and in individuals with cardiovascular risk factors (e.g., hypertension, DM, or smoking) (Cannistraro et al., 2019). Some studies showed that migraine patients with cardiovascular risk factors have a higher risk of harboring WM abnormalities, suggesting that other potential etiologies rather than migraine might explain the presence of these alterations (Cooney et al., 1996; Bashir et al., 2013). An abnormal cerebrovascular reactivity leading to focal oligemia, atherosclerotic rick factors, endothelial dysfunction, and cardiac abnormalities, including PFO and atrial septal defect, are some of the mechanisms that might contribute to the occurrence of WM alterations in migraine patients (Bashir et al., 2013; Lee et al., 2019; Hoogeveen et al., 2020). Increased neuronal activation, neurogenic inflammation, and metabolic dysfunction have also been considered in the pathogenesis of WMHs in patients with migraine (Porter et al., 2005).

The imaging features of WMHs of migraine patients may resemble the WM lesions seen in patients with inflammatory diseases, like MS, representing a diagnostic challenge. The presence of cortical lesions or more than three periventricular lesions or the identification of an intralesional vein may provide important pieces of information in the diagnostic work-up of migraine patients with WMHs, being highly specific for MS (Absinta et al., 2012; Lapucci et al., 2019; Sinnecker et al., 2019).

Much attention has been paid to the differential diagnostics between the migraine aura, especially when presenting as negative scotoma, and the acute ischemic stroke. In fact, on admission to the emergency room, 1 to 41% of patients presenting with stroke-like symptoms are events that mimic a stroke but are not caused by an ischemic brain event (Merino et al., 2013). Among the latter, the migraine aura is the third most frequent cause after epileptic aura and psychiatric disorders (Terrin et al., 2018). An accurate ophthalmological evaluation, including best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, and indirect ophthalmoscopy, by excluding optical media, retinal, or optic nerve diseases, can help in the differential diagnosis. It has

recently been observed that perfusion CT imaging can help in the decision-making process leading to the differential diagnosis of symptoms mimicking a stroke and, therefore, can direct to appropriate treatment (Nieuwkamp et al., 2010; Hansen et al., 2011; Miller and Goldberg, 2012; Campbell et al., 2013; Shah et al., 2013; Angermaier et al., 2014; Rath et al., 2017; Ridolfi et al., 2018; Granato et al., 2020). Diagnostic accuracy can be further improved by refining the diagnostic criteria of transient ischemic attacks, which can help to separate them from mimics (Lebedeva et al., 2018; Dolmans et al., 2019).

Over the last decades, the use of neuroimaging techniques has improved our understanding of the pathophysiology of migraine and provided new insights into the mechanisms underpinning comorbid conditions (Messina R. et al., 2018). A recent study using transcranial sonography reported that migraine patients with depression had a decreased echogenicity of the raphe nuclei. Significant associations between raphe hypoechogenicity and depression have been described in different neurological diseases, supporting their role in the development of depression (Tao et al., 2019). There is evidence showing that migraine patients have functional and structural alterations of limbic areas with a key role in the regulation of mood and affect and in the processing of the emotional aspects of pain (Maizels et al., 2012). Interestingly, a specific involvement of these regions has been demonstrated in migraine patients with anxiety or depression. Functional alterations of the hippocampus (Liu et al., 2015) and thalamus (Wei et al., 2019) have been associated with the presence of anxiety in patients with migraine. Using diffusion tensor imaging, a technique that allows exploring the microstructure of brain WM tracts *in vivo*, Li and colleagues (Li et al., 2011) have shown alterations of the corpus callosum in migraine patients with anxiety or depressive disorder. Similar alterations were also found in the bilateral corona radiata, superior longitudinal fasciculus, thalamic radiation, and internal and external capsules in migraine patients with depression. All these tracts connect different brain regions involved in emotional processing, and their involvement has been described in studies of patients with psychiatric conditions (Yu et al., 2013).

Recent imaging evidence has shown common functional and structural imaging patterns in migraine and RLS, supporting shared pathophysiological mechanisms between these two conditions. Abnormalities of dopaminergic neurons, such as the substantia nigra, and volumetric alterations of the middle frontal gyrus have been demonstrated in patients with comorbid migraine and RLS (Yang et al., 2018; Aldemir et al., 2020). Dysfunction of sensorimotor, attentive, and limbic brain networks is also common to migraine and RLS (Yang et al., 2018).

It has been suggested that increased neuronal excitability and CSD might play a role in the comorbidity between migraine and epilepsy (Nye and Thadani, 2015). So far, only one imaging study has explored imaging biomarkers that might explain the coexistence of these two conditions. Huang and colleagues showed microstructural alterations in the medial lemniscus and cerebellar peduncles in patients with epilepsy and comorbid migraine, suggesting that trigeminal and cerebellar alterations might explain the occurrence of migraine in patients with epilepsy (Huang et al., 2017). Further studies including a larger sample of patients are needed to better understand the mechanisms mediating comorbidities in migraine.

CONCLUSION AND PERSPECTIVES

It is clear from the amount of studies reviewed here that migraine disorders are comorbid with a plethora of pathologies, not only of the CNS (see **Table 1**). This relationship is always two-way,

TABLE 1 | List of the most frequent pathologies showing two-way comorbidity with migraine and their supposed pathophysiological mechanisms of comorbidity.

Comorbid condition	Pathologies	Genetic substrate	Pro-inflammatory	Cortical dysexcitability/CSD	Energetic failure
Cerebrovascular dysfunction	Stroke	X	X	X	X
Metabolic and endocrine comorbidities	Diabetes, obesity, insulin resistance, hypothyroidism, and endometriosis	X	X	X	X
Epilepsy	Benign occipital epilepsy of childhood with occipital paroxysms and benign rolandic epilepsy	X		X	
Psychiatric disorders	Major depressive disorder, bipolar disorder, post-traumatic stress disorder, and anxiety disorder	X	X	X	
Other pain syndromes	Fibromyalgia, chronic low-back pain, pain accompanying dysmenorrhea, and temporomandibular disorder		X	X	
Sleep-related disorders	Insomnia, sleep-disordered breathing, restless legs syndrome, narcolepsy, advanced sleep phase, and parasomnias			X	
Gastrointestinal disorders	Periodontitis, gastroesophageal reflux disease, *Helicobacter pylori* infection, hepatobiliary disorders, celiac disease, irritable bowel syndrome, inflammatory bowel disease, and constipation	X	X		
Immunological disorders	Multiple sclerosis, systemic lupus erythematosus, antiphospholipid syndrome, primary Sjögren's syndrome, rheumatoid arthritis, and atopic diseases	X	X		

CSD, cortical spreading depression.

with migraine patients most frequently affected by comorbidity, just as migraine is frequently comorbid with the pathology under examination.

Overall, we can argue that the bidirectional mechanisms that are likely to underlie this extensive comorbidity between migraine and other medical manifestations are manifold (**Figure 1**). Genetic non-modifiable factors are likely to be a protagonist, with multiple genes playing a role in different areas such as neurotransmission, synaptic plasticity, pain regulation, vascular function, and energetic metabolism. On this genetic basis, modifiable additive factors, such as those that may disturb the normal cerebral homeostatic equilibrium (emotional dysregulation, alterations in wakeful sleep rhythm, incorrect dietary regimes that may increase body weight, hormonal imbalances, musculoskeletal alterations, abnormal work rhythms, and substance abuse) can also play an important role in both setting the cyclical migraine threshold and favoring other medical conditions.

The variable combination of thalamocortical network dysexcitability, of multi-organ transient or persistent pro-inflammatory state, and disproportionate energetic needs induced and promoted by the additive comorbid pathologies, may be causative mechanistic factors of the activation of an ample and diffuse defensive system that includes the trigeminovascular system in conjunction with the neuroendocrine hypothalamic system. The latter, through vagal and spinal extrinsic primary

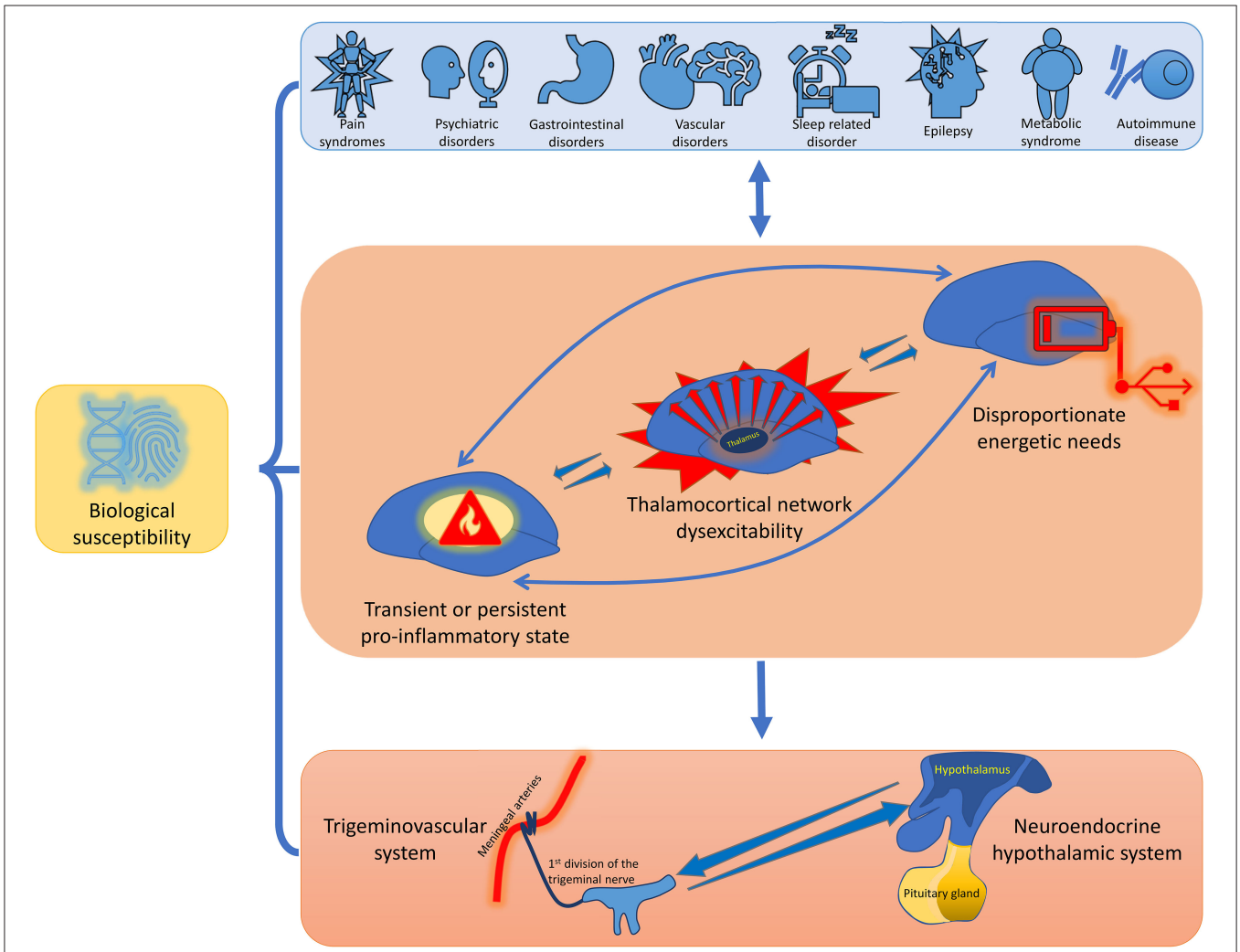

FIGURE 1 | Schematic representation of the pathophysiological model of bidirectional comorbidity between migraine and other medical conditions. A biological susceptibility, constituted by both nuclear and mitochondrial genomic peculiarities, can predispose to different clinical pathological conditions, to the propensity to some physiological mechanisms, and to the lower the activation threshold of some brain structures. Several pathologies can be comorbid with migraine, including neurological, psychiatric, cardio- and cerebrovascular, gastrointestinal, metaboloendocrine, painful, and immunological conditions. The variable combination of thalamocortical network dysexcitability, of multi-organ transient or persistent pro-inflammatory state, and of disproportionate energetic needs induced and promoted by the additive comorbid pathologies may be causative mechanistic factors of the activation of an ample defensive system that includes the trigeminovascular system in conjunction with the neuroendocrine hypothalamic system.

afferent neurons, is involved in coordinating appropriate behavioral responses to aversive and threatening stimuli (Grafe et al., 2017; James et al., 2017). The final product of the activation of this defensive system is the triggering of migraine attack, which sets the alarm on. Therefore, put into a cybernetic system like that of the human organism, migraine pain can be considered the vent valve that keeps the system in stable equilibrium and prevents excessive depletion of energy reserves. On this line of thinking, this could be considered an evolutionary strategy of our brain to try to re-establish a condition of normality and entice or force the patient in search of rest, avoidance of sensory overstimulation, and abstention from food, drink, and other potentially threatening and emotionally distressing behaviors that could continue to compromise the subject in his/her entirety. This strategy of the brain is designed to maintain its homeostasis by regulating homeostatic needs, such as normal subcortico-cortical excitability, energy balance, osmoregulation, and emotional response (Coppola et al., 2021).

Some studies pointed out the headache clinical features and response to acute and preventive treatment can have only minor differences in the two sexes (Vetvik and MacGregor, 2017), but others reported a clear sex disparity in migraine comorbidity (Tietjen et al., 2007; Jensen and Stovner, 2008; Le et al., 2011). Overall, the prevalence of comorbid conditions seems to reflect their epidemiology, with women more frequently affected by psychiatric and immune-mediated disorders and men by vascular and other somatic diseases. Similarly, migraine patients present more often psychological distress at younger ages while somatic comorbidities later in life. However, altogether, migraineurs are affected more frequently by other conditions than age-matched controls, suggesting anticipation of the onset in the disease history (Buse et al., 2020).

Overall, all this implies that the treatment of migraine should always involve a multidisciplinary approach, aimed at identifying and, if necessary, eliminating possible risk and comorbidity factors. This necessarily means that action should be taken as early as possible in life, both as children and as adults when migraine is still episodic. This is to avoid the evolution toward first a chronic form and then toward pharmacological resistance. This educational-behavioral process not only could favor the response to drugs for the attack and prophylaxis but could also allow the therapy to be better tailored to the individual patient.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

CA and GC contributed to the discussion of content, review, and/or editing of the manuscript before submission. All authors researched data for and participated in the writing of the article and proofread the final manuscript before submission.

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Vitamin D, Chronic Migraine, and Extracranial Pain: Is There a Link? Data From an Observational Study

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Several studies focused on the role of vitamin D (vitD) in pain chronification. This study focused on vitD level and pain chronification and extension in headache disorders. Eighty patients with primary headache underwent neurological examination, laboratory exams, including serum calcifediol 25(OH)D, and headache features assessment along with three questionnaires investigating depression, anxiety, and allodynia. The 86.8% of the population had migraine (48% episodic and 52% chronic). The 44.1% of patients had extracranial pain, and 47.6% suffered from allodynia. A vitD deficit, namely a serum 25(OH)D level < 20 ng/ml, was detectable in 46.1% of the patients, and it occurred more frequently ($p = 0.009$) in patients suffering from chronic migraine (CM)–medication overuse migraine (MOH) (62.9%) than in episodic migraine (EM, 25.7%) or tension-type headache (TTH, 11.4%). The occurrence of extracranial pain and allodynia was higher in the CM-MOH than in the EM and in the TTH groups but was not related to the co-occurrence of vitD deficiency (Fisher's exact test $p = 0.11$ and $p = 0.32$, respectively). Our findings show that 25(OH)D deficit is also related to chronic headache, probably because of vitD anti-inflammatory and tolerogenic properties, reinforcing the idea of a neuroinflammatory mechanism underpinning migraine chronification.

Keywords: chronic migraine, episodic migraine, headache, allodynia, vitamin D

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INTRODUCTION

Migraine and tension-type headache (TTH) are common disorders, affecting up to 22 and 78% of the population, respectively (1, 2). Although migraine and TTH are generally episodic and regress taking symptomatic treatments, they may become chronic and necessitate prophylaxis. According to epidemiological studies, each year, 2.5% of episodic migraineurs (EM) progress to chronic migraine (CM), which is characterized by the occurrence of at least 15 migraine attacks per month, at least 8 with migraine features (3–5). CM may favor the development of a wide spectrum of comorbidities, such as psychiatric and sleep disorders, metabolic alterations, along with other forms of pain and medication overuse headache (MOH), diffuse and persistent pain [matching the

American College of Rheumatology criteria for fibromyalgia (FMS)], chronic fatigue pain, and myofascial and musculoskeletal pain (1). Accordingly, more than 70% of patients with FMS complain of headache (4–6). The mechanisms leading from EM to CM are not fully understood. Cortical excitability appears to be abnormal in CM patients, compared to EM patients, but this could be a consequence of the disease itself (3). The role and the contribution of inflammation and central sensitization have been considered (7).

Recently, several studies focused on the possible role of micronutrients and especially of vitamin D (vitD) in chronic pain development.

The Role of Vitamin D in the Pathogenesis of Pain and Headache

Circulating vitD mostly derives from the activation of its endogen precursor (7-dehydrocholesterol) in the epidermis by ultraviolet B radiation, followed by two consecutive hydroxylations (8, 9). In the last decades, a tissue-local production of active vitD was demonstrated (9). Besides the undoubted involvement of vitD in musculoskeletal health, several preclinical studies supported a larger spectrum of activities (8, 10, 11). VitD acts as a developmental neuroactive steroid, influencing various functions of the nervous system and neurotransmitters levels (12, 13). VitD receptors, along with the enzymes involved in vitD synthesis and degradation (25-hydroxylase, 1α-hydroxylase, 24-CYP24A1), are expressed by neurons, astrocytes, and oligodendrocytes distributed in brain regions (14–19), which are therefore able to independently synthetize active vitD and to regulate its local concentrations (12, 16). In the striatum and substantia nigra, vitD seems to be involved in dopamine neurons survival as well as in tonic and phasic dopamine release (20–22). Groves et al. (23) demonstrated that a vitD-deficient diet reduced the expression of enzymes involved in gamma-aminobutyric acid (GABA) synthesis, as confirmed by further experiments (17). Notably, vitD regulates serotonin neurotransmission through the genomic regulation of tryptophan hydroxylase 2 (TPH2) (2, 17). As central nervous system (CNS) cells, most of immune cells express the vitD receptors and the enzymes involved in vitD synthesis and degradation (10). *In vitro* and animal experimental studies could demonstrate that vitD promoted anti-inflammatory and tolerogenic behaviors in both innate and adaptive immune cells, at the expense of proinflammatory subsets (8, 13). Several studies agreed on the existence of a relationship between vitD levels and pain, especially FMS, musculoskeletal pain, and headache (24–27).

The aim of our study was to explore the level of vitD in different kinds of headaches and, more specifically, in relation to pain chronification and the occurrence of chronic extracranial pain and allodynia.

Abbreviations: CM, chronic migraine; vitD, vitamin D; EM, episodic migraine; TTH, tension-type headache; MOH, medication overuse headache; IFN, interferon; IL, interleukin; NF-kB, nuclear factor kappa-light-chain-enhancer of active B cells; NO, nitric oxide; ROS, oxygen free radicals; TNF, tumor necrosis factor; FMS, fibromyalgia; BMI, body mass index; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; FSS, Fatigue Severity Scale.

METHODS

Our observational retrospective study aimed at investigating the potential implications of vitD status on headache characteristics and extracranial pain extension.

