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Headache and neurogenic pain – case report collection 2022

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Case report: Monoclonal CGRP-antibody treatment in a migraine patient with a mutation in the mitochondrial single-strand binding protein (SSBP1)

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Background: There is a growing body of mitochondrial disorders that are associated with headaches, albeit only one of them is currently listed in the latest International Classification of Headache Disorders, 3rd edition (ICHD-3). Headache frequency and headache presentation can vary widely in this respective patient group. Acute and preventive migraine treatment can be quite challenging—the use of several established medications is often limited due to their side effects in the setting of mitochondrial dysfunction and multi-organ disease.

Case presentation: Along with a review of the literature on treatment options in patients with mitochondrial disorders and migraine headaches, we present the case of a 23-year-old male with a homozygous mutation in the mitochondrial single-strand binding protein (*SSBP1*) with chronic migraine with aura. After failing several standard of care prophylactics due to either side effects or inefficacy, he was successfully treated with a monoclonal anti-CGRP-antibody as a preventive migraine treatment. The monoclonal antibody was well tolerated and showed adequate efficacy with a sustained > 50% reduction in monthly headache days after 3 years of treatment.

Conclusion: Migraine is often challenging to treat in patients with mitochondriopathy due to therapy-limiting comorbidities. Monoclonal CGRP-antibodies might be a safe treatment option in the prevention of migraine headaches in patients with a mitochondrial disorder.

KEYWORDS

headache, migraine, mitochondrial disease, prophylactic treatment, CGRP, case report

Introduction

Mitochondrial disorders are characterized by defects in oxidative phosphorylation and caused by mutations in genes in the nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). Mitochondriopathies can present with multisystemic manifestations including non-neurological symptoms with cardiac, renal, muscle, and digestive

involvement as well as neurological symptoms, such as epileptic seizures, ataxia, and headache (1).

The presence of migraine with and without aura and other headache disorders, such as tension-type headaches, is well described in mitochondrial diseases, such as chronic progressive external ophthalmoplegia (CPEO), myoclonic epilepsy with ragged-red fibers (MERRF) and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome (2–5). Headache prevalence in this patient group seems to be higher than in the general population (3). In MELAS, between 50 and 90% of the patients report headaches (3, 5, 6), however, headache frequency and headache presentation can vary widely in this respective patient population. Although headache is associated with several mitochondriopathies, only one of them is currently listed in the latest International Classification of Headache Disorders, 3rd edition (ICHD-3) (7). Headaches associated with MELAS are categorized as secondary headaches attributed to genetic vasculopathy and can be either present as migraine attacks with or without aura or headaches in connection with seizures or/and neurological deficits (7).

Compared with other migraineurs, patients with mitochondriopathies often report inadequate response to acute medication (6). Moreover, the use of several established medications for both prevention and acute treatment of migraine is limited due to their side effects in the setting of mitochondrial dysfunction and multi-organ disease. Therefore, due to the lack of scientific evidence and data, it is challenging to offer these patients an effective and well-tolerated therapy for their headaches.

Herein we describe the case of an adult patient with a mitochondrial disorder, who was successfully treated with a calcitonin gene-related peptide (CGRP)-antibody for the prevention of migraine attacks. Written informed consent for the publication was given by the patient. The present patient was reported for the first time in the article from Del Dotto et al., though without a detailed clinical description of symptoms and response to therapy.

Furthermore, we reviewed the literature for treatment options for migraine headaches in patients with mitochondriopathies.

Case presentation

We present a young male who was first referred to our outpatient clinic for rare movement disorders in 2009 at the age of 23. Since early childhood, the patient has had sensorineural hearing loss and retinitis pigmentosa, ultimately leading to severe visual impairment and deafness. Stance and gait ataxia as well as dyspraxia were present since the age of 4, however without progression over the years. Since the age of 6, the patient suffered from recurrent headache attacks,

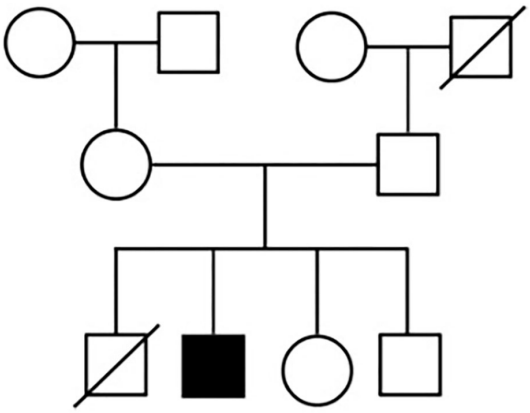

FIGURE 1
Pedigree of the patient's family.

featuring a pulsating quality, unilateral presentation, and severe pain intensity. Headaches were accompanied by photophobia, nausea, as well as vomiting and were preceded by visual aura symptoms—hence, fulfilling the ICHD-3 diagnostic criteria for episodic migraine with aura (7).

The hypertrophic cardiomyopathy (New York Heart Association Class II), for which the patient received treatment with nebivolol 1.25 mg/day, was diagnosed in childhood. Renal impairment (creatinine 1.77 mg/dl), as well as scoliosis, were present from an early age and progressive over the years. Despite the manifold debilitating symptoms, such as mild cognitive impairment, the patient was able to cope with activities of daily living. The patient's family history is illustrated in Figure 1. It was unremarkable on the maternal and paternal sides, however, one brother died 11 days after birth (cause unknown).

At the age of 13, a muscle biopsy of the quadriceps revealed cytochrome-oxidase negative fibers but no ragged-red-fibers. Biochemical evaluation detected the reduced activity of complex I and complex III.

Repeated cerebral magnetic resonance imaging (cMRIs) revealed cerebellar atrophy, particularly of the vermis cerebelli (Figure 2) without intraparenchymal signal alterations. Magnetic resonance spectroscopy (MRS) displayed normal spectra and no lactate peak in supratentorial brain regions, suggesting no anaerobic metabolism and therefore no circulatory disorders. This finding is in line with the absence of stroke or stroke-like-episodes in the patient. Electroencephalography (EEG) showed diffuse intermittent slowing without epileptiform discharges.

Based on the clinical and diagnostic findings, a mitochondrial disease was suspected. Initial genetic testing was negative for Friedreich's-Ataxia, Fabry's disease, and the most common MELAS mutation, *3243 A>G*. Then, a whole exome sequencing (WES) was performed and a homozygous mutation

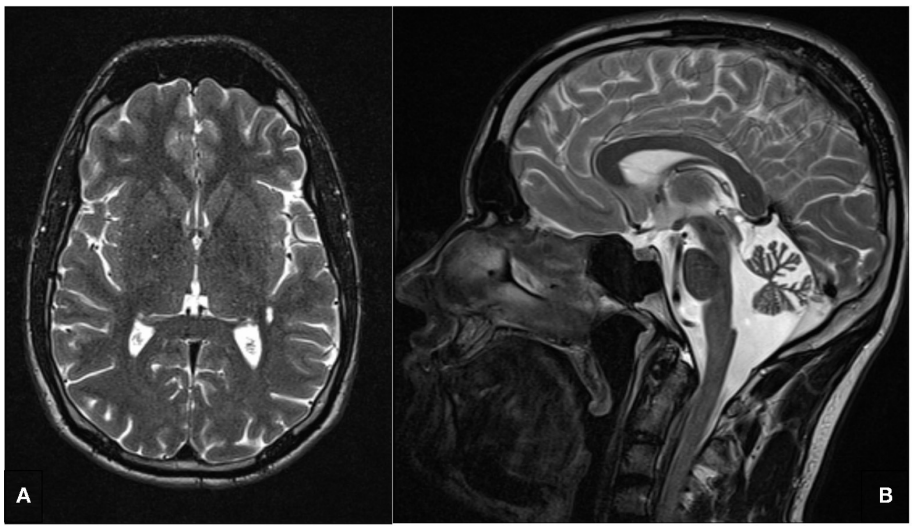

FIGURE 2
T2 weighted cerebral magnetic resonance image. **(A)** No intraparenchymal signal alterations in the axial image. **(B)** Cerebellar atrophy, particularly of the vermis cerebelli.

in the mitochondrial single-strand binding protein (*SSBP1*), *c.394A>G* (p.I132V) was identified. A detailed description of the spectrum and the functional impact of *SSBP1* mutations is demonstrated in the study by Del Dotto et al. (8). The patient presented here is the index patient in family 5 in this respective article.