Subjects

On the basis of literature data, starting from January 2017 to December 2018, all the patients attended at our center with a diagnosis of primary headache were screened with routine laboratory exams and vitD dosage. Retrospectively, we considered the data from 80 patients who were older than 18 years and who were not pregnant, not suffering from active neoplasia, malabsorption, severe kidney, and cardiovascular disorders, and not taking supplementation with vitD and/or calcium or multivitamin drugs or a treatment for osteoporosis. The patients were divided into six diagnostic subgroups depending on the ICHD-3 criteria (5): EM with and without aura, CM, MOH, TTH, and chronic TTH. For each patient, we acknowledged the following: age, sex, height, weight, body mass index [computed as index and recoded as underweight if <18.49 kg/m^2, normal if between 18.5 and 24.99 kg/m^2, overweight if between 25 and 29.99 kg/m^2, and obese if ≥ 30 kg/m^2 (28)], episodes frequency and use of symptomatic drugs that were recorded on specific diaries, the occurrence of chronic extracranial pain (neck, upper and lower back, upper and lower limbs), and allodynia, defined as an Allodynia Symptoms Check (ASC-12) score > 2 with the validated "12-item Allodynia Symptom Check list" (29). We also acknowledged job, physical activity, dairy intolerance, comorbidities, and family history of headache. We administered two questionnaires to each patient: the "Hospital Anxiety and Depression Scale-Anxiety (HADS-A)," which is a well-validated tool to test the presence of depression and anxiety in somatic patients (30–33), and the "Fatigue Severity Scale (FSS)," which investigates fatigue. The HADS-A scale consists of seven items, each with four answer options (scored between 0 and 3 points). The final score defines the absence of anxiety (<7 points), a mild form (8–10 points), a moderate form of anxiety (11–14 points), or a serious disturbance (15–21 points). The FSS questionnaire evaluates the impact of fatigue through nine items, each scored from 1 to 7 points, building a final score between 9 and 63 points (34, 35). The study was conducted in accordance with the "Declaration of Helsinki" and "Good Clinical Practice guidelines." For this kind of study in which the data are collectable from the clinical records of the patients, we are not required to a have a specific permission from the local ethical committee (Comitato Etico dell'Insubria).

Blood Samples

Fasting venous blood samples were taken in the morning at least 48 h from the last migraine attack. Serum calcifediol [25(OH)D] concentration is widely considered the most reliable indicator of vitD reserve, reflecting both dietary intake and exposure to UV radiation. Serum [25(OH)D] levels can be assessed by different analytical methods (36); we used a chemiluminescence assay (sensitivity, 1.5 ng/ml; precision interval, 7–11%). The definition of vitD status is still on debate.

In this study, according to recent position statement, vitD status was categorized as insufficient for 25(OH)D values < 20 ng/ml (37, 38). Intact parathyroid hormone (PTH) was measured by a two-step immunoradiometric assay, sensitivity of 1 pg/ml, normal range of 15–88 pg/ml. Normal values for chemistry and hematology determinations were as follows: calcium (8–10 mg/dl), folates (8.1–45 nmol/L), vitamin B12 (133–675 pmol/L), homocysteine (<12 μmol/L), iron (33–193 μg/dl), and phosphorus (2.5–4.5 mg/dl).

Statistical Analyses

Demographic and clinical characteristics have been summarized as mean values (±standard deviation) or proportions. The continuous variables were also categorized as normal or abnormal depending on whether the specific value for a given subject fell inside or outside the normal limits. Depending on the type of variable, the analyses were based on either parametric (ANOVA) or non-parametric (chi-square test) methods. The significance value was set at $p = 0.05$.

RESULTS

The 86.8% of the sample was diagnosed with migraine, episodic (with or without aura) in 48% of the cases and chronic in the remaining 52%. Since CM was complicated by medication overuse (MOH) in 91% of the cases, the CM and MOH groups were lumped together in the CM-MOH group. The remaining 13.2% of the patients suffered from episodic TTH. Thus, a three-category study variable (EM, CM-MOH, and TTH) was taken into consideration for headache diagnosis.

Table 1 displays how the categorial variables were distributed in the three headache diagnostic groups.

The mean age of the CM-MOH group (51.8 years; standard deviation, 11) was slightly but significantly ($F = 4.87$, $p = 0.01$) larger than those of the EM (43.1, 15.4) and of the TTH (40.1, 14.1) groups, and this was reflected by the higher occurrence of menopause in the CM-MOH than in the two other diagnostic groups.

The 44.1% of the cephalalgic patients also had extracranial pain and significantly more (chi-square = 10.4; $p = 0.006$) in the CM-MOH (64.7%) than in the EM (26.9%) and in the TTH (12.5%) groups. The 47.6% of the patients suffered from allodynia, and again, the occurrence in the CM-MOH group was significantly larger (chi-square = 10.4; $p = 0.006$) (66.7%) in the CM-MOH than in the other groups (EM, 29.2%; TTH, 16.7%). On the other hand, the number of subjects with extracranial pain and allodynia was not related to the co-occurrence of vitD deficit as shown in **Table 2**.

Table 3 shows the mean values and the out of normal range values (i.e., percent of subjects falling outside the normal limits) of the continuous variables in the three headache diagnostic groups.

The analyses of variance invariably proved that the mean values of the three groups were not statistically different. As for the occurrence of out of range values, the only significant comparison involved the vitD deficit that was larger in the CM-MOH than in the other two groups.

The season of enrolment (**Table 4**) did not significantly influence 25(OH)D concentrations. In detail, almost half of the patients suffering from vitD deficit (45.8%) were enrolled during spring–summer season. Moreover, the mean value of vitD measured during the spring (20.09 pg/ml) and the one measured during autumn (20.7 pg/ml) were not statistically different ($F = 0.69$; $p = 0.79$).

Regarding the analyses of questionnaires, the mean FFS scale final score in the whole sample was 36 points. The subgroups suffering from EM and CM-MOH got higher scores at FFS (respectively, 43 ± 15.1 and 41 ± 14.7 points) compared to the TTH group (29.3 ± 14.4), but these differences were not statistically significant ($F = 0.98$; $p = 0.38$). According to the results of the HADS-A questionnaire, the three groups suffered from a mild state of anxiety (respectively, EM 10.5 ± 4.7, CM-MOH 8.9 ± 4.5, and TTH 10 ± 2.6 points), again not statistically significant ($F = 0.44$, $p = 0.65$).

We compared the mean values and the occurrence of an abnormal values using the occurrence of vitD deficit as the explanatory variable, but all these comparisons did not prove to be significant.

The BMI group that the subjects belonged to was independent from the diagnostic group; moreover, if BMI was considered as a continuous variable, the BMI mean values did not depend on the occurrence of vitD deficit ($F = 1.3$; $p = 0.252$) nor on the diagnostic group ($F = 0.3$; $p = 0.74$). The level of vitD and BMI were not significantly correlated ($r = -0.22$; $p = 0.096$).

Finally, the ongoing pharmacological treatment (both prophylactic and abortive) was not different depending on the headache diagnostic group and on the occurrence of vitD deficit.

DISCUSSION

The main result of our study was that the occurrence of vitD deficiency was more frequent in the CM-MOH than in the EM and TTH groups. A similar results was detectable both for monthly migraine days and the migraine symptomatic intake that were larger in the vitD-deficit group, but these results are explicable because the patients with a high frequency of attack and of symptomatic intake belong to the CM-MOH group; moreover, pain killers are not listed among the causes for vitD deficit.

This result, neither influenced by the season of evaluation nor by the patient lifestyle or headache treatment, supported the hypothesis of a relationship between vitD status and the diagnosis of CM-MOH. The vitD deficiency was not significantly associated with any of the other variables that we considered, not to clinical features such as extracranial pain, allodynia, and prophylactic treatment, nor to biological parameters. None of the other micronutrients tested proved to be different in the three diagnostic groups.

Our findings are in keeping with recent data that showed that poor vitD status was correlated to chronic pain (39) and with a high frequency of migraine episodes (40), but it is

TABLE 1 | Demographic and clinical data.

	EM ($n = 32$) 42.1%	CM-MOH ($n = 34$) 44.7%	TTH ($n = 10$) 13.2%	F/chi-square (χ^2); p
Age (years)	43.1 (15.4)	51.8 (11)	40.1 (14.1)	$F = 4.9$; $p = 0.01$
MMD [mean (standard deviation)]	6.1(3.4)	18.9 (4.9)	3.7 (1.5)	$F = 107.8$; $p < 0.001$
MSI [mean (standard deviation)]	5.6 (3.4)	20.4 (9.9)	3.6 (1.8)	$F = 48.8$; $p < 0.001$
Gender				
Male	6.2%	8.8%	10%	
Female	93.8%	91.2%	90%	$\chi^2 = 0.22$; $p = 0.89$
Work				
Inside	79.2%	79.4%	88.9%	$\chi^2 = 0.46$; $p = 0.70$
Outside	20.8%	20.6%	11.1%	
Sport				
None	66.7%	71%	50%	$\chi^2 = 2.478$; $p = 0.65$
Inside	25%	16.1%	12.5%	
Outside	8.3%	12.9%	37.5%	
BMI				
<18 kg/m^2	0%	6.5%	25%	$\chi^2 = 5.83$; $p = 0.44$
18–24.99 kg/m^2	75%	63.5%	50%	
>25 kg/m^2	25%	25%	25%	
Dairy-free diet				
Yes	88%	82.4%	87.5%	$\chi^2 = 0.774$; $p = 0.679$
No	12%	17.6%	12.5%	
Comorbidities				
Autoimmune diseases	2.5%	5%	0%	$\chi^2 = 12.098$; $p = 0.598$
Diabetes mellitus	0%	1.3%	0%	
Fibromyalgia	2.5%	1.3%	3.8%	
Endometriosis and PCOS	3.8%	2.5%	1.3%	
Menopause				
Yes	25.8%	51.6%	11.1%	**$\chi^2 = 7.15$; $p = 0.03$**
No	74.2%	48.4%	88.9%	
Extracranial pain				
Yes	26.9%	64.7%	12.5%	$\chi^2 =$ **12.2; $p = 0.002$**
No	73.1%	35.3%	87.5%	
Allodynia			35.3%	
Yes	29.2%	66.7%	6.7%	$\chi^2 =$ **10.40; $p = 0.006$**
No	70.8%	33.3%	83.3%	
Prophylactic treatment				
Yes	42.3%	30.4%	30%	$\chi^2 = 0.91$; $p = 0.63$
No	57.7%	69.6%	70%	

EM, episodic migraine; TTH, tension-type headache; CM-MOH, chronic migraine and medication overuse headache; BMI, body mass index; MMD, monthly migraine days; MSI, monthly symptomatic intake; POCS, polycystic ovary syndrome. The statistically significant values are reported in bold.

worth pointing out that the absence of correlation between vitD deficit and extracranial pain or allodynia, despite that they frequently occur in MOH patients, suggests that they do not stem from the same pathophysiological mechanism of chronification. The mechanisms underpinning migraine chronicity are not fully clarified, but they seem to be connected to a sensitization process acting at a peripheral level first and at a central level afterwards (3). Central sensitization, driven by increased neuronal responsiveness and neuroinflammation, might perpetuate pain, even in the absence of any trigger (41). More recently, the role of the immune system along with neuropeptides release and blood flow modifications was also highlighted in the mechanism of chronification (41–43).

VitD mitigates inflammation by the reduction in proinflammatory mediators [such as interferon (IFN)-gamma; interleukin (IL)-1 beta, IL-6, and IL-17; tumor necrosis factor alpha (TNF-alpha)], favoring expansion of anti-inflammatory molecules (IL-4, IL-5, IL-10) (44). Notably, vitD reduces levels of the "nuclear factor kappa-light-chain-enhancer of activated B cells" (NF-kB), which is a pivotal agent in inflammation (45). Thus, vitD is supposed to counteract neuroinflammation as well (46, 47).

TABLE 2 | Association between headache type, pain extension, and vitamin D levels.

	All patients ($n = 76$)		
	VitD > 20 ($n = 41$)	**VitD < 20 ($n = 35$)**	**F/chi-square (χ^2); p**
Age (years)	45.5 (15.3)	47.9 (12.5)	$F = 0.5$; $p = 0.45$
MMD [mean (standard deviation)]	**9.4 (7.2)**	**14 (7.9)**	**$F = 7.1$; $p = 0.009$**
MSI [mean (standard deviation)]	**8.75 (7.2)**	**15.7 (12.2)**	**$F = 9.5$; $p = 0.003$**
Diagnostic group			
EM	56.1%	25.7%	
CM-MOH	29.3%	62.9%	
TTH	14.6 %	11.4%	**$\chi^2 = 9.05$; p = 0.011**
Extracranial pain			
Yes	36.8%	53.3%	$\chi^2 = 1.85$; p = 0.133
No	63.2%	46.7%	
Allodynia			
Yes	42.4%	53.3%	$\chi^2 = 0.75$; p = 0.27
No	57.6%	46.7%	
Prophylactic treatment			
Yes	33.3%	37.9%	$\chi^2 = 0.14$; p = 0.46
No	66.7%	62.1%	

EM, episodic migraine; TTH, tension-type headache; CM-MOH, chronic migraine and medication overuse headache; vitD, vitamin D; MMD, monthly migraine days; MSI, monthly symptomatic intake. The statistically significant values are reported in bold.

TABLE 3 | Main biochemical parameters.

Variables	**EM ($n = 32$)**		**CM-MOH ($n = 34$)**		**TTH ($n = 10$)**		**Chi-square; p**	**F; p**
Variable (abnormal range)	**OOR**	**Mean ± SD**	**OOR**	**Mean ± SD**	**OOR**	**Mean ± SD**		
VitD, ng/ml (<20)	28.1%	19.9 ± 11.4	**64.7%**	20.1 ± 5.9	40%	23.8 ± 17.5	**$\chi^2 = 9.05$; $p = 0.011$**	$F = 0.6$; $p = 0.57$
Ca, mg/dl (<8.6–>10.2)	3.1%	9.9 ± 0.6	5.9%	9 ± 1.9	0%	9.4 ± 0.2	$\chi^2 = 0.80$; $p = 0.7$	$F = 0.31$; $p = 0.74$
P, mg/dl (<2.5)	3.1%	3.4 ± 0.4	0%	3.3 ± 0.3	0%	3.4 ± 0.3	$\chi^2 = 1.39$; $p = 0.5$	$F = 0.3$; $p = 0.74$
PTH, pg/ml (<15–>88)	8%	33.4 ± 19.6	10.7%	32.5 ± 25.1	0%	37 ± 27.7	$\chi^2 = 0.64$; $p = 089$	$F = 0.08$; $p = 0.92$
Folate, ng/ml (<8.1)	21.4%	15 ± 10.8	33.3%	12.1 ± 5.3	26.8%	17.7 ± 16.2	$\chi^2 = 2.06$; $p = 0.7$	$F = 1.14$; $p = 0.33$
Vit B12, pg/ml (<133)	20.7%	270.1 ± 145.3	6.9%	315.5 ± 141.8	0.0%	385 ± 144.7	$\chi^2 = 3.84$; $p = 0.15$	$F = 2.17$; $p = 0.12$
Homocysteine, μmol/L (>12)	25%	12.8 ± 9.4	47.4%	12.1 ± 3.7	71.4%	14.8 ± 5.8	$\chi^2 = 5.1$; $p = 0.08$	$F = 0.31$; $p = 0.73$
Fe, μmol/dl (<33)	15.4%	97.9 ± 43.3	19.2%	76.2 ± 41.8	0.0%	97.7 ± 22.3	$\chi^2 = 1.38$; $p = 0.5$	$F = 1.98$; $p = 0.15$

EM, episodic migraine; CM-MOH, chronic migraine and medication overuse headache; TTH, tension-type headache; Ca, calcium; Fe, iron; OOR, out of range; P, phosphate; VitB12, Vitamin B12; vitD, Vitamin D; OOR, out of range. The statistically significant values are reported in bold.

TABLE 4 | Seasons of enrolment in the whole sample divided by vitamin D levels and headache categories.

Season	**All ($n = 76$)**	**VitD > 20 ng/ml ($n = 41$)**	**VitD < 20 ng/ml ($n = 35$)**	**Chi-square; p**	**EM ($n = 32$)**	**CM-M0H ($n = 34$)**	**TTH ($n = 10$)**	**Chi-square; p**
Aut–Wint	42.1%	43.9%	40%)	$\chi^2 = 0.118$; $p = 0.46$	40.6%	38.2%	60%	$\chi^2 = 1.55$; $p = 0.46$
Spring–Sum	57.9%	56.1%	60%		59.4%	61.8%	40%	

Aut–Wint, Autumn–Winter; Spring–Sum, Spring–Summer; EM, episodic migraine; CM-MOH, chronic migraine and medication overuse headache; TTH, tension-type headache; vitD, vitamin D.
Data are reported as number (frequency).

An intervention study demonstrated that the reduction in proinflammatory cytokines by vitD supplementation was correlated to the improvement of musculoskeletal pain (48).

The regulation of oxidative balance is another potential mechanism of vitD anti-inflammatory action (17, 49, 50). As demonstrated by several trials, neurogenic inflammation in

chronic migraine is mediated by oxygen free radicals (ROS) and nitric oxide (NO) concentrations (51–54). Togha et al. (52) demonstrated that chronic migraineurs had lower total antioxidant non-enzymatic capacity and higher ROS levels than EM patients (52). Physiological vitD level decreases intracellular oxidative stress-related activities, upregulating the expression of several genes implicated in mitochondrial activity, defense against oxidative burst and aging, and particularly of the nuclear factor erythroid-2(Nf-E2)-related factor and of Klotho (45, 55–59).

Obesity is a proinflammatory condition and bears the potential to intensify neurovascular inflammation. Previous reports observed that high BMI was correlated to severity and frequency of migraine episodes (60). In our study, this association was not confirmed, but the small number of overweight people (none suffering from obesity) could be a possible explanation. Moreover, in our patients, the BMI and vitD deficiency were no related.

Limitations

Our study has two main limitations. It is a retrospective not interventional study, and the sample size is not so large. The availability of many parameters for each patient partly compensate for the first limitation, but, on the other hand, their usability is still statistically limited by the sample size.

CONCLUSION

Although, preliminary, our results show an association between CM-MOH and vitD deficit, probably reflecting the vitD anti-inflammatory and tolerogenic properties, we did not find the same relationship between vitD deficit and extracranial pain and allodynia, thus suggesting that their pathophysiological mechanism is not exactly the same of pain chronification in CM-MOH.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

VR, LP, DG, and PT collected the data and performed the neurological and endocrinological assessment. MM and MV did the statistical analyses. All authors contributed in interpreting the data and writing the manuscript, read and approved the final manuscript, and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature.

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MINI REVIEW
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Migraine Is More Than Just Headache: Is the Link to Chronic Fatigue and Mood Disorders Simply Due to Shared Biological Systems?

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Migraine is a symptomatically heterogeneous condition, of which headache is just one manifestation. Migraine is a disorder of altered sensory thresholding, with hypersensitivity among sufferers to sensory input. Advances in functional neuroimaging have highlighted that several brain areas are involved even prior to pain onset. Clinically, patients can experience symptoms hours to days prior to migraine pain, which can warn of impending headache. These symptoms can include mood and cognitive change, fatigue, and neck discomfort. Some epidemiological studies have suggested that migraine is associated in a bidirectional fashion with other disorders, such as mood disorders and chronic fatigue, as well as with other pain conditions such as fibromyalgia. This review will focus on the literature surrounding alterations in fatigue, mood, and cognition in particular, in association with migraine, and the suggested links to disorders such as chronic fatigue syndrome and depression. We hypothesize that migraine should be considered a neural disorder of brain function, in which alterations in aminergic networks integrating the limbic system with the sensory and homeostatic systems occur early and persist after headache resolution and perhaps interictally. The associations with some of these other disorders may allude to the inherent sensory sensitivity of the migraine brain and shared neurobiology and neurotransmitter systems rather than true co-morbidity.

Keywords: migraine, mood, cognition, fatigue, sleep

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INTRODUCTION

Migraine is much more than a disorder of pain and involves symptomatic heterogeneity with a constellation of painful and painless symptoms, which can occur before, during, and after headache (Karsan and Goadsby, 2018). These symptoms can include mood and cognitive change and fatigue and disorders of arousal (Karsan et al., 2020b). Recognition of these symptoms being associated with the migraine attack by both patients and their physicians, particularly when they occur in the absence of headache, is variable and is likely to have increased with time (Bose et al., 2018; Karsan et al., 2018), not owing to increased prevalence but to increased understanding of the biology of

migraine as a neural disorder of sensory processing, and therefore appreciation of these features of the attack (Goadsby et al., 2017).