Migraine and therapeutic approach

In 2012, frequent migraine attacks (ranging from 2 to 3 days/week) led to an enormous impairment of the patient's quality of life. The patient's stance and gait ataxia aggravated during migraine attacks, and he suffered from a prolonged postdromal phase, where he experienced severe fatigue and a decline in cognitive functions. Due to renal insufficiency, options for acute treatment were limited. The patient used frovatriptan 2.5 mg and metamizole 500–1,000 mg, both with poor effect. As prophylactic therapy, flunarizine 10 mg/day was started with sufficient treatment response and tolerability, resulting in a significant reduction of monthly migraine days. However, after 3 years, the headache frequency increased, despite regular prophylaxis intake, indicating the loss of treatment response. Flunarizine was withdrawn and, after consulting a cardiologist, the premedication with nebivolol was changed to bisoprolol 2.5 mg, as better evidence on its efficacy in migraine prevention has been reported (9, 10). Due to low blood pressure, increasing the dosage of bisoprolol was not attempted, yet the number of migraine days declined satisfactorily.

In 2019, the patient experienced another exacerbation of the monthly migraine days—more than 20 days/month were reported—fulfilling the diagnostic criteria for chronic migraine, despite ongoing therapy with bisoprolol. Therefore, an additional prophylactic treatment with galcanezumab 120 mg monthly (with a 240 mg loading dose) was started. After 2 months of treatment, the patient reported a >50% reduction in the monthly migraine days. Thereafter, he even experienced headache-free months. No side effects were reported. During the follow-up till 2022, a sustained satisfactory effect of galcanezumab was observed, without side effects on renal and cardiac function.

Literature review

We performed a literature search of the electronic database PubMed on treatment options for patients with mitochondrial disorders and experiencing migraine headache. We used the search terms "mitochondrial disorder," "mitochondriopathy/mitochondriopathies," and "migraine/headache," and "treatment/therapy" and included results from January 1985 until February 2022. The language was restricted to English and full text only. No randomized controlled trials are available—current treatment options are based on case reports and small case series. Altogether, we identified 4 other cases, comprising a total of 65 patients, on the preventive and acute treatment of migraine headaches in patients with a mitochondrial disorder (as shown in Table 1). The male to female ratio was 1:2.8. Phenotypes included MELAS, CPEO, MERRF, Leigh Syndrome, and other

TABLE 1 An overview of the reports on the use of acute or prophylactic migraine treatment in patients with a mitochondrial disorder and their clinical symptoms.

Source	No. of cases	% Female	Genotype	Phenotype	MHD	A	UL	P	PTP	PNP	N	V	DG	PT	AT	abnormal EEG	Comorbidities
Present case	1	0	c.394A > G	Other MD	10–12	+	+	+	+	–	+	+	EM	Flunarizine, bisoprolol, galcanezumab	Analgesics, Triptan	+	Cardiomyopathy, Retinitis pigmentosa, renal impairment, stand and gait ataxia
Naegel et al. (11)	1	100	m.3243A > G	MELAS	10–20	–	+	+	+	+	+	+	CM	Topiramate, onabotulinumtoxin, flunarizine, erenumab	Triptans	+	SLE
Tiehuis et al. (6)	29	83	m.3243A > G and non - m.3243A > G	MERRF; MELAS; Leigh Syndrome;	n.a.	12	n.a.	12	23	18	20	8	n.a.	Metoprolol, propranolol	Triptan, NSAIDs, Acetaminophen, combinational analgesics	n.a.	Diabetes, Impaired hearing, impaired vision, GIT problems, muscle related problems
Vollono et al. (4)	33	64	m.3243A > G m. 8344A > G m. 8356T > C single/ multiple mtDNA deletion OLGI; TYMP m.9242insA	MELAS; CPEO; MERRF; Other MD; MNGIE	3.9 ± 6.3	6	22	n.a.	23	22	16	6	EM	n.a.	NSAIDs; Acetaminophen; Triptan, Codeine; Analgesic	20	SLE; epilepsy; myoclonus; stroke
Iizuka et al. (12)	2	100	n.a.	MELAS	n.a.	–	1	+	1	–	+	+	EM	n.a.	Triptan	1	SLE

A, Aura; AT, acute treatment; CM, chronic migraine; CPEO, Chronic progressive external ophthalmoplegia; DG, Diagnosis; EEG, electroencephalogram; EM, episodic migraine; GIT, gastrointestinal; MD, mitochondrial disease; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; MHD, mean headache days/month; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; N, nausea; n.a., not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; PT, prophylactic treatment; SLE, stroke-like-episodes; UL, unilateral headache; PTP., photophobia; PNP, phonophobia; V, vomiting.