Migraine is common, and while the global prevalence is around one in seven people (GBD 2016 Headache Collaborators, 2018), it is estimated that the lifetime consultation rate for headache in the United States is 79.8%, suggesting that, overall, migraine biology is more common than the rate of diagnosis suggests (Lipton et al., 2018). Epidemiological studies have suggested that migraine is associated with other systemic conditions such as depression (Bruti et al., 2012; Ligthart et al., 2013; Yang et al., 2016; Amoozegar, 2017; Peres et al., 2017; Amiri et al., 2019; Zhang et al., 2019), anxiety (Wacogne et al., 2003; Seng et al., 2017), irritable bowel syndrome (Cole et al., 2006; Cady et al., 2012; Chang and Lu, 2013; Lau et al., 2014; van Hemert et al., 2014; Cámara-Lemarroy et al., 2016; Le Gal et al., 2016; Perveen et al., 2016; Doulberis et al., 2017; Grassini and Nordin, 2017; Wu et al., 2017; Arzani et al., 2020), fibromyalgia (Nicolodi and Sicuteri, 1996; Peres et al., 2001; Peres, 2003; Marcus et al., 2005; Ifergane et al., 2006; Vij et al., 2015; Cho et al., 2017; Do et al., 2018; Whealy et al., 2018; Penn et al., 2019), sleep disorders (Cevoli et al., 2012; Engstrøm et al., 2013; Kim et al., 2017; Rains, 2018; Buse et al., 2019; Ferini-Strambi et al., 2019; Bertisch et al., 2020), and chronic fatigue (Peres et al., 2002; Lucchesi et al., 2016; Seo and Park, 2018), as well as cognitive disorders (Gil-Gouveia and Martins, 2017, 2019; Vuralli et al., 2018; Lo Buono et al., 2019). Many reasons have been postulated for these associations, including comorbidities, cause and effect, and shared pathophysiological mechanisms.

Human functional imaging studies have alluded to brain areas, which may be involved before (Maniyar et al., 2014; Schulte and May, 2016; Meylakh et al., 2018; Karsan et al., 2020a), during (Weiller et al., 1995; Bahra et al., 2001; Afridi M. et al., 2005; Afridi S. K. et al., 2005; Denuelle et al., 2007; Amin et al., 2016; Coppola et al., 2016a, 2018; Hougaard et al., 2017), and after migraine pain (Schulte and May, 2016; Marciszewski et al., 2018). The objective alterations in brain function in brain areas outside of the pain network, starting hours to days before headache onset, and persisting after headache resolution, associated with clinical symptoms during this time, indicate that each individual attack involves widespread brain dysfunction, within networks encompassing various neurotransmitter systems. These areas have been suggested to functionally correlate with the clinical symptoms experienced at each stage (Karsan and Goadsby, 2020). Brain regions that have been implicated include areas of the limbic pathway, hypothalamic and thalamic areas, and more typical regions within the pain network such as periaqueductal gray, amygdala, dorsolateral pons, and rostroventral medulla (Weiller et al., 1995; Bahra et al., 2001; Afridi M. et al., 2005; Afridi S. K. et al., 2005; Denuelle et al., 2007; Maniyar et al., 2014; Schulte and May, 2016). These brain areas overlap with those thought to be affected in mood disorders (Anand and Shekhar, 2003; Deckersbach et al., 2006; Savitz and Drevets, 2009; Price and Drevets, 2010; Scharinger et al., 2010; Myers-Schulz and Koenigs, 2012; Baker et al., 2019; Nugent et al., 2019; Stickel et al., 2019), as well as cognitive disorders (Devous, 2002; Herholz et al., 2007; Woodard and Sugarman, 2012; Roy et al., 2016; Bayer, 2018; Jalilianhasanpour et al., 2019) and disorders of arousal (Nofzinger, 2005a,b, 2008; Chee and Chuah, 2008; Desseilles et al., 2008; Dijk, 2012; Chee, 2013; Elvsåshagen et al., 2019). In addition, these different disorders are likely to be connected to and affected by each other; for example mood and cognitive disorders are often linked, in that low mood worsens cognition.

The paucity of objective measures used in routine clinical practice to quantify such patient complaints among migraineurs and the lack of change on any clinical investigations, such as structural brain imaging to account for these complaints, often lead to the mislabel of these as being psychosomatic in nature or attributed to the possible migraine-related worsening of coexistent mood and fatigue problems. While it is feasible that chronic pain of any kind could predispose to mood and fatigue issues, migraine has distinct features that differentiate it from other episodic and chronic pain conditions, in that there seems to be a somewhat distinct brain signature of the acute attack, which involves regions outside of the pain matrix within the brain, and seems to strongly involve activation of limbic pathways even prior to pain onset (Maniyar et al., 2014). Intermittent or continuous presence of similar symptomatology in those with more frequent attacks, or indeed chronic pain, is possible and, rather than suggesting the presence of three different disorders, which may be managed under different specialties, is perhaps more of an indicator of dynamic and perhaps long-term altered brain network dysfunction in migraine.

This review will focus on the literature supporting associations between migraine and some of these other conditions, as well as literature regarding brain areas and systems, and we therefore hypothesize that shared biological mechanisms between common conditions, rather than true comorbidity, may be the reason for these associations. In addition, the fact that migraine is a threshold disease with a hypersensitivity to sensory input is likely to contribute. This theory suggests that, in some cases, treating the migraine may have benefits on some of the other symptoms, although incorporation of these other non-headache symptoms into clinical trials and understanding of their effects on migraine-related disability and function are required to allow systematic evaluation of treatment effects going forward.

NON-PAINFUL SYMPTOMS IN MIGRAINE (ICTALLY DURING ANY PHASE OR INTERICTALLY)

It has been alluded to as far back at the 19th century by Gowers (1899) that migraine involved prominent fatigue and lethargy. Despite this recognition, the full phenotype of symptoms that can be associated with migraine excluding headache and aura has been enhanced over the years, and it is now clear that symptoms can start hours to day prior to pain onset and in some individuals warn of impending headache (premonitory symptoms) (Giffin et al., 2003) and can persist during pain and following pain resolution (postdrome symptoms) (Giffin et al., 2016). The duration of time that any of these symptoms are present marks the entire duration of a single attack, which can be significantly longer than the canonical upper limit

of 72 h, highlighted in the International Classification for Headache Disorders [Headache Classification Committee of the International Headache Society (IHS), 2018], thus prolonging the morbidity associated with each attack and altering function before, during, and after headache.

The premonitory phase has been studied in some detail in the literature over the years, in both adults and children, with a variety of study designs and patient populations (Blau, 1980; Drummond and Lance, 1984; Waelkens, 1985; Rasmussen and Olesen, 1992; Russell et al., 1996; Giffin et al., 2003; Kelman, 2004; Quintela et al., 2006; Schoonman et al., 2006; Cuvellier et al., 2009; Guo et al., 2016; Karsan et al., 2016, 2020b; Laurell et al., 2016; Jacobs and Pakalnis, 2019; Onderwater et al., 2020; Wang et al., 2021). While some studies have looked at prevalence and the ability of these symptoms to predict impending headache, others have focused on phenotype. Across four decades of studies, the similarities in phenotype reported when looking at the most common symptoms are remarkably consistent irrespective of patient population and study design. The most common symptoms reported during this time in both adults and children and adolescents are tiredness, yawning, and mood change.

In comparison, the postdrome phase is relatively much less studied. However, again over the years, a few studies have shown a phenotype dominated by fatigue and cognitive change after headache resolution, along with a number of other symptoms (Blau, 1982; Kelman, 2006; Ng-Mak et al., 2011; Bose et al., 2016; Giffin et al., 2016; Mamouri et al., 2018). These symptoms often impair return to normal function following headache resolution, sometimes up to days later. Studies suggest that these symptoms may be more common than premonitory symptoms (reported prevalences 7–88% for premonitory symptoms and 68–91% for postdrome symptoms).

It is therefore clear that from before the headache starts, through to even days after its resolution, migraine can be associated with dominant fatigue, mood, and cognitive change, among other symptoms. Ictal studies during headache have been more difficult to conduct, and perhaps these affective symptoms become less noticeable in the presence of pain, but there remains a suggestion that these alterations are also present during headache (Gil-Gouveia and Martins, 2017; Barbanti et al., 2020). Certainly, interictal alterations in cognitive function (Mulder et al., 1999; Martins et al., 2012), mood (Minen et al., 2016; Peres et al., 2017), and fatigue or arousal (Seo and Park, 2018) have been reported in migraine relative to healthy controls, suggesting that the inherent sensory sensitivity of the migraine brain may oscillate with attacks but may not be truly normal at baseline.

MOOD AND MIGRAINE

A study of 36,000 participants in a population-based Canadian study showed that major depression, bipolar disorder, panic disorder, and social phobia were all at least twice as prevalent in migraine subjects, and these findings were independent of demographic and socioeconomic variables (Jette et al., 2008). Similarly, anxiety is also common, with a cumulative lifetime incidence among migraineurs of 50% (Minen et al., 2016). Studies have estimated that depression is 2–2.5 times more likely to occur among migraineurs than healthy controls (Lipton et al., 2000; Breslau et al., 2003; Jette et al., 2008), and concomitant depression is present in approximately 40% of migraineurs (Lipton et al., 2000). This relationship seems to be bidirectional, with one disorder increasing the risk of the other (Breslau et al., 1994).

The risks of depression and anxiety in migraine are unsurprisingly related to headache burden, with one study showing a linear relationship between headache frequency and the odds ratio of depression or anxiety (Zwart et al., 2003) and another showing increased odds ratios for both depression and anxiety in chronic migraine compared to episodic migraine (Adams et al., 2015).

FATIGUE AND AROUSAL IN MIGRAINE

Fatigue is a vague and multifactorial symptom, which is clearly influenced by sleep and arousal, systemic health, mood, and other exogenous factors including medications. While sleepiness and fatigue are different, there is clearly an interaction between them and a general difficulty among patients distinguishing the two. To our knowledge, the two separate issues or the distinction between them has not been studied in migraine studies. While it has been historically recognized that fatigue is a dominant feature of migraine (Gowers, 1899), more recently, associations with sleep disorders (Kelman and Rains, 2005; Nesbitt et al., 2014; Lucchesi et al., 2016; Rains, 2018; Buse et al., 2019) and shared physiological mechanisms with sleep pathways have been recognized (Holland and Goadsby, 2007; Holland, 2014, 2017; Vila-Pueyo et al., 2019). In addition, sleep disruption (oversleeping or undersleeping) is a commonly reported migraine trigger among sufferers (Pellegrino et al., 2018).

In general, it is estimated that approximately 60% of migraineurs report pathologic fatigue, based on several questionnaires including the Karolinska Sleepiness Scale, the Insomnia Severity Index, and the Fatigue Severity Scale (Seo and Park, 2018). Interestingly, emerging work using the novel CGRP pathway antibodies has suggested a beneficial impact on symptoms including fatigue and concentration on non-headache days and therefore improved function (VanderPluym et al., 2018).

At least a half of headache sufferers in one large study reported sleep disturbance (Kelman and Rains, 2005). A Norwegian-based population study found that migraineurs were three times more likely to have an Epworth Sleepiness Scale score of $\geq$10 compared to those without headache in nearly 300 subjects sampled and that migraineurs were five times more likely to have a high Karolinska Sleepiness Scale score compared to those without headache (Hagen et al., 2018).

SHARED NEUROANATOMY AND NEUROTRANSMITTER SYSTEMS

We here propose some brain areas and neurotransmitter systems that may be shared in migraine and disorders of

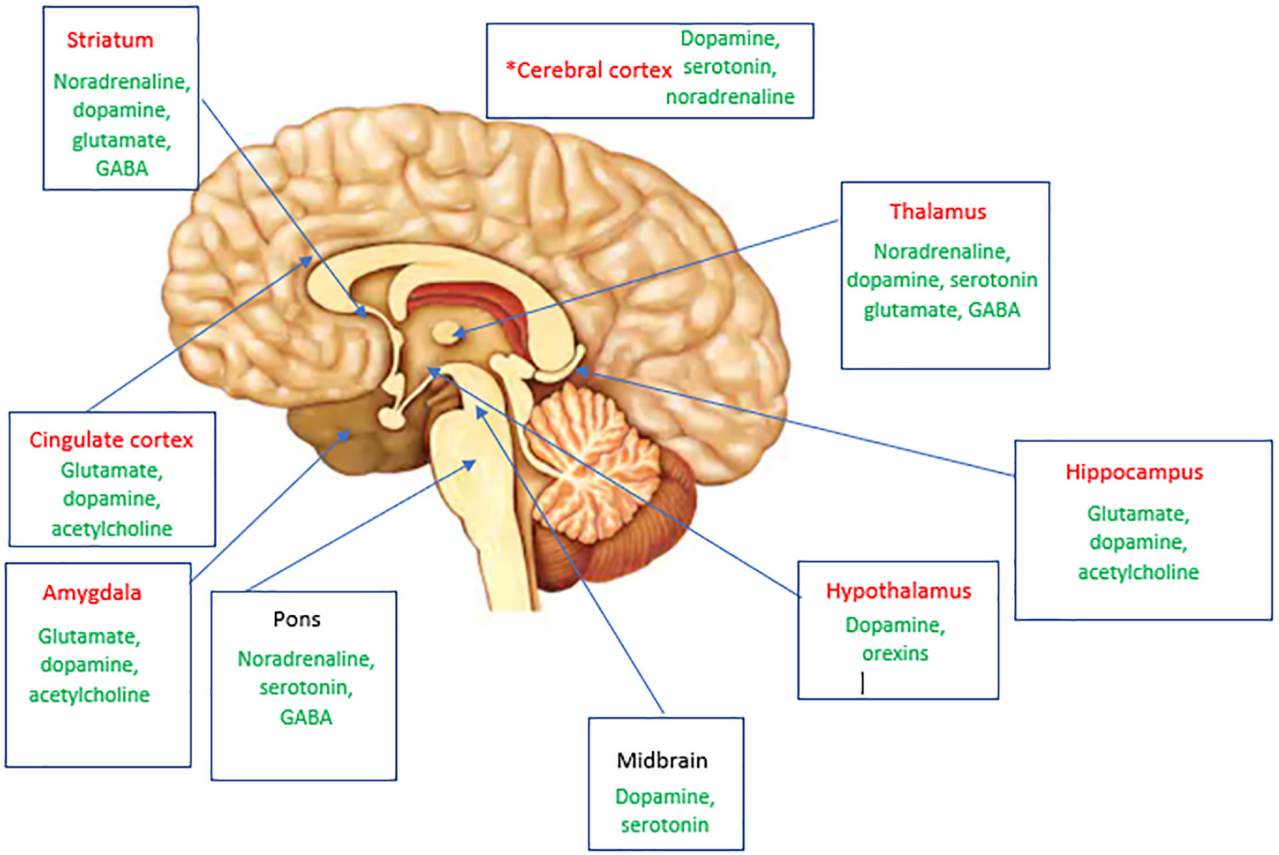

FIGURE 1 | A summary of brain areas likely to be involved in mediating both pain and mood and arousal complaints in migraine via structural and functional connections. Thalamocortical pathways that modulate sensory and cognitive processing are also involved. Neurotransmitters implicated in these areas in migraine are shown in green. *Specific cortical areas implicated include dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, and the primary somatosensory cortex. Areas highlighted in red are likely to also have a role with their associated neurotransmitters in fatigue and mood.

mood and fatigue (**Figure 1**). These brain areas and their functional and structural brain connections and corresponding neurotransmitter networks are likely involved in shared neurobiology between these disorders.

Anterior Cingulate, Orbitofrontal, and Dorsolateral Prefrontal Cortex, as Well as Other Limbic Areas

The involvement of limbic areas on functional brain imaging in pain states is thought to be related to the higher processing of nociceptive input, cumulating the sensory, cognitive, and affective components of pain (Derbyshire et al., 1997; Tracey, 2008). The involvement of such areas prior to pain onset in migraine has been more recently shown (Maniyar et al., 2014) and suggests that this is not an affective or cognitive consequence of pain and is probably responsible for mediating attentional, mood, and cognitive deficits early in the attack. Some of these areas are part of the default mode network (DMN), which has been implicated in the sensory integration, cognitive, and attentional aspects of pain in migraine (Tessitore et al., 2013).

The anterior cingulate (ACC) is an area in the ventromedial frontal cortex often divided into anterior and posterior subregions anatomically, or affective and cognitive regions functionally (Devinsky et al., 1995). Historically, bilateral cingulotomy in psychiatric practice has been used to help treat severe treatment-resistant obsessive–compulsive disorder (OCD), chronic pain, depression, and substance abuse, and the success of this surgery (success rates of between 30 and 80% have been reported) has raised the likely role of the ACC in emotional behavior modulation (Gasquoine, 2013). Neuropsychological follow-up of patients exposed to this surgery has suggested a role of the ACC in cognition and executive functioning. Supportive functional neuroimaging findings have shown abnormal ACC activation or its involvement in OCD (Menzies et al., 2008), chronic pain (Peyron et al., 2000), and other conditions, including addictions. Other frontal cortical areas have also been implicated in these conditions, including the orbitofrontal cortex in OCD (Meunier et al., 2012; Weygandt et al., 2012) and cocaine addiction (Risinger et al., 2005).

In various pain states, involvement of the ACC on functional imaging studies is almost constantly observed (Watanabe et al.,

2018; Shackman et al., 2011; Silvestrini et al., 2020), with a suggested role in affective and attentional responses to pain and in the selection of the response to pain. Additional areas of prefrontal cortex are thought to represent attentional and memory networks, which are also activated by noxious stimulation (Peyron et al., 2000). Support for prefrontal cortex involvement in pain states comes from functional neuroimaging evidence of the involvement of this brain area in acute pain in both clinical and experimental pain conditions (Apkarian et al., 2005). Even interictally in the absence of pain, migraineurs seem to display altered cerebral processing of negative and sensory stimuli, with increased activity on functional brain imaging in posterior cingulate cortex (PCC), caudate, amygdala, and thalamus (Wilcox et al., 2016), thereby implicating dysfunctional limbic networks in migraine, even in the absence of pain.

There have been studies demonstrating brain metabolite differences in the ACC of migraineurs compared to healthy controls using magnetic resonance spectroscopy, suggesting altered neurochemistry in this region in migraineurs. It is postulated that this difference may contribute to neuronal hyperexcitability in migraine (Becerra et al., 2016). Another study has also suggested orbitofrontal cortex hypofunction in migraine, in the context of medication overuse headache, using ^{18}F-FDG positron emission tomography imaging. It was demonstrated that, although most of the pain matrix areas recovered to almost normal metabolism following medication withdrawal from hypometabolism during analgesic overuse, the orbitofrontal cortex remained hypoactive (Fumal et al., 2006).

Connectivity studies have demonstrated altered functional connectivity between these regions of cingulate and frontal cortex and other areas of interest in migraine. Russo et al. (2012); Tessitore et al. (2015), Yu et al. (2012), and Xue et al. (2013) have shown that migraineurs with and without aura in the resting state display reduced connectivity within regions of the frontoparietal network, including the middle frontal gyrus and ACC and areas of the DMN such as ACC, prefrontal cortex, and orbitofrontal cortex, relative to healthy controls. Other functional imaging studies have also shown that some of these regions may have altered metabolism in migraineurs (Kim et al., 2010; Becerra et al., 2016).

The ACC and orbitofrontal cortex have been shown to be functionally connected and involved in emotional processing, as well as having interlinked downstream output pathways to thalamus and amygdala (Garcia-Cabezas and Barbas, 2017). Disrupted thalamocortical connections to the ACC and prefrontal cortex through ischemic damage can lead to a dysexecutive syndrome (Serra et al., 2014), suggesting that functional integrity of these thalamocortical pathways is required for emotional processing and executive function. Both the hypothalamus and thalamus have limbic connections to the ACC (Morgane et al., 2005), and these regions may also be implicated in aversion to negative sensory stimuli in migraine, as part of a hypersensitive corticolimbic network (Wilcox et al., 2016).

These studies into the ACC and other frontal cortical areas in migraine and in other pain states suggest the role of these regions in the emotional processing of pain, as well as their roles in other behavioral and cognitive modalities.

Thalamus

While classically the thalamus is well-recognized as part of the pain network within the brain and altered thalamocortical activity prior to pain onset in migraine has been shown and is likely involved in mediating early altered sensory processing (Maniyar et al., 2014; Karsan et al., 2020a). Its early role is unsurprising, given it has bidirectional projections to areas including limbic and cortical sensory areas.

The involvement of the thalamus and its cortical connections have been thought to mediate the hyperexcitability of the migraine brain to sensory stimulation and the sensitivities of the migraine brain to homeostatic alterations (Noseda et al., 2014, 2017). Functional resting state connectivity studies have demonstrated altered thalamocortical connectivity interictally in migraine and hypothesized that these changes may be involved in the mood and cognitive symptoms migraineurs can experience particularly with increasing attack frequency (Coppola et al., 2016a,b), the interictal sensitivity to homeostatic alterations and in mediating the threshold to pain through regulation of inhibition or facilitation of pain (Wang et al., 2016), as well as the role of the thalamus in chronification in migraine (Coppola et al., 2013).

We have previously demonstrated reduced functional connectivity between the thalamus and cuneus/precuneus region during the premonitory phase of migraine (Karsan et al., 2020a). The precuneus is a cortical parietal region involved in a wide spectrum of activities, including memory, visuospatial imagery, and self-consciousness (Cavanna and Trimble, 2006). The precuneus is also part of the DMN, and altered connectivity in this network has been demonstrated in migraine, predominantly interictally, with regard to decreased connectivity between the precuneus and areas outside the DMN, namely, other cortical pain-processing areas (Zhang et al., 2016). Wang et al. (2016) also used thalamic seeds to examine resting state functional connectivity between the thalami and other brain regions in interictal migraine without aura and found reduced connectivity between the posterior thalamus and precuneus/PCC region.

The cuneus is dorsal to the precuneus and is involved in primary visual processing. The cuneus and other regions of the occipital lobe (such as the lingual gyrus) have been implicated structurally and functionally in migraine, particularly in those with aura (Palm-Meinders et al., 2017). Despite its predominant role in vision, the cuneus has been implicated as playing a role in psychiatric disease such as depression (Zhong et al., 2017) and dementia with Lewy bodies (Minoshima et al., 2002); these studies thereby suggest its likely role in multisensory integration and cognitive processing.

Basal Ganglia

Of particular recent interest in migraine is the highly dopaminergic ventral tegmental area (VTA). The substantia nigra is a dense dopaminergic nucleus in the ventral tegmentum and has emerged in a few migraine imaging studies as a potential area of interest in migraine (Welch et al., 1998; Cao et al., 2002), in particular prior to the onset of pain in the premonitory phase (Maniyar et al., 2014).

Three main dopaminergic brain pathways evolve from the VTA and substantia nigra: the mesocortical (cognitive control, motivation, and emotional response), mesolimbic (motivation, desire, reinforcement, learning, and fear), and nigrostriatal (reward, memory consolidation, and direct and indirect motor pathways) pathways. These pathways all arise from the substantia nigra and VTA areas and project to other brain areas of interest in migraine, via subcortical and cortical connections using dopamine, glutamate, and γ-aminobutyric acid (Bannon and Roth, 1983; Bertolucci-D'Angio et al., 1990; Haber et al., 2000).

The dorsal raphe nucleus (DRN) is serotoninergic and also located in the midbrain tegmentum region (Hornung, 2003). It receives afferents from several brain regions and sends projections to various other brain regions, including the caudate, putamen, and substantia nigra, as well as to the trigeminal nucleus caudalis (Imai et al., 1986) and to medial prefrontal cortex (Stratford and Wirtshafter, 1990). As well as its roles in pain (Wang and Nakai, 1994), the DRN is also involved in sleep–wake regulation via its connections to locus coeruleus and hypothalamus (Monti, 2010a,b). In addition, the DRN has been demonstrated to have a role in depression; the dorsomedial part of this nuclei group is innervated by other brain structures that can regulate mood states (Lowry et al., 2008). This nuclei group and its dopaminergic and serotoninergic projections are therefore of interest in migraine, especially as this region could be involved in the effective therapeutic response of migraine to dihydroergotamine and triptans (Vila-Pueyo et al., 2018).

In addition to the midbrain and substantia nigra, several pain imaging studies have also previously implicated other regions in the basal ganglia in pain processing and indeed in migraine (Kobari et al., 1989; Welch et al., 1998; Maleki et al., 2011; Yuan et al., 2013; Shokouhi et al., 2016). The basal ganglia circuitry with the thalamus and cortex has been implicated in the integration of motor, cognitive, emotional, and autonomic responses to pain (Chudler and Dong, 1995; Borsook et al., 2010). Additional evidence for basal ganglia involvement in migraine comes from a study demonstrating neuronal activity alterations in the caudate following cortical spreading depression, which may contribute to pain as well as other alterations in cognition and behavior in migraine (Seghatoleslam et al., 2014).

ALTERED BRAIN ACTIVITY IN MIGRAINE AND RELATIONSHIP TO CHRONICITY

Common structural areas and functional pathways between brain areas in migraine and mood and fatigue states, as well as aminergic neurotransmitter systems involving dopamine, serotonin, and noradrenaline, are therefore likely involved in the association between migraine and mood and fatigue states.

Emerging functional imaging work has suggested that longstanding and chronic disease in migraine can alter brain network function (Aurora et al., 2007; Coppola et al., 2013, 2017; Goadsby, 2013; Schwedt et al., 2013; Hubbard et al., 2014; Androulakis et al., 2017a,b; Schulte et al., 2017), and it is clear that these networks can be modulated by various means including medication overuse (Fumal et al., 2006; Grazzi et al., 2010; Riederer et al., 2013; Lai et al., 2016). Pain is a complex experience, and migraine clearly involves altered function in brain areas both within and external to regions of the pain network. Inherent to migraine as a disorder is the theory of thresholding and disordered sensory processing. Such brain alterations may be dynamic and therefore also susceptible to exogenous (Panconesi et al., 2012; Ashina et al., 2017) or endogenous (Pakalnis, 2016) triggering. Brain alterations may also become fixed with time and may be a cause or an effect of disease chronification. Chronic migraine studies have suggested fixed changes in brain structure with increased disease burden (Aurora et al., 2007; Valfre et al., 2008; Coppola et al., 2013, 2017; Goadsby, 2013; Hubbard et al., 2014; Schulte et al., 2017).

SUMMARY

Through review of the current and evolving literature, we have here summarized the possible links between migraine as a neural disorder, and disorders of fatigue and mood. We hypothesize that shared biological mechanisms via brain regions and neurotransmitter pathways are likely involved in the bidirectional links between migraine and these disorders, rather than true comorbidity due to other reasons. Treating underlying migraine in those with mood and fatigue complaints is likely to form an important aspect to their management. Further understanding of these diseases' associations can be developed through increased attention to clinical trial design and prospective symptom recording by patients, as well as systematic documentation of therapeutic responses of non-painful symptoms to migraine treatments.

FURTHER WORK

Systematic and objective quantification of non-painful disability associated with migraine will help us better understand how to classify this symptomatology in migraine and who and how we could best manage these symptoms for the benefit of patients. This increased understanding of dynamic and oscillating brain changes throughout a migraine attack, as well as more fixed functional and structural changes related to disease activity and chronicity, suggest that we now have a plausible anatomical, biological, and neurochemical link between migraine and disorders of mood and fatigue. Emerging evidence suggests that the strong implication of limbic connectivity in migraine is a feature throughout the attack (O'Carroll, 2007; Burstein and Jakubowski, 2009; Stankewitz and May, 2011; Hadjikhani et al., 2013; Wilcox et al., 2016; Chen et al., 2017; Chong et al., 2017; Karsan et al., 2020a).

This work provides a novel avenue to think about the associated mood and cognitive symptomatology in migraine and to consider objectively measuring migraine-associated disability in clinical trials, in the clinic and for research purposes, with validated measures of mood, fatigue, and cognition, so that the association of these conditions with migraine can be systematically studied in a randomized and controlled way,

and associated with headache burden. In particular, given that emerging evidence suggests that effective migraine treatment could improve scores on validated measures of fatigue and cognition, incorporation of these factors involved in non-headache disability into clinical trial capture is important (VanderPluym et al., 2018). Such strategies going forward would help explore the relationship between migraine and depression or fatigue, or lead to the acceptance of depression and fatigue as accepted features of the disorder, not necessarily warranting separate treatment but being managed as part of the disorder itself.

CONCLUSION

The understanding of what a migraineur actually experiences and the effective management of this are vital to the physician–patient alliance in headache medicine and in communicating disease and attack-related disability to family, friends, colleagues, employers, and schools. Many sufferers feel that their disease burden is underrecognized, ill managed, and largely attributed to psychological disease and therefore mismanaged. We hypothesize based on the current evidence that perhaps for classification, diagnosis, management, and clinical trial design, migraine should be considered a neural disorder of mainly aminergic brain function, in which alterations in networks integrating the limbic system with the sensory and homeostatic systems occur early via the thalamus, and the involvement of the pain system is one part of the process but not invariable. These networks are likely also implicated in the disorders of mood and fatigue, but in migraine have an additional role in mediating sensory hypersensitivity and pain. Systematic and objective quantification of non-painful disability associated with migraine will help us better understand how to classify this symptomatology in migraine and who and how we could best manage these symptoms for the benefit of patients. In addition, systematic data capture of non-painful symptoms in migraine and their associated disability in clinical trials going forward, and the effects of treatment, will allow evaluation of therapeutic effects on these symptoms.

AUTHOR CONTRIBUTIONS

NK was responsible for reviewing the literature, collating the data, and writing the manuscript. PG was responsible for reviewing the manuscript and giving expert input prior to submission. Both authors contributed to the article and approved the submitted version.

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Migraine With Aura Is Related to Delayed Motor Control Reaction and Imbalance Following External Perturbations

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Background: It is evidenced that migraineurs present balance deficits. However, the balance recovery following unexpected ground perturbations, which reflect conditions of everyday activities, has not been investigated in this population.

Aim: We aimed to assess the reactive postural responses among patients with migraine with and without aura, chronic migraine, and controls. We further aimed to assess the factors associated with greater self-report of falls.

Methods: Ninety patients diagnosed by headache specialists were equally classified into three migraine subgroups according to the presence of aura and chronic migraine. Thirty controls were also recruited. All participants underwent the motor control test (MCT) and adaptation test (ADT) protocols of dynamic posturography tests (EquiTest®, NeuroCom, USA). Clinical and headache features and information on falls in the previous year, fear of falling, and vestibular symptoms were also assessed.

Results: Patients with aura presented a greater sway area in most of the MCT conditions than the other three groups ($p = 0.001$). The aura group also presented delayed latency responses after perturbations compared with controls and patients without aura ($p < 0.03$). In the ADT, a greater sway area was observed in patients with aura than in groups without aura, chronic migraine, and controls ($p < 0.0001$). The MCT and ADT sway area, the frequency of aura, and the fear of falling explained 46% of the falls in the previous 12 months.

Conclusion: Patients with aura exhibited greater delay and sway area after unexpected ground perturbations than controls and other migraine subgroups, which are related to the reported number of falls.

Keywords: migraine disorders, aura, postural control, clinical evaluation, posturography

INTRODUCTION

Postural control depends on the integrity of multiple complex mechanisms to achieve (1) upright stability under different sensory conditions, (2) coordination and balance during voluntary movements, and (3) motor reactions under external destabilizing conditions, such as a slip or push (1, 2). For upright stability, recent studies have demonstrated alterations among patients with migraine in quiet standing conditions, including firm and foam surfaces, with open and closed eyes (3–6). Performance and balance deficits during voluntary movements are also verified in this population in contrast to controls during daily activities (5, 7, 8). While stability during upright standing is impaired in migraine with aura and chronic migraine compared with patients without aura (5, 6, 9), their performance during voluntary movements does not differ among the migraine subtypes (7).

Despite these findings associating migraine with lower functionality and balance changes, aspects related to balance recovery after sudden external perturbations remain largely unexplored in this population. The ability to perform a successful reactive response following an unexpected perturbation is crucial to prevent a fall (10). The performance of adequate corrective motor responses requires an adequate integration among neural, sensory, and musculoskeletal systems (11, 12).

The detection of postural deficits following a perturbation is essential to tailor rehabilitation programs (13), once they reflect conditions underlying everyday activities that involve feedback-based postural reactions, such as slips or trips (14). Accordingly, we aimed to assess the reactive postural responses among patients with migraine with and without aura, chronic migraine, and healthy controls. Furthermore, we aimed to determine which factors are associated with a greater number of self-reported falls in the last year. Based on previous evidence of postural control impairment among migraineurs (3–8), we hypothesized that deficits in reactive postural responses would also be verified in all migraine subtypes in contrast to controls.

METHODS

Participants

This cross-sectional study was approved by the Investigation Review Board of the University Clinical Hospital of Ribeirão Preto (process number: 15572/2016). All included participants provided written informed consent before enrollment in the study. The sample of migraineurs was recruited in a tertiary headache center and the local community, with migraine diagnosis made by neurologists, following the criteria established by the International Headache Society in the third edition of the International Classification of Headache Disorders (15). Patients with migraine ($n = 90$) were stratified equally into three subgroups according to the presence of aura (migraine with and without aura, MA and MoA, respectively) and frequency of attacks over 15 days within a month (chronic migraine, CM). A group of healthy participants (CG, $n = 30$) composed of family members of the patient or hospital staff were also recruited.

We included women from 18 to 55 years old. Migraine participants had to have a minimum of 3 days of headache per month within the last 3 months. Controls were included if they reported no primary headache, and any secondary headache with occurrence greater than two times within the last 6 months. Exclusion criteria encompassed the diagnosis of any rheumatic, neurologic, cardiovascular, or vestibular pathology [such as neuritis, benign paroxysmal positional vertigo (BPPV) or Ménière's disease], as well as pregnancy or any chronic pain condition. Abnormal neurological examination results and patients with any concomitant primary or secondary headaches (i.e., tension-type headache or medication-overuse headache) were also excluded. For the homogeneity of the sample, patients with aura had to be diagnosed with typical aura, and therefore, we did not include the diagnosis of brainstem aura, hemiplegic migraine, or retinal migraine. Furthermore, if patients reported a migraine attack on the appointment day, the evaluation was rescheduled to a headache-free day.

Procedures

Participants who met the inclusion and exclusion criteria answered a questionnaire recording age, height and weight, migraine frequency, onset, intensity and duration, medication intake, presence of vestibular symptoms, and the number of falls within the last 12 months. Falls were defined according to the World Health Organization (WHO) (16). Furthermore, participants were instructed to answer the Falls Efficacy Scale-International (FES-I), which measures the level of concern with fall occurrence during functional daily living activities (17). The FES-I scores range between 16 and 64, and higher scores indicate greater concern levels and fear of falling.

Afterward, the participants were referred to an examiner blinded toward the study groups, who guided the physical exam in the computerized dynamic posturography equipment (EquiTest®, NeuroCom, OR, USA). The participants were instructed to step over the platform, positioning the feet apart at a standardized distance, according to their height as described by the guide brochure of the manufacturer (18). They were secured by an overhead harness, which would prevent falls without limiting body movement. Participants performed the motor control (MCT) and adaptation (ADT) tests in the EquiTest®.

The MCT consisted of assessing the motor reactions of the participants following an unexpected translation of the support surface in forward and backward directions in three levels (small, medium, and large). For both forward and backward directions, the small translation consisted of 0.7° of equivalent sway for 250 ms, the medium translation has 1.8° of equivalent sway for 300 ms, and the large translation has 3.2° of equivalent sway for 400 ms (18). Each excursion was repeated three times. The mean latency was determined by the elapsed time in milliseconds (ms) between the onset of the support translation until the active sway response of the participant. Furthermore, a composite latency was assessed considering all the test conditions. This test is considered a valid and reliable measure (19–21), with no significant learning effect (20). It is also highly correlated with motor performance and falls occurrence, and has been used to assess several neurologic and vestibular conditions (1, 14, 22).

TABLE 1 | Mean (SD) and percentages (%) of the sample demographic characteristics.

	Control group	Migraine without aura	Migraine with aura	Chronic migraine	*Statistical result*
Age (years)	31.3 (9.3)	32.5 (8.7)	32.2 (8.3)	34.6 (10.0)	$F = 0.68$, $p = 0.556$
BMI (kg/cm^3)	24.9 (4.1)	24.1 (3.6)	24.5 (4.2)	23.8 (2.9)	$F = 0.51$, $p = 0.67$
Migraine onset (years)	–	15.5 (7.8)	18.0 (9.2)	18.0 (10.9)	$F = 0.73$, $p = 0.48$
Migraine frequency (attacks/month)	–	7.3 (3.3)‡	7.6 (2.9)‡	23.3 (5.8)	**$F = 141.17$, $p < 0.0001$**
Aura frequency (attacks/month)	–	0 (0)	4.10 (2.54)†	1.87 (4.07)†	**$F = 16.46$, $p < 0.0001$**
Migraine duration (h)	–	17.8 (20.5)	34.0 (29.4)	26.2 (27.5)	$F = 2.87$, $p = 0.06$
Migraine intensity (NRS: 0–10)	–	7.4 (1.3)	7.6 (1.9)	8.1 (1.7)	$F = 1.15$, $p = 0.31$
Prophylactic medication intake (%)	10%	30%	40%	56.7%	**$x^2 = 15.23$, $p = 0.002$**
Interictal vestibular symptoms (%)	13%	37%	57%	50%	**$x^2 = 13.81$, $p < 0.003$**
Ictal vestibular symptoms (%)	0%	60%	87%	77%	**$x^2 = 54.98$, $p < 0.001$**
Number of falls (last 12 months)	0.3 (0.5)	1.4 (2.4)	4.6 (5.8)*	4.4 (7.2)*	**$F = 5.92$, $p = 0.001$**
Falls efficacy scale (FES-I)	20.1 (4.5)	23.7 (5.5)	27.5 (4.9)*	27.3 (7.8)*	**$F = 10.82$, $p < 0.0001$**

*SD, standard deviation; BMI, body mass index; NRS, numeric rating scale (0–10). Bonferroni post-hoc: *$p < 0.02$ vs. control group. †$p < 0.03$ vs. migraine without aura group. ‡$p < 0.0001$ vs. chronic migraine group. Bold expresses significant results.*

The ADT also assessed motor reactions, but following abrupt platform rotations to the direction of toes up and down, with an amplitude of 8° and duration of 400 ms. Participants performed five trials for each direction, and the mean of the trials and conditions was considered. The mean sway energy (ranging from 0 to 200) for toes up and down was measured. This outcome is calculated by the Equitest® software, based on the weighted sum of the RMS velocity and acceleration of the anteroposterior center of pressure (CoP) displacement. Lower scores reflect better adaptation on minimizing sway after the support surface rotation (18).

Both MCT and ADT tests started after random delays lasting between 3 and 5 s to prevent movement prediction and consider the response based on the automatic postural control system (18). Furthermore, we also considered, for both tests, the CoP sway area as an outcome, which comprised 90% of the displacement ellipse (cm^2) in the MCT and ADT tests. This outcome reflected the body instability induced by the support surface excursion during the attempt to recover balance. Based on the exported raw CoP data obtained by the force plates, the sway area was calculated using the MATLAB 2019a software (23).

Statistical Analysis

The sample size for this study was calculated based on a pilot study with 10 patients with MoA and 10 controls, considering a difference between groups of 12 ms in the composite latency score of the MCT test. A minimum of 28 subjects was required to detect differences between groups with an effect size of 0.8, alfa of 5%, and 90% of power. Mean, standard deviations, or 95% confidence interval (CI) were calculated to present clinical characteristics of each group. Variables with normal distribution (non-significant Kolmogorov–Smirnov test) were compared through analysis of variance (ANOVA) for independent samples with Bonferroni *post-hoc* test. The distribution of nominal data was presented through percentages, and groups were compared through Chi-squared tests.