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mitochondrial diseases. Information on the presentation of migraine (headache characteristics and accompanying symptoms) was not fully reported in the studies. Similarly, there was insufficient information about comorbidities, such as stroke-like-episodes (SLE) or epilepsy. Only two studies reported the use of prophylactic medications. In the study by Tiehuis et al., prophylactic migraine treatment (propranolol and metoprolol) was used by four patients, and which was partially effective for two of them (6). In the case report by Naegel et al., the patient used several preventive drugs. Two (topiramate and onabotulinumtoxinA) showed no efficacy and flunarizine had to be discontinued due to side effects. Regarding acute treatment, various drugs were used by the patients, among them triptans, which seemed to be well tolerated. The efficacy of acute medication was often not adequate—some patients had to use triple medication, which was still not effective (6).

Discussion

We present a patient with a genetically confirmed mitochondrial disorder [homozygous missense change in *SSBP1; c.394A>G* (p.I132V)] with episodic/chronic migraine with aura who received galcanezumab for preventive migraine treatment, after having failed two standard-of-care treatment approaches. Herein, we describe the second case of the successful and safe use of a monoclonal anti-CGRP-antibody in a patient with a mitochondrial disease (11), and we report for the first time a long-term follow-up of 3 years. Treatment with galcanezumab was well tolerated and showed adequate efficacy with a sustained > 50% reduction in monthly headache days.

Due to the possible involvement of various organ systems, especially those with high energy requirements, several medications need to be used with caution in this patient population (13). First-line medications for acute migraine treatment, such as non-steroidal anti-inflammatory drugs (14), are contraindicated in the setting of renal impairment, as it was the case in our patient. The frequent use of acetaminophen as acute medication may deplete glutathione and cause hepatopathy (13). Triptans seem to be effective and well tolerated in such patients and therefore might be considered for the acute treatment of migraine attacks (11, 12).

For migraine prevention, antiepileptic drugs (AEDs) have been proven beneficial (15). However, some AEDs, such as valproic acid are mitochondrion-toxic and could, moreover, lead to irreversible liver failure (13, 16). Topiramate as prophylaxis could cause lactate acidosis and therefore has also to be used with reluctance. Coenzyme Q_{10}, magnesium, and riboflavin (vitamin B_2) are substances that have shown only minor benefits in reducing headache intensity and headache duration in migraine patients (17–20). Since all of them are also used in the treatment of mitochondrial disorders (21), a common underlying pathogenic mechanism could be suspected—not only due to similarities in therapeutic approaches but also based on genetic and biochemical evidence (22). Up to date, reports on the effectiveness of these agents on migraine in patients with mitochondriopathies are lacking.

Mitochondrial dysfunction is considered to increase neuronal excitability, thus lowering the threshold for a migraine attack (23). Imaging studies showed impaired mitochondrial oxidative phosphorylation during and between migraine attacks, implying a disrupted energy metabolism in migraineurs (24). The dysfunction of mitochondria is linked to an increase in reactive oxygen species (ROS). In addition, in migraine patients, the antioxidative capacity is lowered, exposing them more easily to higher levels of oxidative stress (23). Many potential migraine triggers, such as fasting, hypoxia, and sleep deprivation, enhance oxidative stress. CGRP, a neuropeptide that seems to play an important role in the development of migraine, is assumed to be released as a response to oxidative stress (25, 26) and is responsible, among other transmitters, for the pain signaling in the trigeminovascular system (27). Blocking CGRP or its receptor with monoclonal antibodies or gepants aborts migraine attacks and reduces their frequency (28). As CGRP is a potent vasodilator and supposedly has cardioprotective effects, an increased risk for cardiovascular events could be feared when inhibiting the CGRP pathway (29). This would also be of relevance in patients with mitochondriopathies, as cardiac involvement is often the predominant clinical manifestation. However, recent data showed a safe cardiovascular profile for CGRP-receptor and CGRP-ligand blocking monoclonal antibodies, respectively (30–32). Regular follow-up over 3 years of therapy with galcanezumab reported no worsening of cardiac functions or cardiac symptoms in our patient.

Headaches account for one of the five most debilitating symptoms of mitochondrial diseases (6). Headaches, especially migraine, have a substantial impact on social functioning and everyday life in patients with mitochondriopathies (5). However, both, acute as well as a preventive treatment for migraine in patients with mitochondrial disease are challenging—data on the use and efficacy of medication are scarce. The literature search revealed only 4 other reports on the use of preventive and/or acute migraine treatment in this respective patient group, and these were either ineffective or had to be discontinued due to side effects. Frequently, it is not possible to use the medication in the appropriate dosage due to therapy-limiting comorbidities. Due to the lack of randomized control trials and particularly due to the heterogenous presentation of mitochondrial disorders, treatment recommendations cannot be provided, and therapy remains empirical (33).