All the MCT and ADT test outcomes were analyzed through multiple generalized linear models considering all the test conditions and further corrected for multiplicity by Bonferroni correction. Furthermore, a multiple linear regression using backward elimination was calculated to explain the variability of the number of reported fall events in the last 12 months. The following clinical and motor control variables were included in the model: migraine onset, frequency of attacks, frequency of aura, fear of falling scores (FES-I), intake of prophylactic medication, ADT sway area, MCT composite latency, and sway area during the medium and large backward and forward translations of the MCT. A minimum of 10 participants per variable was considered in the linear regression analysis (24).

RESULTS

Table 1 presents the demographic data of the participants. Differences among groups were found regarding prophylactic medication intake ($x^2 = 15.23$, $p = 0.002$), migraine frequency ($F = 141.17$, $p < 0.0001$), self-report of ictal ($x^2 = 54.98$, $p < 0.001$) and interictal vestibular symptoms ($x^2 = 13.81$, $p < 0.003$), self-report of falls within the last 12 months ($F = 5.92$, $p = 0.001$), and FES-I scores ($F = 10.82$, $p < 0.0001$). No differences between groups were found regarding age, BMI, migraine onset, duration, or intensity.

In the MCT test, patients with migraine with aura presented greater sway area after medium backward perturbation than the other three groups [MA: 10.51 (8.43 to 12.59) vs. CG: 4.44 (2.36 to 6.52), vs. MoA: 5.63 (3.55 to 7.71), vs. CM: 6.22 (4.14 to 8.30); $F = 6.34$, $p = 0.001$] and after large backward perturbation than controls [MA: 16.17 (13.45 to 18.90) vs. CG: 8.93 (6.20 to 11.65); $F = 4.71$, $p = 0.004$]. Following the forward perturbations, patients with aura presented a greater sway area than controls and migraineurs without aura in the small [MA: 8.23 (5.96 to

TABLE 2 | Mean and 95% CI of sway area and latency during the motor control test (MCT) and adaptation test (ADT) among migraine groups and controls.

		Control group	Migraine without aura	Migraine with aura	Chronic migraine
MCT area (cm^2)	Small backward	2.57 (−3.02 to 8.17)	3.90 (−2.69 to 9.50)	11.02 (5.42 to 16.62)	3.54 (−2.05 to 9.14)
	Medium backward	4.44 (2.36 to 6.52)	5.63 (3.55 to 7.71)	10.51 (8.43 to 12.59)*†‡	6.22 (4.14 to 8.30)
	Large backward	8.93 (6.20 to 11.65)	11.75 (9.03 to 14.48)	16.17 (13.45 to 18.90)*	11.86 (9.14 to 14.59)
	Small forward	2.21 (−0.04 to 4.48)	3.12 (0.86 to 5.39)	8.23 (5.96 to 10.49)*†	4.20 (1.94 to 6.47)
	Medium forward	6.63 (3.51 to 9.74)	7.23 (4.12 to 10.35)	13.54 (10.43 to 16.66)*†	11.66 (8.54 to 14.77)
	Large forward	13.90 (7.79 to 20.02)	15.40 (9.28 to 21.51)	27.37 (21.55 to 33.48)*†	22.24 (16.31 to 28.36)
MCT latency (s)	Small backward	133.83 (127.20 to 140.47)	129.67 (123.03 to 136.30)	142.77 (136.70 to 149.40)†	137.33 (130.70 to 143.97)
	Medium backward	124.78 (118.63 to 130.93)	129.83 (123.68 to 135.98)	138.00 (131.84 to 144.15)*	130.83 (124.68 to 136.98)
	Large backward	122.67 (117.02 to 128.31)	125.63 (119.98 to 131.28)	130.00 (124.35 to 135.64)	124.67 (119.02 to 130.31)
	Small forward	142.50 (133.66 to 151.34)	149.00 (140.16 to 157.84)	159.00 (150.16 to 167.84)	149.67 (140.82 to 158.51)
	Medium forward	133.53 (126.23 to 140.83)	140.00 (132.69 to 147.30)	150.00 (142.70 to 157.30)*	141.00 (133.69 to 148.30)
	Large forward	126.00 (120.67 to 131.32)	132.33 (127.01 to 137.66)	135.50 (130.17 to 140.82)	128.50 (123.17 to 133.82)
	Composite	126.67 (121.90 to 131.43)	132.00 (127.22 to 136.77)	138.37 (133.60 to 143.14)*	131.30 (126.53 to 136.07)
ADT area (cm^2)		10.18 (7.66 to 12.7)	13.15 (10.63 to 15.67)	19.04 (16.52 to 21.56)*†‡	13.79 (11.26 to 16.31)
ADT sway energy		58.73 (54.97 to 62.49)	57.86 (54.1 to 61.62)	59.33 (55.57 to 63.09)	58.85 (55.09 to 62.61)

MCT, motor control test; ADT, adaptation test.
**$p < 0.01$ vs. control group; †$p < 0.04$ vs. migraine without aura; ‡$p = 0.03$ vs. chronic migraine.*

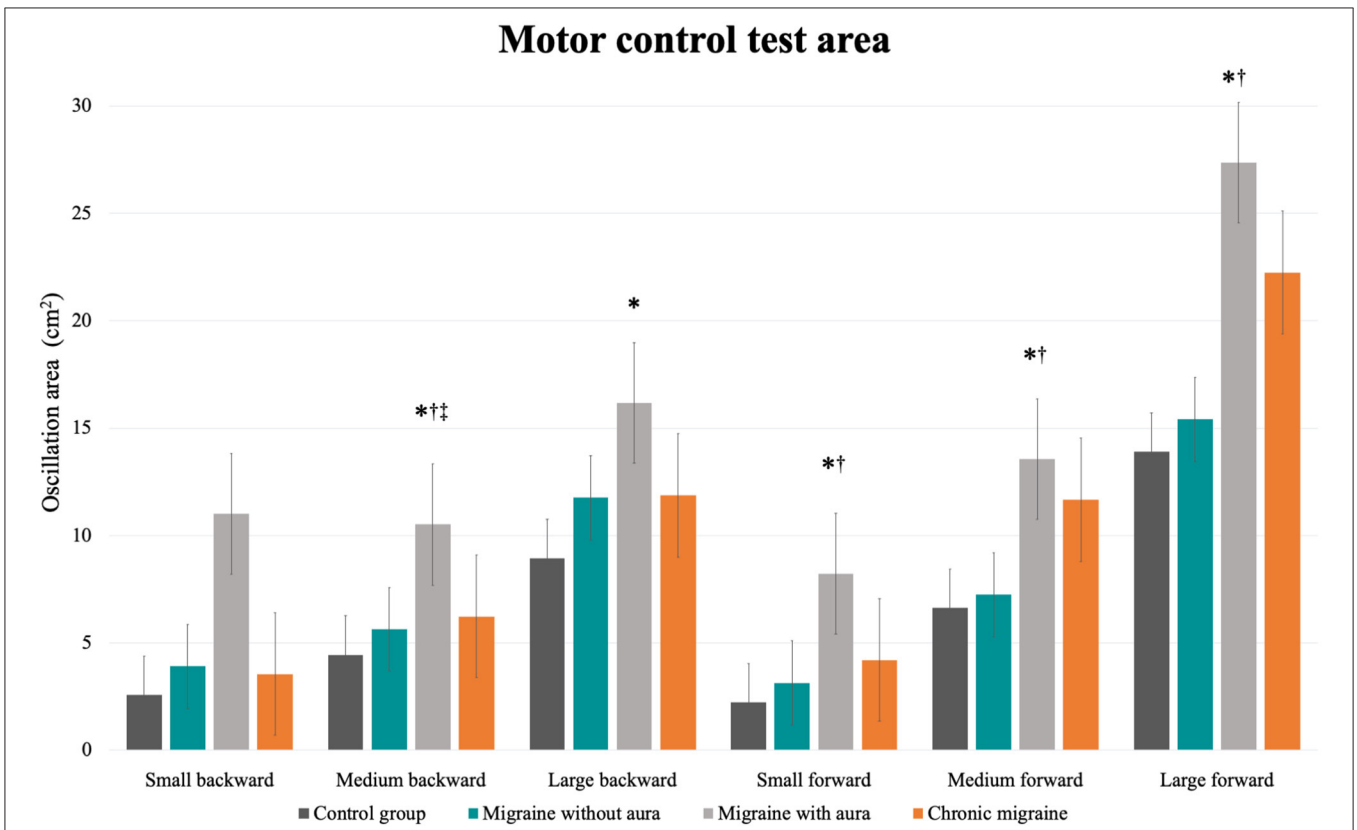

FIGURE 1 | Mean and standard errors of the oscillation area (cm^2) of each condition of the motor control test among patients with migraine with and without aura, chronic migraine, and controls. *$p < 0.01$ vs. control group; †$p < 0.04$ vs. migraine without aura; ‡$p = 0.03$ vs. chronic migraine.

10.49) vs. CG: 2.21 (−0.04 to 4.48), vs. MoA: 3.12 (0.86 to 5.39); $F = 5.38$, $p = 0.002$], medium [MA: 13.54 (10.43 to 16.66) vs. CG: 6.63 (3.51 to 9.74), vs. MoA: 7.23 (4.12 to 10.35); $F = 4.59$, $p = 0.004$], and large amplitudes [MA: 27.37 (21.55 to 33.48) vs. CG: 13.90 (7.79 to 20.02), vs. 15.40 (9.28 to 21.51); $F = 4.10$, $p = 0.008$]. The aura group also presented delayed latency

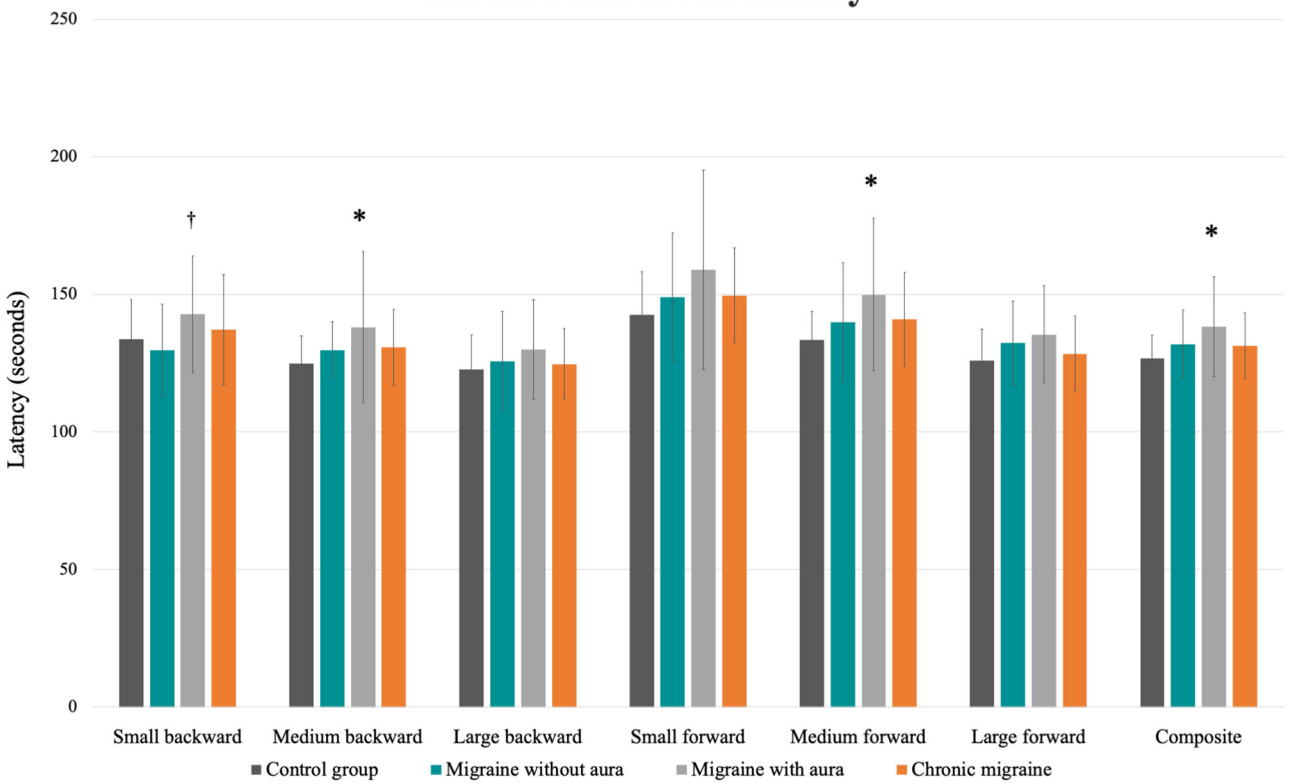

FIGURE 2 | Mean and standard errors of the latency (s) of each condition of the motor control test among patients with migraine with and without aura, chronic migraine, and controls. *$p < 0.01$ vs. control group; †$p < 0.04$ vs. migraine without aura.

responses after perturbation in contrast to controls for medium backward [MA: 138.00 (131.84 to 144.15) vs. CG: 124.78 (118.63 to 130.93); $F = 3.07$, $p = 0.03$] and medium forward [MA: 150.00 (142.70 to 157.30) vs. CG: 133.53 (126.23 to 140.83); $F = 3.38$, $p = 0.02$] perturbations, and composite latency [MA: 138.37 (133.60 to 143.14) vs. CG: 126.67 (121.90 to 131.43); $F = 3.99$, $p = 0.01$]. In contrast to migraineurs without aura, delayed latency response was verified in patients with aura for the small backward perturbation [MA: 142.77 (136.70 to 149.40) vs. MoA: 133.83(127.20 to 140.47); $F = 2.74$, $p = 0.04$]. These results are presented in **Table 2** and **Figures 1**, **2**.

No differences among groups were verified for the mean sway energy for the ADT test ($F = 0.10$, $p = 0.96$). However, patients with aura presented a greater sway area following the perturbations than the groups without aura, chronic migraine, and controls [**Table 2**; **Figure 3**: MA: 19.04 (16.52 to 21.56) vs. CG: 10.18 (7.66 to 12.7), vs. MoA: 13.15 (10.63 to 15.67), vs. CM: 13.79 (11.26 to 16.31); $F = 8.39$, $p < 0.0001$].

Table 3 shows the results of the multiple linear regression. The initial model presented a significant regression equation [$F_{(11,108)} = 9.14$, $p < 0.0001$], with an R^2 of 0.48. After the backward criteria for variable exclusion, the last model included five significant predictors [$F_{(5,114)} = 19.18$, $p < 0.0001$] with an R^2 of 0.46. Predicted number of falls of the participants are influenced by the frequency of aura (+0.62), FES-I scores (+0.28), by the MCT medium front oscillation area (−0.19), by MCT large front oscillation area (+0.08), and by the ADT area (+0.10).

DISCUSSION

Our results partially confirmed our initial hypothesis that altered responses following the support surface perturbation would be verified in all migraine subtypes compared with healthy controls. Increased response delay and postural sway area were observed only among patients with aura vs. controls and in some conditions compared with the remaining migraine groups. We further found that the MCT and ADT sway area, the frequency of aura, and fear of falling explained 46% of the falls in the previous 12 months.

The presence of aura seems to have a negative impact on the static balance of the migraineurs (5, 6, 9), and this is a strength of our work since most of the previous studies did not distinguish groups based on migraine subdiagnosis (4, 8, 25–29). However, for postural control during dynamic tasks such as gait, sit to stand, climb up and down the stairs, or limits of stability, comparable performance was verified among patients with and without aura and chronic migraine, with all

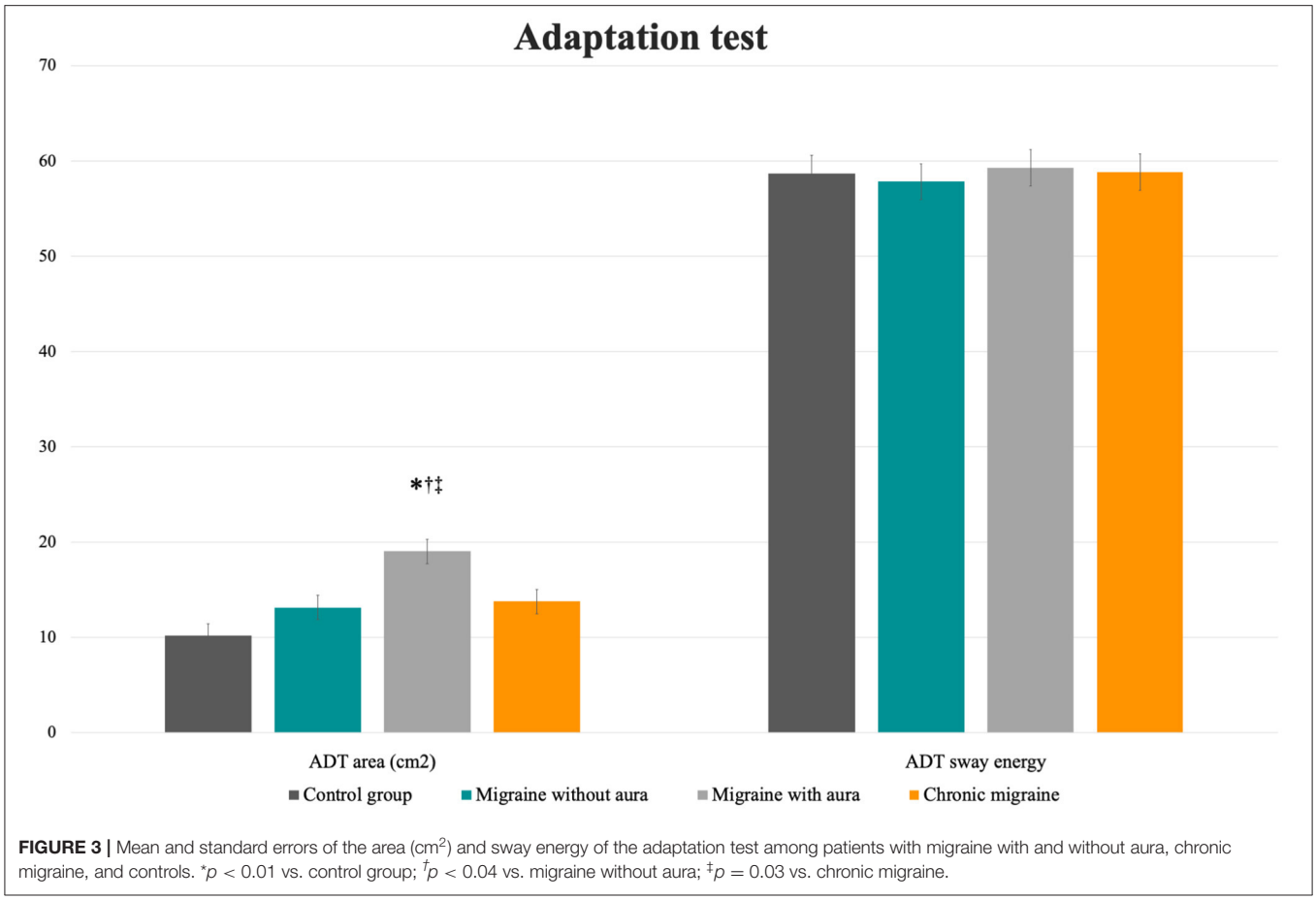

FIGURE 3 | Mean and standard errors of the area (cm^2) and sway energy of the adaptation test among patients with migraine with and without aura, chronic migraine, and controls. $^{*}p < 0.01$ vs. control group; $^{\dagger}p < 0.04$ vs. migraine without aura; $^{\ddagger}p = 0.03$ vs. chronic migraine.

differing from controls (6, 7). Interestingly, contrary to previous studies on static balance (5, 9), patients with chronic migraine did not show a decreased performance while reacting from external perturbations.

This specific task of external perturbation reaction involves a complex sequence of balance correcting synergies based on preprogrammed muscle patterns within the postural control networks in the central nervous system (14). The muscle synergy activation elicits a motor response combining trunk, upper, and lower limb movements to stabilize balance (30), after a triggering input from the somatosensory, visual, and/or vestibular systems (11). Peripheral and central areas, including the spinal cord, brainstem, cerebellum, basal ganglia, parietal, and frontal areas, are involved in controlling the standing balance when external perturbations are present (14, 31).

In contrast to migraineurs without aura, patients with aura often present an additional burden, including greater self-reported vestibular disorders (32, 33), depression (34), greater stroke risk, and presence of subclinical ischemic brain lesions (35). In our sample, patients with aura and chronic migraine presented a greater prevalence of vestibular symptoms, both ictally and interictally. The lack of motor control differences between chronic migraineurs and headache-free subjects suggests that the presence of vestibular symptoms in migraine may not influence balance, as previously suggested (5, 9, 26, 27).

Despite numerous neurophysiological and neuroimaging studies have evidenced somatosensory and motor dysfunctions in the migraine brain (36), the present study showed clinical alterations in the motor control reactions just in patients with aura. These findings could be related to specific neurophysiological alterations among patients with aura, such as greater motor-evoked potential amplitudes, lack of blink reflex habituation, visual and motor cortex excitability abnormalities, reduced cerebellar inhibition, and neuromuscular transmission dysfunctions (36, 37). Studies investigating the evoked potentials in patients with aura frequently reported greater neural response to any kind of sensory stimuli, which could be explained by abnormal short- and long-term adaptive processes to external stimuli (36) and can be directly influenced by the migraine phase (38). This is complemented by experimental studies, which suggest that these alterations reflect the activation of trigeminovascular nociceptors *via* cortical spreading depression (36). Despite the ongoing debate about migraine with and without aura being considered distinct disorders, our results demonstrate a specific clinical presentation of this disease subtype, possibly reflecting the observed neurophysiological alterations—which so far were considered to be subclinical.

TABLE 3 | Multiple linear regression for prediction of the number of falls based on clinical and motor reaction variables.

Models		Unstandardized coefficients		Standardized coefficients							
		B	Std. error	Beta	*t*	Sig.	*R* square	Adjusted *R* square	*df*	*F*	Sig.
1	Constant	−8.13	3.67		−2.22	0.03	0.48	0.43	11	9.14	<0.0001
	Migraine onset	−0.06	0.04	−0.12	−1.35	0.18					
	Migraine frequency	0.09	0.05	0.16	1.92	0.06					
	Frequency of aura	0.64	0.14	0.37	4.59	<0.0001					
	Intake of prophylactic medication	−0.47	0.51	−0.07	−0.91	0.36					
	Fear of falling scores (FES-I)	0.27	0.07	0.34	3.94	<0.0001					
	MCT medium back area	−0.07	0.08	−0.09	−0.91	0.37					
	MCT large back area	0.01	0.06	0.02	0.23	0.82					
	MCT medium front area	−0.17	0.06	−0.29	−2.75	0.01					
	MCT large front area	0.07	0.03	0.26	2.46	0.02					
	MCT composite latency	0.02	0.03	0.04	0.52	0.60					
	ADT area	0.12	0.06	0.18	2.12	0.04					
9	Constant	−6.27	1.47		−4.26	<0.0001	0.46	0.43	5	19.19	<0.0001
	Frequency of aura	0.62	0.14	0.36	4.60	<0.0001					
	Fear of falling scores (FES-I)	0.28	0.06	0.36	4.53	<0.0001					
	MCT medium front area	−0.19	0.06	−0.34	−3.38	0.001					
	MCT large front area	0.08	0.03	0.29	2.85	0.01					
	ADT area	0.10	0.05	0.14	1.80	0.07					

MCT, motor control test; ADT, adaptation test.

We also found that reduced motor reaction performance, fear of falling, and aura frequency can predict the fall events reported in the previous year. These findings have a substantial relevance in the clinical setting and are in line with previous studies that highlighted the relevance of balance perturbation-based tests to assess fall risk in stroke and older adult populations (13, 30, 39). It is further known that perturbation-based balance training reduces fall risk among older adults and patients with Parkinson's disease (40). Further research is warranted to state whether specific balance rehabilitation programs should also be implemented for patients with migraine with aura, aiming to decrease the balance deterioration and fall risk, also seen in perturbation-based assessment protocols.

Our study has some limitations. The inclusion of just females in our study, does not allow for a generalization to other populations. Furthermore, our study cannot make any statements regarding etiology due to its cross-sectional design. Although all patients were pain-free during the assessment, we cannot exclude that they were pre-ictal or post-ictal. This can be considered a factor of bias, along with the group differences in the prophylactic medication intake. On the other hand, no differences were found between the group with higher attack frequency and greater medication intake (chronic migraine) in contrast to controls. Finally, it is important to point out as a limitation that our evaluation of the number of fall events within the last 12 months might not be free of recall bias, and the results should therefore be interpreted with caution. However, this is the first study to assess the responses to perturbations in different subgroups of patients with migraine, shedding light on a precise knowledge of musculoskeletal and neuromuscular deficits among this population. The characterization of meaningful and functional mechanisms of balance control, which mimic daily life sensory conditions, can potentially improve the clinical assessment and provide valuable tools for answering clinical research questions (13).

CONCLUSION

Patients with migraine with aura exhibited greater response delay and sway area than controls and other migraine subgroups during the assessment of balance following unexpected ground perturbations. The imbalance after the ground perturbation along with the frequency of aura and fear of falling explained almost half of the fall events reported during the last year. These findings indicate additional comorbidities related to motor control in patients with migraine aura, and etiologies remain to be elucidated in future studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Investigation Review Board of the Clinics Hospital (process number: 15572/2016). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GC, MB, and DB-G conceptualized the study. GC and CP performed the data curation. GC, TL, and RM performed the formal analysis. GC and DB-G acquired the funding. GC, KL, RM, MB, DB-G, and FD formulated the methodology. MB and DB-G supervised the study. GC wrote the original draft. GC, KL, CP, RM, MB, FD, and DB-G reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Circadian Variation of Migraine Attack Onset Affects fMRI Brain Response to Fearful Faces

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Background: Previous studies suggested a circadian variation of migraine attack onset, although, with contradictory results – possibly because of the existence of migraine subgroups with different circadian attack onset peaks. Migraine is primarily a brain disorder, and if the diversity in daily distribution of migraine attack onset reflects an important aspect of migraine, it may also associate with interictal brain activity. Our goal was to assess brain activity differences in episodic migraine subgroups who were classified according to their typical circadian peak of attack onset.

Methods: Two fMRI studies were conducted with migraine without aura patients ($n = 31$ in Study 1, $n = 48$ in Study 2). Among them, three subgroups emerged with typical Morning, Evening, and Varying start of attack onset. Whole brain activity was compared between the groups in an implicit emotional processing fMRI task, comparing fearful, sad, and happy facial stimuli to neutral ones.

Results: In both studies, significantly increased neural activation was detected to fearful (but not sad or happy) faces. In Study 1, the Evening start group showed increased activation compared to the Morning start group in regions involved in emotional, self-referential (left posterior cingulate gyrus, right precuneus), pain (including left middle cingulate, left postcentral, left supramarginal gyri, right Rolandic operculum) and sensory (including bilateral superior temporal gyrus, right Heschl's gyrus) processing. While in Study 2, the Morning start group showed increased activation compared to the Varying start group at a nominally significant level in regions with pain (right precentral gyrus, right supplementary motor area) and sensory processing (bilateral paracentral lobule) functions.

Conclusion: Our fMRI studies suggest that different circadian attack onset peaks are associated with interictal brain activity differences indicating heterogeneity within migraine patients and alterations in sensitivity to threatening fearful stimuli. Circadian variation of migraine attack onset may be an important characteristic to address in future studies and migraine prophylaxis.

Keywords: pain, headache onset, emotional processing, brain imaging, emotional faces task, circadian rhythm

INTRODUCTION

Migraine is a serious and debilitating neurological disorder affecting 1.1 billion people worldwide (Safiri et al., 2022). The most frequent type is episodic migraine without aura characterized by recurrent attacks with typically unilateral, pulsating, moderate or severe headache, accompanying nausea or vomiting, photo- and/or phonophobia. Painful migraine attacks represent only a part of a multiphasic disease with various symptoms usually appearing in a timely order during three phases (excluding migraine aura): (1) *premonitory* (or *prodromal*) *phase* (preceding the headache phase by up to 48–72 h) with symptoms including fatigue, irritability, phonophobia, stiff neck, changes in mood, activity, appetite and sleep-waking rhythms; (2) *migraine attack*; and (3) *postdromal phase* (lingering for 24–48 h after the headache) with symptoms similar to prodromal ones (including tiredness, stiff neck, and difficulties in concentration) (Giffin et al., 2003; Goadsby et al., 2017; May, 2017).

At the moment, we cannot exactly understand or predict the onset of a migraine attack. There are known migraine trigger factors, but many of them may overlap with symptoms of an already ongoing premonitory phase (including sleeping problems, hunger or phonophobia) (Goadsby et al., 2017). Some researchers also suggest that migraine attack onset may show a circadian variation. Recent reviews (Baksa et al., 2019; Poulsen et al., 2021) show contradictory results: although, many authors reported an early morning or late night attack onset peak, others also revealed an afternoon peak and a biphasic diurnal cycle of attacks. One study also reported that most of their investigated migraine patients did not show a constant circadian rhythm of attack onset (de Tommaso and Delussi, 2018). Among the emerging theories, a possible hypothalamic dysfunction has been suggested to explain the diurnal distribution of migraine attacks through hypothalamic involvement in pain modulation and circadian rhythmicity (Park et al., 2018). The main circadian oscillator, the suprachiasmatic nucleus also takes place in the hypothalamus (Saper et al., 2005; Gannon et al., 2014) – the probable causal role of the suprachiasmatic nucleus in migraine periodicity has been suggested more than two decades ago (Zurak, 1997).

A possible explanation for the contradictory results regarding the daily distribution of attack onset may be that subgroups with different circadian attack onset peaks exist within migraine patients. Environmental effects may also contribute to differences in attack onset during the day: morning migraine may be induced by lack of sleep (Alstadhaug et al., 2008), while a peak onset in the afternoon may be connected to work- or school-related stress (Alstadhaug et al., 2008; van Oosterhout et al., 2018). Chronotype, defined broadly as individual differences in preference of daily activity and rest periods, may also influence migraine attack onset: early chronotype was related to earlier attack onset, while late chronotype associated with later attack onset (van Oosterhout et al., 2018). A novel study (Im et al., 2019) revealed that migraineurs with a time preference of headache attack were more likely to have an earlier chronotype compared to migraineurs without a preferential attack time; and migraine patients with later chronotype reported higher attack frequency and later preferential attack time – these associations were specific to migraineurs in contrast to participants with tension-type headache.

Migraine is primarily a brain disorder (Goadsby et al., 2017). Imaging studies revealed that the "migraine brain" shows structural and functional alterations in comparison with healthy controls, even between attacks (i.e., interictally). Although, definitive neuroimaging biomarkers of migraine are still lacking (Russo et al., 2019; Skorobogatykh et al., 2019), functional magnetic resonance imaging (fMRI) studies consistently show altered neural processing of sensory (mostly painful and visual) stimuli interictally compared to healthy controls in several regions, including pre- and postcentral gyrus, superior temporal gyrus, middle and anterior cingulate cortex, visual cortex, middle temporal cortex (for a review see Schwedt et al., 2015). Besides these migraine-specific sensory hypersensitivities, emotional factors are also relevant in migraine: emotional stress is commonly reported as a trigger factor for headache (Andress-Rothrock et al., 2010), increased emotionality during the prodrome is among the best predictors for migraineurs for their attack (Giffin et al., 2003), high level of neuroticism (or emotional lability) is a risk factor for migraine (Magyar et al., 2017) and interestingly, emotional abuse during childhood had a stronger association with migraine (even, after controlling for lifetime depression and anxiety) compared to physical and sexual abuse in a study with a nationally representative sample of young adults in the United States (Tietjen et al., 2017). In accordance with these data, fMRI studies confirmed altered cerebral response to emotional stimuli interictally among migraineurs versus healthy controls in areas including superior and middle frontal gyrus, frontal pole, caudate, thalamus, amygdala, posterior cingulate gyrus, precuneus, cerebellum (Wilcox et al., 2016; Wang et al., 2017; Szabó et al., 2019).

If diversity in daily distribution of migraine attack onset reflects an important aspect of migraine, it may also associate with interictal brain activity. Therefore, our goal was to assess brain activity differences in subgroups of episodic migraineurs who were classified according to their typical circadian peak of attack onset. Comparing these subgroups in an implicit

emotional processing fMRI task, we expected activity differences between them in regions previously associated with migraine and related to circadian rhythmicity (hypothalamus), sensory (e.g., superior temporal gyrus, middle and anterior cingulate cortex, visual cortex) and emotional processing (e.g., amygdala, middle frontal gyrus, posterior cingulate gyrus).

MATERIALS AND METHODS

Data from two fMRI studies with different participants and MRI scanners were included. In the followings, we detail our methods highlighting differences between Study 1 and Study 2. Study 1 was considered as an exploratory study since it is the first investigation that aims to connect circadian variation of migraine attack onset to fMRI brain activation and typical circadian attack onset peak was based on self-reported questionnaire data. While, in Study 2, our main goal was to replicate the results of Study 1 applying a headache diary to capture typical circadian attack onset peak in a more thorough way.

Participants

Migraineurs without aura were recruited via advertisements in universities, articles and neurological clinics. Episodic migraine without aura was diagnosed by headache specialists according to the International Classification of Headache Disorders-III criteria (Headache Classification Committee of the International Headache Society [IHS], 2018). Our inclusion criteria comprised of (1) right handedness according to the Edinburgh Handedness Inventory (Oldfield, 1971); (2) normal or corrected to normal vision; (3) lack of history of any chronic medical, neurological (except migraine) or psychiatric disorders diagnosed by senior neurologist and psychiatrist researcher colleagues; (4) lack of daily medication use (except oral contraceptives). Selected migraineurs agreed to avoid to take any prophylactic medication for 3 months and any analgesics or migraine attack medication 48 h before the scan sessions. Further details on response rates and exclusion due to technical problems were published earlier (Kocsel et al., 2019; Szabó et al., 2019).

For Study 1, 34 subjects met the inclusion criteria, further exclusion due to missing data resulted in the final sample of 31 patients with migraine without aura (24 females; mean age: 26.97 years, *SD* = 4.83). In Study 2, applying the same inclusion and exclusion criteria 48 participants (43 females; mean age: 27.02 years, *SD* = 6.29) were eligible for our study with non-missing data.

Written informed consent was provided by all participants, in accordance with the Declaration of Helsinki. The studies were approved by the Scientific and Research Ethics Committee of the Medical Research Council (Hungary).

Self-Report Measures

In Study 1, subgroups were defined based on self-reported *typical circadian attack onset peak* measured with the following question: "Typically, when does your migraine headache start? Please, choose one answer" from the options of (1) "always in the morning," (2) "rather in the morning," (3) "in the forenoon," (4) "in the afternoon," (5), "rather in the evening," (6) "always in the evening," (7) "at night, during sleep (waking up because of it)," (8) "varying," and (9) "other." Options number (1), (2), (3), and (7) represent morning or dawn start (collectively the first half of day) and were combined as *Morning start*; and options (4), (5), and (6) capture afternoon or evening start (covering the second half of the day) and were combined under the name of *Evening start*. A similar categorization to assess a circadian pattern of migraine headache start (namely: "usually before noon" and "usually after noon") was used in a previous study (Shin et al., 2015). Furthermore, a *Varying start* group was defined: based on options (8) and (9) representing migraineurs without a typical circadian attack onset peak.

In Study 2, all participants were asked to fill a paper headache diary to capture *typical circadian attack onset peak*. An inclusion criterion regarding headache diary was at least two reported migraine attacks (as in the study of de Tommaso and Delussi, 2018) separated at least by a 24 h long headache-free period (as in Alstadhaug et al., 2007). Every reported headaches were separately reviewed, and among them, a migraine-type headache was classified in case of showing at least four of the six migraine attack features listed by ICHD-III (Headache Classification Committee of the International Headache Society [IHS], 2018): (1) 4–72 h long duration, (2) unilateral pain, (3) pulsating pain quality, (4) moderate or severe intensity, (5) aggravation by routine physical activity, and (6) any of the concomitant symptoms (nausea or vomiting, photo- and/or phonophobia). In case of use of an acute migraine treatment, we expected the fulfillment of at least three of the six features. For more details about the used headache diary and exact migraine attack criteria, see **Supplementary Appendix 1**. Using these inclusion criteria, completed headache diaries covered an average time-span of 2.15 months (minimum: 1, maximum: 6, *SD*: 1.08 months) with 255 migraine-type headaches for the 48 participants. Each patient was included to a typical circadian attack onset peak group based on at least 60% of his/her attack occurrence in the two time slots: from 0:00 to 11:59 (Morning start); 12:00–23:59 (Evening start). Varying start group category was used if someone's attacks were below 60% in any of the two categories.

The following five variables were used for both studies to control possible confounding effects. *Age* and *sex* are known to be related to migraine (Todd et al., 2018; Straube and Andreou, 2019). *Migraine attack frequency per month* was measured by the question: "How many migraine attacks do you have per month?". Attack frequency represents an important clinical feature of migraine as it was connected to migraine severity and extent of functional changes in the brain (Maniyar and Goadsby, 2013). It is also a reliable variable: previously, it has been reported as a reasonably accurate self-estimated characteristic of migraine (Niere and Jerak, 2004). As stated in Introduction, chronotype and sleeping problems may affect circadian variation of migraine attack onset. *Chronotype* was measured with the following question: "Do you consider yourself as a morning or an evening type of person?" with the options of (1) "definitely morning," (2) "rather morning," (3) "rather evening," (4) "definitely evening," (5) "I don't know." To gain bigger sample sizes, we combined the first two categories ("definitely/rather morning") and also

categories number (3) and (4) ("definitely/rather evening"). *Sleeping problems* was captured in the following way: "Do you have problems falling asleep or waking up in the middle of the night?" with the options of (1) "never or rarely," (2) "sometimes," (3) "frequently or usually."

Experimental Task

To measure neural activity, an implicit emotional processing fMRI task was implemented. Subjects were shown gray-scale pictures of adult faces expressing *neutral, fearful, sad,* and *happy* emotions. For face stimuli, a standard set of images (Ekman and Friesen, 1976) was presented in block design. Ensuring attention to stimuli, participants were asked to categorize the sex of faces – this implicit strategy was successfully implemented in neuroimaging studies of emotional facial expressions provoking activation mostly in limbic structures and extrastriate cortical regions (Morris et al., 1998; Surguladze et al., 2003; Radua et al., 2010; Anderson et al., 2011).

Pictures of six adult faces (3–3 males and females) with cropped non-facial features were presented on black background. Three 20 s long rest blocks (white fixation cross at the center) separated the three 20 s long blocks of each emotional expression (happy, sad, and fearful) in a pseudo-random order, distributed with twelve neutral blocks. One block contained six faces. During the 8 min long task, the presentation time for each faces was 3000 ms, and for the interstimulus interval 333 and 334 ms.

The task was presented with the E-Prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, United States). In the MRI scanner, participants in lying position viewed the face stimuli on a screen through a mirror fixated to the head coil. A two-button response device was used by the participants to indicate the sex of the faces: the participants were instructed to finger-press one button with index finger in case of female faces and the other button with thumb in case of male faces. Before the scan, a brief practice session with neutral faces was completed by the participants on a laptop, outside the scanner room. Behavioral data (accuracy and reaction time) were registered. Previously, the task was thoroughly described and successfully used by our research group (Thomas et al., 2011; Arnone et al., 2012; Szabó et al., 2017, 2019; Dobos et al., 2021).

fMRI Data Acquisition

MRI scans were timed after 3:00 p.m in the late afternoon/early evening hours. Subjects were asked to avoid to eat, smoke and consume caffeine 4 h prior to the examination.

In Study 1, fMRI data acquisition was performed on a 3 T MRI scanner (Achieva 3 T, Philips Medical System) using a BOLD-sensitive T2*-weighted echo-planar imaging sequence (repetition time TR = 2500 ms, echo time TE = 30 ms, field of view FOV = 240 × 240 mm) with 3 × 3 mm in-plane resolution and contiguous 3 mm slices providing whole-brain coverage. A series of high-resolution anatomical images were also acquired during the imaging session using a T1-weighted 3D TFE sequence with 1 × 1 × 1 mm resolution.

In Study 2, a 3.0 T MAGNETOM Prisma Siemens Syngo scanner was used, with the following parameters: TR = 2220 ms, TE = 30 ms, FOV = 222 × 222 mm, with a 3 × 3 × 3 mm resolution. High-resolution anatomical images were acquired similarly with a 1 × 1 × 1 mm resolution, using a 3D MPRAGE sequence.

Self-Report and Behavioral Data Analysis

Self-report and behavioral data were analyzed with IBM SPSS Statistics 23. In case of scale variables, to measure potential differences between the subgroups, non-parametric tests were used because of the failure of normality: Kruskal–Wallis test and *post hoc* pairwise Mann–Whitney test with a two-tailed $p < 0.05$ threshold.

In case of categorical variables, Freeman–Halton extension of the Fisher exact probability test was performed for two-rows by three-columns and three-rows by three-columns contingency tables at VassarStats website (Lowry, 2021). Similarly, a two-tailed $p < 0.05$ threshold was set.

fMRI Data Analysis

For imaging data analysis, Statistical Parametrical Mapping (SPM12) software (The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, United Kingdom) was used in Matlab R2016a (Mathworks). Standard preprocessing steps were implemented: (1) realignment of functional images; (2) coregistration of the mean functional image to the structural image; (3) segmentation; (4) normalization to the Montreal Neurological Institute (MNI) space; (5) smoothing with an 8 mm fullwidth-at-half-maximum (FWHM) Gaussian kernel. Artifact Detection Tools (ART) were used to screen for motion outliers with the following deviation thresholds: more than 3 standard deviations for the global signal; and more than 1 mm in case of scan-to-scan motion. Exclusion criteria was: higher than 15% of volumes registered as outliers. Motion outliers were included as regressors with no interest to the fMRI model.

For first-level analysis, a general linear model (GLM) was applied in SPM12 to measure BOLD-responses to emotional facial expressions with three contrasts: *fear-neutral, sad-neutral, happy-neutral* – the same method was previously used in works of Szabó et al. (2017, 2019). The created contrast maps were entered into second-level analysis. To compare the task-related activation in the whole brain between groups with different typical circadian peak of attack onset, we used one-way ANOVA with five covariates: age, sex, migraine attack frequency per month, chronotype, and sleeping problems. To determine the effect directions between the subgroups with different typical circadian peak of attack onset, *post hoc* pairwise two-sample *t*-tests were implemented with the same five covariates. All fMRI data analyses were performed with an initial threshold of $p < 0.001$ (uncorrected) with a cluster size of $k \geq 10$ voxels. To adjust for multiple testing, results with a cluster level family-wise error corrected threshold of $p_{FWE} < 0.05$ were considered as statistically significant. Significantly activated clusters were identified with the Automated Anatomical Labeling atlas (aal) (Tzourio-Mazoyer et al., 2002). For

visualization of statistical maps, the MNI 152 template brain in MRIcroGL was used.

RESULTS

Results of Study 1

Self-Reported and Behavioral Results

Answers to the question of *typical circadian attack onset peak* resulted in three subgroups: (1) Morning start ($n = 8$), (2) Evening start ($n = 9$), (3) Varying start ($n = 14$); (nobody selected the options of "in the forenoon" or "other").

Self-reported characteristics of the Study 1 sample and the subsamples with different typical circadian peak of attack onset, which will be referred as M_{circ} subgroups in the manuscript, are collected in **Table 1**. There was a significant difference in age between the M_{circ} subgroups: the Varying start group was older than the Evening start group. No other significant differences were found between the M_{circ} subgroups regarding other self-reported data (sex, attack frequency per month, chronotype, sleeping problems).

Behavioral results of Study 1 are summarized in **Supplementary Table 1**. No differences were found between the M_{circ} subgroups in reaction time and accuracy. Comparing behavioral data in response to different emotions in the total sample, significant differences were detected in reaction time: fear evoked higher reaction time in comparison with happy and neutral faces (for details see **Supplementary Table 1**).

fMRI Results

Main effect of task processing different emotions is summarized in **Supplementary Table 4**.

Group Differences in Brain Response to Emotional Faces

Comparison of whole-brain activation between the three subgroups with different typical circadian peak of attack onset, controlling for five covariates (age, sex, migraine attack frequency per month, sleeping problems, chronotype) resulted in significant differences only in response to fearful faces in one cluster. The cluster included regions of left superior temporal gyrus and left supramarginal gyrus (for details see **Table 2**). There was no

TABLE 1 | Details of the Study 1 sample and statistical results of the comparison between M_{circ} subgroups.

	Total	Morning start (M)	Evening start (E)	Varying start (V)	Group comparisons
Participant number (*n*)	31	8	9	14	
Sex (*n*, %)					
Female	24 (77.4%)	7 (87.5%)	6 (66.6%)	11 (78.6%)	Fisher's exact $p = 0.655$
Male	7 (22.6%)	1 (12.5%)	3 (33.3%)	3 (21.4%)	
Age (mean, SD)	26.97 (4.83)	26.12 (4.32)	23.67 (2.0)	29.57 (5.1)	$H = 7.516$, $p = 0.023$* (V > E; $U = 21$, $p < 0.008$)*
Attack frequency per month (mean, SD)	3.34 (3.15)	2.31 (1.13)	4.55 (4.44)	3.14 (2.88)	$H = 0.139$, $p = 0.933$
Chronotype (*n*, %)					
Definitely/rather morning	13 (41.9%)	4 (50.0%)	2 (22.2%)	7 (50.0%)	Fisher's exact $p = 0.223$
Definitely/rather evening	17 (54.8%)	3 (37.5%)	7 (77.8%)	7 (50.0%)	
Do not know	1 (3.2%)	1 (12.5%)	0 (0%)	0 (0%)	
Sleeping problems (*n*, %)					
Never/rarely	14 (45.2%)	4 (50%)	4 (44.4%)	6 (42.9%)	Fisher's exact $p = 0.953$
Sometimes	14 (45.2%)	4 (50%)	4 (44.4%)	6 (42.9%)	
Often/usually	3 (9.7%)	0 (0%)	1 (11.1%)	2 (14.3%)	

*H, Kruskal–Wallis test statistic; SD, standard deviation; U, Mann–Whitney test statistic; *, significant effect; M_{circ} subgroups: M, Morning start; E, Evening start; V, Varying start.*

TABLE 2 | Brain regions with significant activation differences responding to fearful faces comparing the three M_{circ} subgroups in Study 1.

Contrast	Cluster size	Cluster *p* (FWE)	Region	Coordinates (MNI)			Peak *F*-value
				x	*y*	*z*	
Fear-neutral	51	0.013	L superior temporal gyrus	–57	–37	17	16.61
			L superior temporal gyrus	–45	–37	20	14.54
			L superior temporal gyrus	–51	–40	20	13.15
			L supramarginal gyrus	–63	–34	23	11.04

Cluster p (FWE), cluster level family-wise error corrected p-value; L, Left hemisphere; MNI, coordinates in Montreal Neurological Institute (MNI) space; Peak F-value, peak test-statistic of one-way ANOVA.
Covariates in the analysis: age, sex, migraine attack frequency per month, sleeping problems, chronotype.

significant difference between the groups in neural response to sad and happy faces.

Post hoc Pairwise Group Comparisons in Neural Response to Fearful Faces

Pairwise group comparisons of the fear-neutral contrast revealed significantly increased brain activation in the Evening start M_{circ} subgroup compared to the Morning start subgroup. Three clusters of increased activation were found covering regions of left and right superior temporal gyrus, left supramarginal gyrus, left postcentral gyrus, right Rolandic operculum, right Heschl's gyrus, left middle cingulate gyrus, left posterior cingulate gyrus and right precuneus (see **Table 3** and **Figure 1**). No other pairwise group comparisons resulted in significant difference.

Results of Study 2

Self-Reported and Behavioral Results

Regarding *typical circadian attack onset peak*, the same three M_{circ} subgroups were detected: (1) Morning start (n = 13), (2) Evening start (n = 26), and (3) Varying start (n = 9).

Self-reported characteristics of the Study 2 sample and the three M_{circ} subgroups are presented in **Table 4**. Again, a significant difference in age was shown between the M_{circ} subgroups: the Morning start group was older than the other two groups. No other significant differences were found between the M_{circ} subgroups regarding other self-reported data (sex, attack frequency per month, chronotype, sleeping problems).

Self-reported data was also compared between total samples and M_{circ} subgroups of Study 1 and Study 2. The Varying start group was a bit older in Study 1 sample compared to Study 2 sample. Furthermore, distribution of the M_{circ} subgroups significantly differed between the two studies: the Morning start and the Evening start group showed higher participant number in Study 2, while the Varying start group had higher participant number in Study 1. For details, see **Supplementary Table 3**.

Behavioral results of Study 2 are summarized in **Supplementary Table 2**. Significant differences were found in accuracy between the M_{circ} subgroups: the Evening start group processed sad faces with higher accuracy compared to the other two groups, and also neutral faces compared to the Varying start group. Comparing behavioral data in response to different emotions in the total sample, significant differences were detected. Fearful, happy and neutral faces evoked higher accuracy in comparison with sad faces. Furthermore, sad faces associated with higher reaction time compared to happy and neutral faces, and also fearful faces compared to neutral ones. For all details see **Supplementary Table 2**.

fMRI Results

Main effect of task processing different emotions is summarized in **Supplementary Table 5**.

Group Differences in Brain Response to Fearful Faces

Our main goal was to replicate the primary result of Study 1, namely: increased brain activation in response to fearful faces in the Evening start M_{circ} subgroup compared to the Morning start subgroup.

Whole-brain activation with the same five covariates as in Study 1 (age, sex, migraine attack frequency per month, sleeping

TABLE 3 | Brain regions with significantly increased activation responding to fearful faces: Evening start > Morning start (Study 1).

Contrast	Group comparison	Cluster size	Cluster *p* (FWE)	Region	Coordinates (MNI)			Peak *t*-value
					x	*y*	*z*	
Fear-neutral	Evening > Morning	132	<0.001	L superior temporal gyrus	–45	–37	20	5.27
				L superior temporal gyrus	–57	–34	17	4.92
				L supramarginal gyrus	–60	–31	23	4.42
				L postcentral gyrus	–51	–22	29	4.26
				L supramarginal gyrus	–60	–25	23	4.19
				L supramarginal gyrus	–57	–31	32	4.03
				L supramarginal gyrus	–60	–40	29	3.75
		63	0.022	R Rolandic operculum	54	–19	11	4.59
				R Heschl's gyrus	45	–25	14	4.37
				R superior temporal gyrus	42	–28	11	4.08
				R superior temporal gyrus	48	–31	14	3.99
		71	0.013	L middle cingulate gyrus	–9	–40	35	4.36
				L posterior cingulate gyrus	–9	–34	32	4.32
				L middle cingulate gyrus	–15	–46	35	4.26
				L posterior cingulate gyrus	–18	–43	32	4.09
				L middle cingulate gyrus	–12	–43	38	4.06
				L posterior cingulate gyrus	–6	–43	32	4.02
				R precuneus	3	–46	41	3.73

Cluster p (FWE), cluster level family-wise error corrected p-value; L, Left hemisphere; R, right hemisphere; MNI, coordinates in Montreal Neurological Institute (MNI) space; Peak t-value, peak test-statistic of the two-sample t-test.
Covariates in the analysis: age, sex, migraine attack frequency per month, sleeping problems, chronotype.

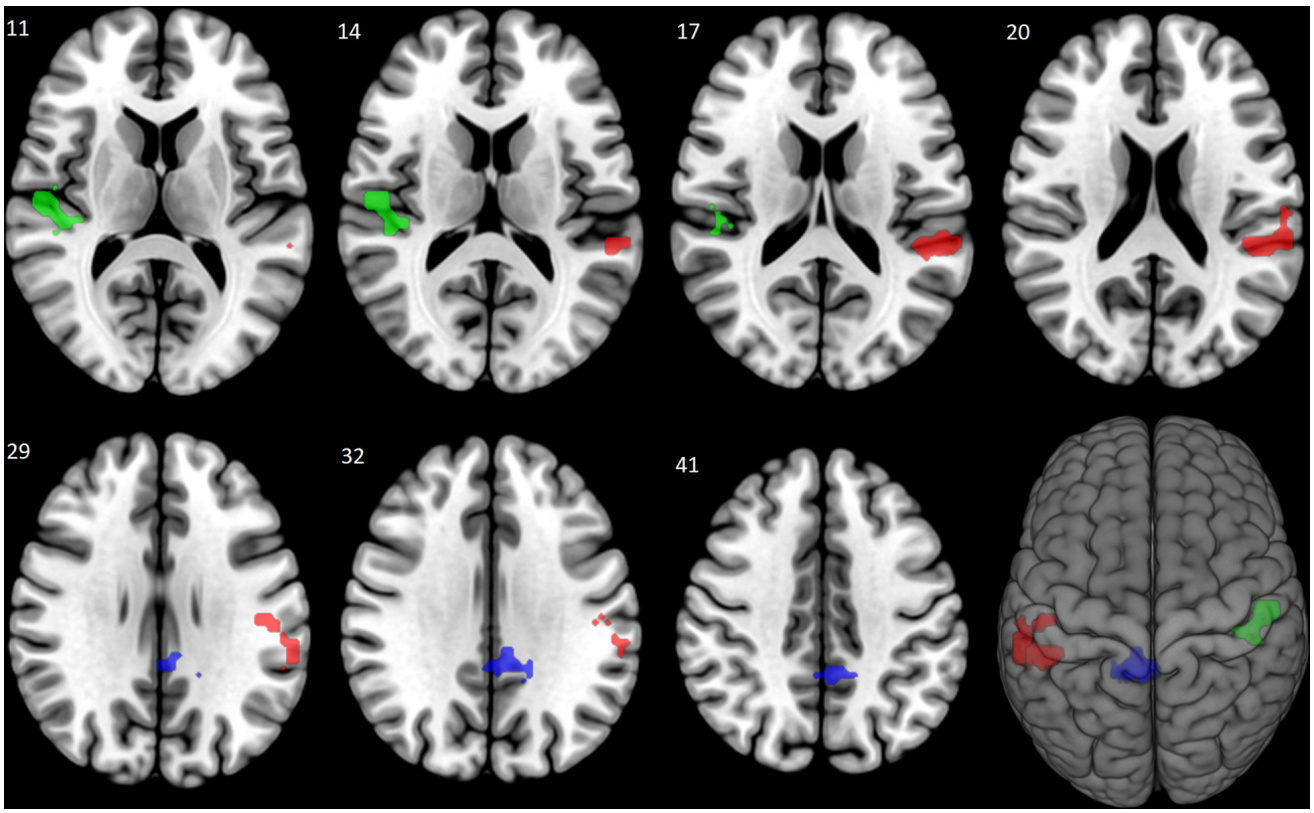

FIGURE 1 | Increased brain activation to fearful faces: Evening start > Morning start (Study 1). The Evening start M_{circ} subgroup showed increased brain activation compared to the Morning start subgroup in response to fearful faces. The significantly activated three clusters are shown (in corresponding order shown in **Table 3**) with red (left superior temporal, left supramarginal and left postcentral gyri), green (right superior temporal gyrus, right Rolandic operculum and right Heschl's gyrus), and blue (left middle and left posterior cingulate gyri, right precuneus) colors at a cluster level $p_{FWE} < 0.05$, corrected for multiple comparison.

problems, chronotype) was compared between the three M_{circ} groups. The ANOVA showed no significant differences between the three groups, however, considering the notably unequal participant number distributions between the M_{circ} groups in Study 2, we decided to also run pairwise group comparisons. Among these analyses, only one nominally significant result was found: in response to fearful faces, the Morning start group showed increased brain activation compared to the Varying start group in one cluster covering regions of bilateral paracentral lobule, right precentral gyrus and right supplementary motor area (see **Table 5** and **Supplementary Figure 1**). However, this result does not survive correction for multiple comparison (in case of six *t*-tests: $p = 0.05/6 = 0.008$).

No other significant differences were found between the groups in neural response to sad or happy faces.

DISCUSSION

Two fMRI studies were conducted to reveal differences in interictal brain activation in an implicit emotional face processing fMRI task as a function of circadian peak of attack onset. In Study 1, later typical circadian attack onset peak was related to significantly increased activation in many brain regions in response to fearful faces in comparison with earlier typical circadian attack onset peak. In Study 2, similarly only fearful (and not happy or sad) faces evoked brain activation differences. However, in this case, higher activation associated with earlier typical circadian attack onset peak compared to varying attack onset peak, and only at a nominal significance level. This is the first investigation connecting circadian variation of migraine attack onset to fMRI brain activation. There may be some important differences between the two studies, mostly the method to capture typical circadian attack onset and the use of different MRI scanners. We will discuss the potential effects of these factors later on. Before that, we would like to highlight that despite the significant methodological differences between the two studies, there are still some overlaps between the results. Although, we have to note that results from Study 2 were significant only at a nominal level, so these should be interpreted with caution.

Emergence of Migraine Subgroups With Different Typical Circadian Peak of Attack Onset

Our results suggest that subgroups with different typical circadian attack onset peaks may exist within migraine patients. We were

TABLE 4 | Details of the Study 2 sample and statistical results of the comparison between M_{circ} subsamples with different typical circadian peak of attack onset.

	Total	Morning start (M)	Evening start (E)	Varying start (V)	Group comparisons
Participant number (*n*)	48	13	26	9	
Sex (*n*, %)					
Female	43 (89.6%)	11 (84.6%)	24 (92.3%)	8 (88.9%)	Fisher's exact $p = 0.822$
Male	5 (10.4%)	2 (15.4%)	2 (7.7%)	1 (11.1%)	
Age (mean, SD)	27.02 (6.29)	31.23 (7.81)	25.62 (5.2)	25 (4.09)	$H = 7.354$, $p = 0.025$* (M > E; $U = 86$, $p = 0.013$*; M > V; $U = 25$, $p = 0.025$*)
Attack frequency per month (mean, SD)	3.06 (2.68)	2.77 (2.1)	3.02 (2.73)	3.62 (3.46)	$H = 0.021$, $p = 0.99$
Chronotype (*n*, %)					
Definitely/rather morning	18 (37.5%)	6 (46.2%)	7 (26.9%)	5 (55.6%)	Fisher's exact $p = 0.474$
Definitely/rather evening	28 (58.3%)	7 (53.8%)	17 (65.4%)	4 (44.4%)	
Do not know	2 (4.2%)	0 (0%)	2 (7.7%)	0 (0%)	
Sleeping problems (*n*, %)					
Never/rarely	26 (54.2%)	6 (46.2%)	17 (65.4%)	3 (33.3%)	Fisher's exact $p = 0.342$
Sometimes	16 (33.3%)	6 (46.2%)	6 (23.1%)	4 (44.4%)	
Often/usually	6 (12.5%)	1 (7.7%)	3 (11.5%)	2 (22.2%)	
Headache diary duration (months) (mean, SD)	2.15 (1.08)	2.23 (0.8)	2.12 (1.2)	2.11 (1.14)	$H = 0.773$, $p = 0.68$

*H, Kruskal–Wallis test statistic; SD, standard deviation; U, Mann–Whitney test statistic; *, significant.*

TABLE 5 | Brain regions with nominally significantly increased activation responding to fearful faces: Morning start > Varying start (Study 2).

Contrast	Group comparison	Cluster size	Cluster *p* (FWE)	Region	Coordinates (MNI)			Peak *t*-value
					x	*y*	*z*	
Fear-neutral	Morning > Varying	97	0.012	R paracentral lobule	6	–34	65	4.32
				R precentral gyrus	18	–31	74	4.2
				R supplementary motor area	9	–19	62	3.82
				L paracentral lobule	–3	–37	68	3.69

Cluster p (FWE), cluster level family-wise error corrected p-value; L, Left hemisphere; R, right hemisphere; MNI, coordinates in Montreal Neurological Institute (MNI) space; Peak t-value, peak test-statistic of the two-sample t-test. Covariates in the analysis: age, sex, migraine attack frequency per month, sleeping problems, chronotype.

able to detect all three predefined M_{circ} subgroups in both studies: a Morning start, an Evening start, and a Varying start subgroup. Distribution of the M_{circ} subgroups significantly differed between the two studies. In Study 1, using a self-reported question, 45.16% reported Varying start, 29.03% Evening start, and 25.8% Morning start. In Study 2, where a headache diary was used, the Evening start group represented 54.16% of the sample, the Morning start group 27.08% and the Varying start group 18.75%. Altogether, the Evening start group had the highest participant number covering 44.3% of the two samples, while the other two groups showed similar distributions: 29.1% with Varying start and 26.6% with Morning start. Based on these results, even with a broader definition, Evening start (representing the second half of the day) was much more frequent than Morning start (covering the first half of the day). This result might sound surprising because most of the studies conclude that the morning migraine attack start is the most frequent one, however, recent reviews show a much more mixed picture of the field (Baksa et al., 2019; Poulsen et al., 2021). Furthermore, almost one third of the two samples (and nearly half of Study 1 sample) did not report a typical circadian attack onset peak (i.e., Varying start) – this group also needs to be taken into account. In a previous study with episodic and chronic migraineurs, almost 60% did not report a typical diurnal attack onset peak (de Tommaso and Delussi, 2018).

Overlaps Between fMRI Results of Study 1 and Study 2

First, the Morning start subgroup is involved in both results. In Study 1, this group showed lower neural activation compared to the Evening start group, while in Study 2, higher activation compared to the Varying start group. Thus, we were not able to replicate the results of Study 1 in the same direction, however, these results are not necessarily opposing. A main question about circadian phenomena in migraine: are they related to biological and/or environmental factors? Previously, it was suggested that stress- and sleep-related effects might be more determining in diurnal patterns of migraine attacks than the actual biological clock mechanism (Alstadhaug et al., 2008). We still do not have an answer to this question. At least, the results presented here suggest brain activity differences

between migraine subgroups with different typical circadian attack onset peaks.

Second, activity differences between the three groups were found in brain regions with similar functions. Specifically, areas of pain processing, including for example middle cingulate cortex (MCC), postcentral gyrus from Study 1 and precentral gyrus, supplementary motor area (SMA) from Study 2; and regions of sensory processing, including Heschl's gyrus, precuneus from Study 1 and paracentral lobule from Study 2 were detected. These regions are thought to contribute to migraine attacks (for a review see Schwedt et al., 2015), and some of them also associated with circadian rhythm-related phenomena in previous fMRI studies, including precuneus (Kyeong et al., 2017; Facer-Childs et al., 2019), postcentral gyrus (Kyeong et al., 2017; Fafrowicz et al., 2019), precentral gyrus (Kyeong et al., 2017), posterior cingulate cortex (PCC) (Kyeong et al., 2017), and MCC (Wu et al., 2021).

Third, only fearful (but not happy or sad) faces evoked significant differences in brain activation between the three subgroups – again, suggesting a similar phenomenon detected in Studies 1 and 2. Similarly to pain, fear is also an aversive stimuli and they often co-occur suggesting a strong relation (Vowles et al., 2006) which may be supported by a core aversion-related brain circuit that is commonly responsible for processing painful and non-painful aversive stimuli (Hayes and Northoff, 2011) involving regions overlapping with our identified areas including MCC, PCC (both from Study 1) and SMA (Study 2).

To put our results into broader perspective, next, we discuss them in light of previous emotional processing fMRI studies in migraine.

Emotional Processing in Migraine

Two previous fMRI studies on processing of emotional stimuli in adult migraineurs compared to healthy controls showed enhanced response selectively to negative (and not positive) emotional stimuli among migraineurs in interictal state (Wilcox et al., 2016; Wang et al., 2017). Increased neural activation was found in regions of superior and middle frontal gyrus, frontal medial cortex, frontal pole, PCC, precuneus, cuneal cortex, caudate, thalamus, left amygdala, right hippocampus, brainstem, and cerebellum in the study of Wilcox et al. (2016) and also cerebellum anterior lobe/culmen, lingual gyri, precuneus and left cuneus in the work of Wang et al. (2017). A recent study of our research group, with the same task implemented here, similarly identified overactive brain regions to fearful faces among migraineurs versus healthy controls in right middle frontal gyrus and frontal pole; and also showed increased activation to fear in association with migraine frequency in regions including right precentral and postcentral gyri (Szabó et al., 2019). All these studies made group comparisons between migraineurs and healthy controls, while we used migraine subgroups, so it is hard to compare our results with those previous ones. Nevertheless, our results overlap with the mentioned fMRI data in two ways: (1) we also found cerebral overactivation in case of a negative emotion, namely fear in both of our studies; and (2) the identified brain areas with increased activation included three regions that were connected to hypersensitivity to aversive emotional stimuli, specifically: in Study 1, left PCC (previously in Wilcox et al., 2016) and right precuneus (previously in Wilcox et al., 2016; Wang et al., 2017); while in Study 2, right precentral gyrus (previously in Szabó et al., 2019). Interestingly, both the PCC and adjacent precuneus are important parts of the default mode network (Raichle, 2015) representing cortical midline structures which have been associated with self-referential processing and self-focus (Northoff et al., 2006; Nejad et al., 2013) and in case of PCC, also the assessment of self-relevance of emotional stimuli (Vogt, 2005).

Sadness is also a negative emotion, but only fear was associated with an enhanced neural response in both of our studies. This specific role of fearful faces is not surprising, because fearful faces represent a threat stimuli and are evaluated even without awareness, gaining prioritized access to conscious visual processing (Hedger et al., 2015). Among the identified brain regions with increased activation in the Evening start group (in Study 1), superior temporal gyrus was previously shown to have a positive trend of activation in response to facial expressions with increasing intensity of fear among healthy controls (but not schizophrenic patients) (Radua et al., 2010). Higher attention to fear was also reflected by behavioral results in both of our studies: fearful faces evoked higher reaction time compared to neutral (Studies 1 and 2) and happy faces (Study 1). Slower reaction to fear is in line with previous interpretations of similar results: procession of fearful faces can lead to increased vigilance to detect the potential threat in the environment which can slow down response speed (Whalen, 1998; Davis and Whalen, 2001; Mirabella, 2018).

Interestingly, in Study 2, sad faces also associated with higher reaction time compared to neutral and happy faces. Furthermore, the accuracy rate was lower in case of sad faces in comparison with all the other conditions and higher among the Evening start group compared to the other two subgroups (Study 2). However, this slower and less accurate response to sad faces and the differences between M_{circ} subgroups did not correlate with alterations at a neural level.

Pain Processing in Migraine

In a broader context, regions identified in our studies with increased activation may be also related to processing of other aversive or threatening stimuli, including pain.

The superior temporal gyrus (Study 1) is among regions that show typically different activation in response to pain among migraineurs (for a review see Schwedt et al., 2015). Other pain processing regions, many identified in previous migraine-studies, were also found in our studies. The MCC (Study 1) is a pain processing area, its increased activation among migraineurs was found in studies using painful stimuli (Stankewitz et al., 2013; Schwedt et al., 2014). The PCC is not related to direct physical pain, rather it is involved in secondary processing of psychological pain (Meerwijk et al., 2013; Wilcox et al., 2016). The pain processing network (PPN) includes the precentral (Study 2) and postcentral gyri (containing Rolandic operculum) (Study 1), and both were found to have different pain-induced activations in migraineurs compared to controls, interictally (Schwedt et al., 2015). The SMA (Study 2) is also part of the pain matrix, its pain-induced activation is thought to alert the body to move

away from pain (Schwedt et al., 2014). The supramarginal gyrus (Study 1) is activated to intranasal ammonia (Stankewitz et al., 2013; Schwedt et al., 2015) and was found in many functional connectivity studies of migraine (Schwedt et al., 2015). These data belong to the numerous fMRI results suggesting an elevated pain sensitivity interictally among migraineurs as a consequence of recurrent painful attacks or migraine-associated prolonged pain (Schwedt et al., 2015). Increased activation interictally in all these pain processing regions in our study without using painful stimuli may suggest that these brain regions are more sensitive to threatening emotional stimuli, not just pain, in migraineurs with later typical circadian attack onset peak compared to the Morning start group (according to Study 1) and with earlier typical circadian attack onset peak compared to the Varying start group (according to Study 2).

The Potential Role of Multisensory Integration in Migraine

In Study 1, increased activation was also found in right Heschl's gyrus (or temporal transverse gyrus) containing the human primary auditory cortex (Warrier et al., 2009). Similarly to hypersensitivities to pain and other sensory stimuli, phonophobia is most prominent during attacks, but also detectable interictally with decreased intensity among many migraineurs (Schwedt, 2013). Different modes of sensory stimuli are not processed in isolation, but rather in a simultaneous way, creating an integrated perception of the environment during a process called multisensory integration which may be relevant in migraine pathophysiology (Schwedt, 2013). For example, the superior temporal gyrus is involved in auditory processing (Gernsbacher and Kaschak, 2003) and was related to olfactory processing among migraineurs, together with PCC (Demarquay et al., 2008). In our study, we found increased activation in the right precuneus that previously showed greater activation to visual stimuli in migraineurs compared to healthy controls (Griebe et al., 2014), also in the supramarginal gyrus which together with the adjacent angular gyrus form the inferior parietal lobule (also known as ventral parietal cortex) which supports higher cognitive functions where multimodal sensory (including somatosensory, proprioceptive, auditory and visual) information converge (Catani et al., 2017). Interestingly, this higher order function of the inferior parietal lobule was also detected in decoding high level features of dynamic emotional faces (Sarkheil et al., 2013; Vollstädt-Klein et al., 2019). Thus, besides auditory processing, regions involved in somatosensory, olfactory, visual and multisensory processing also showed increased activation in migraineurs with later typical circadian attack onset peak in Study 1 – suggesting an elevated level of sensory perception during the procession of fearful faces.

In Study 2, frontal lobe areas with motor functions were found to show higher activation among the Morning start migraineurs compared to the Varying start group. SMA and precentral gyrus were already discussed regarding their pain-related roles. The paracentral lobule (PCL) contains the primary motor and sensory regions for lower limbs and genitalia (Johns, 2014) and recently, its higher activation was shown during migraine episode compared to interictal state (Lei and Zhang, 2021). The PCL is part of the sensorimotor network (SMN) (which also includes precuneus), an associative cortex which have an important role in multisensory integration, too (Lei and Zhang, 2021). The observed increased PCL activation might suggest an elevated sensory processing of fearful stimuli in the Morning start group compared to the Varying start group.

In summary, in Study 1, areas with increased activation in response to fearful stimuli in the Evening start group compared to the Morning start group are involved in emotional, self-referential, pain and sensory processing. Some of the identified regions represent all or many of these functions, especially PCC and superior temporal gyrus. In Study 2, in the Morning start group, regions with similar pain and multisensory functions also showed increased activation to fearful faces compared to the Varying start group.

Circadian Factors in Migraine Attack Onset

Appearance of emotional, pain-related and sensory stimuli during the day and their following processing may all be influenced by the circadian clock mechanism (Kim et al., 2017; Segal et al., 2018). Diurnal distribution of these and other similar factors might have an important role in migraine attack onset. For instance, it has been shown with various painful stimuli that perceived pain intensity peaks early in the morning and some studies also suggest that morning migraines are accompanied with more severe symptoms compared to migraine attacks at other times (Hsu et al., 1977; Kowanko et al., 1981; Göbel and Cordes, 1990; Gori et al., 2015; Park et al., 2018). Interestingly, a circadian variation was consistently detected for positive affective states but not for negative affect (Wood and Magnello, 1992; Murray et al., 2002; Bódizs et al., 2010) suggesting that negative affect might be more related to environmental factors (Wood and Magnello, 1992). Negative affect-related environmental effects, especially stress, are known migraine triggers and some authors suggested an environment-dependent or social nature of diurnal migraine attack onset: as we mentioned before, excessive sleep or sleep deprivation are more likely to contribute to morning migraine attacks, while work- or school-related stress to an afternoon or evening onset (Soriani et al., 2006; Alstadhaug et al., 2008; Park et al., 2018). However, in an arctic population, insomnia-related migraine attacks showed a biphasic diurnal pattern (one peak in the morning and another one in the afternoon) while not insomnia-related attacks peaked only in the afternoon (Alstadhaug et al., 2007). Regarding the circadian variation of migraine attack onset, an interaction between environment-dependent migraine triggers and the innate circadian clock mechanism is also possible (Park et al., 2018).

Recognizing the relevance of circadian variation of migraine attack onset might also contribute to migraine therapy. For instance, administration of pharmacological therapy to the typical circadian attack onset peak of the migraine patient could help prevent attacks and be a step in the direction of precision medicine. Successful implementation

of this opportunity was already presented by the design of a pulsatile press coated drug delivery system containing sumatriptan succinate which was created specifically to achieve drug delivery in the early morning hours using a bedtime administration in order to prevent early morning migraine attacks (Jagdale and Pawar, 2014).

Methodological Differences Between the Two Studies

Differences between the results from the two studies might have been originated partly from methodological differences between Study 1 and Study 2. Distinct methods were used to capture typical circadian attack onset. Answers to the self-reported question may be more subjective and deceptive than completing the headache diary. Beyond retrospective memory bias, the participants may fail to discriminate between migraines and non-migraine headaches. Furthermore, most of the studies using headache diaries even miss to elaborate on how the authors accounted for whether the reported headaches represent phenotypically migraine attacks (Poulsen et al., 2021). Furthermore, this differentiation is not obvious. For example, a previous study (Park et al., 2018) with headache diary classified migraine-type headaches based on criteria A, C, and D for migraine without aura in ICHD-3 beta, but not applied criterion B because headache duration may be significantly affected by acute migraine treatment. We decided to use a quite rigorous categorization to identify migraine headaches in the headache diary also taking account of the effect of medication (for full details, see **Supplementary Appendix 1**). Future studies definitely should include exact migraine attack criteria to use in headache diaries to differentiate between migraines and non-migraine headaches. The study of Park et al. (2018) also showed differences between the circadian variation of occurrence of migraine-type and non-migraine headaches.

Another important methodological difference between the two studies is the use of different MRI scanners. Recently, more and more multisite fMRI studies are conducted with different MRI scanners to enhance statistical power (Gee et al., 2015; Noble et al., 2017; Pornpattananangkul et al., 2019). However, it is known that MRI scanners from different manufacturers vary in details of construction and operation and this will be reflected in performance differences which can affect the analysis (e.g., through a main effect of scanner) causing a lower signal-to-noise ratio. Many multisite fMRI studies reported substantial site- or scanner-related effects (for details, see the work of Yu et al., 2018). This non-biological source of variation can be even more robust in case of significant site-related differences, including differences in study group ratios (Gee et al., 2015). Since we detected significant differences between the two studies in distribution of the M_{circ} subgroups and our study designs also differed in the methods to capture typical circadian attack onset, we decided to analyze the data from the two studies separately.

At the same time, our two samples and the M_{circ} subgroups showed high similarity regarding most measured descriptive variables (sex, headache frequency, sleeping problems, chronotype), only the age of the Varying start group was slightly higher in Sample 1 compared to Sample 2. Furthermore, our results survived correction for all of these factors.

LIMITATIONS

Main limitation of our study is the low sample size limiting statistical power and generalizability of our results. Furthermore, unequal subsample sizes also might have affected our results – especially in Study 2, where only nominally significant results were found. However, we were able to show differences in neural activity between migraine subgroups, even after correcting for many relevant covariates. Our work demonstrates that besides case-control studies, investigations comparing migraine subgroups are also important because of the heterogeneous nature of migraine.

We used an implicit emotional processing fMRI task, comparing emotional (fearful, happy, and sad) facial stimuli to neutral ones which is a widely used method to control simple perceptual effects (Sabatinelli et al., 2011) and the main effect of the task processing different emotions was in line with previous meta-analysis data (Fusar-Poli et al., 2009; Lindquist et al., 2012) in both studies. The same or similar emotional processing task can be used in different ways with potential consequences on the results – recent studies with a Go/No-go facial emotional processing task showed significant differences in behavioral outcomes (including reaction time and error rate) of task-relevant versus task-irrelevant (i.e., implicit) facial emotional processing (Mirabella, 2018; Mancini et al., 2020, 2021). In future fMRI studies, it would be interesting to test the effect of the context of emotional processing in a similar way in relation to neural processing.

A cross-sectional design was used, therefore the causative effect of circadian variation of migraine attack onset on neural activity could not be investigated. In Study 1, we did not use a headache diary to measure typical circadian attack onset peak. Chronotype and sleeping problems were also captured with simple self-report measures in both studies. In Study 2, our participants filled headache diaries, however, with variation in participation time. Seasonal variation of migraine attacks also might have affected diary data. At the same time, we used exact and quite rigorous migraine attack criteria to differentiate between migraine- and non-migraine-type headaches. Another strength of our study is the proper medical diagnosis of migraine by headache specialists. Furthermore, all our subjects were thoroughly screened for chronic medical, neurological (besides migraine) and psychiatric disorders – so, we can also exclude the effect of comorbidities.

One could argue with our typical circadian attack onset peak categorization. Typically, 6-h long time slots are used, but we decided to merge the first two slots (i.e., 00:00–06:00 and 06:00–12:00) to capture the first half of the day and the last two (i.e., 12:00–18:00 and 18:00–00:00) representing the second half of the day to gain larger sample sizes. Additionally, this type of

categorization is not unprecedented (Shin et al., 2015). Of course, future fMRI studies with bigger sample sizes could reveal more detailed results using four time slots.

We adjusted for the effect of age in all our analyses, but considering the association of age with both migraine and circadian rhythms (Kelman, 2006; Duffy et al., 2015; Hood and Amir, 2017), an age-stratified analysis to capture potentially age-related factors in diurnal migraine attack onset would be an interesting topic to address in future studies with bigger sample sizes and diverse age groups.

Finally, MRI scans were timed in the late afternoon/early evening hours. Investigations with a scan session in the morning/forenoon hours are needed to understand the possible effect of the timing of MRI scans on neural activity of migraine subgroups with different typical circadian attack onset peaks.

CONCLUSION

According to our knowledge, this is the first investigation that tried to unfold potential biological mechanisms behind the observed phenomena of the diurnal distribution of migraine attacks. Migraineurs with very similar characteristics were grouped based on a simple circadian factor: their typical circadian attack onset peak, and this distinction associated with brain activity differences. Although, in Study 2 we could not replicate our results from Study 1, we consider our investigation as a promising first step to capture such an association since, despite the significant methodological differences between Study 1 and 2, our results from the two studies showed some important overlaps suggesting a similar mechanism: morning start migraineurs showed different brain activation patterns in both studies related specifically to fear, in regions important to emotional, pain and sensory processing-related functions. At the moment, it is highly difficult and probably too early to make conclusions about potential functional brain processes in association with circadian variation of migraine attack onset, nevertheless, our results suggest that circadian variation of migraine attack onset reflects migraine heterogeneity, and represents an important characteristic to address in future studies and prophylactic treatment of migraine.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Scientific and Research Ethics Committee of the Medical Research Council (Hungary). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GJ and GK conceived and designed the study. ES, NK, AG, AE, DP, TZ, MM, KG, DD, and DB were responsible for subject recruitment and data collection. DB performed the data analysis with special assistance from ES, GJ, GK, and LK. GJ, GK, GB, KG, and DD contributed to the interpretation of the data. DB wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.842426/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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