The strength of the study presented here is the detailed description of the patient's migraine headache, comorbidities, imaging and genetic findings, the rationale of the used acute and preventive treatments, as well as the documentation of the long-term therapeutic outcome. The efficacy, tolerability, and safety of a monoclonal CGRP-antibody in the prevention of

migraine headaches could be demonstrated in our patient with a homozygous missense change in *SSBP1*.

However, further research, including randomized controlled trials and a precise and comprehensive patient as well as headache characterization is needed to provide treatment guidelines for patients with migraine due to mitochondrial disorders.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical University of Innsbruck. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KK: conceptualization and writing—original draft. EI and GB: writing—review and editing. SB: conceptualization, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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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References

1. Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, et al. Mitochondrial diseases. *Nat Rev Dis Primers.* (2016) 2:16080. doi: 10.1038/nrdp.2016.80

2. Altmann J, Büchner B, Nadaj-Pakleza A, Schäfer J, Jackson S, Lehmann D, et al. Expanded phenotypic spectrum of the m.8344A>G "MERRF" mutation: data from the German mitoNET registry. *J Neurol.* (2016) 263:961–72. doi: 10.1007/s00415-016-8086-3

3. Kraya T, Deschauer M, Joshi PR, Zierz S, Gaul C. Prevalence of headache in patients with mitochondrial disease: a cross-sectional study. *Headache.* (2018) 58:45–52. doi: 10.1111/head.13219

4. Vollono C, Primiano G, Della Marca G, Losurdo A, Servidei S. Migraine in mitochondrial disorders: prevalence and characteristics. *Cephalalgia.* (2018) 38:1093–106. doi: 10.1177/0333102417723568

5. Burow P, Meyer A, Naegel S, Watzke S, Zierz S, Kraya T. Headache and migraine in mitochondrial disease and its impact on life-results from a cross-sectional, questionnaire-based study. *Acta Neurol Belg.* (2021) 121:1151–6. doi: 10.1007/s13760-021-01630-4

6. Tiehuis LH, Koene S, Saris CGJ, Janssen MCH. Mitochondrial migraine; a prevalence, impact and treatment efficacy cohort study. *Mitochondrion.* (2020) 53:128–32. doi: 10.1016/j.mito.2020.05.004

7. Headache Classification Committee of the International Headache Society (IHS) the international classification of headache disorders, 3rd edition. *Cephalalgia.* (2018) 38:1–211. doi: 10.1177/0333102417738202

8. Del Dotto V, Ullah F, Di Meo I, Magini P, Gusic M, Maresca A, et al. SSBP1 mutations cause mtDNA depletion underlying a complex optic atrophy disorder. *J Clin Invest.* (2020) 130:108–25. doi: 10.1172/JCI128514

9. van de Ven LL, Franke CL, Koehler PJ. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. *Cephalalgia.* (1997) 17:596–9. doi: 10.1046/j.1468-2982.1997.1705596.x

10. Wörz R, Reinhardt-Benmalek B, Föh M, Grotemeyer KH, Scharafinski HW. Prevention of migraine using bisoprolol. Results of a double-blind study versus metoprolol. *Fortschr Med.* (1992) 110:268–72.

11. Naegel S, Burow P, Holle D, Stoevesandt D, Heintz S, Thaele A, et al. Erenumab for migraine prevention in a patient with mitochondrial encephalopathy, lactate acidosis, and stroke-like episodes syndrome: a case report. *Headache.* (2021) 61:694–6. doi: 10.1111/head.14101

12. Iizuka T, Sakai F, Endo M, Suzuki N. Response to sumatriptan in headache of MELAS syndrome. *Neurology.* (2003) 61:577–8. doi: 10.1212/01.wnl.0000078931.87815.b3

13. Parikh S, Goldstein A, Karaa A, Koenig MK, Anselm I, Brunel-Guitton C, et al. Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med.* (2017) 19:10. doi: 10.1038/gim.2017.107

14. Eigenbrodt AK, Ashina H, Khan S, Diener HC, Mitsikostas DD, Sinclair AJ, et al. Diagnosis and management of migraine in ten steps. *Nat Rev Neurol.* (2021) 17:501–14. doi: 10.1038/s41582-021-00509-5

15. Parikh SK, Silberstein SD. Current status of antiepileptic drugs as preventive migraine therapy. *Curr Treat Options Neurol.* (2019) 21:16. doi: 10.1007/s11940-019-0558-1

16. Finsterer J. Toxicity of antiepileptic drugs to mitochondria. *Handb Exp Pharmacol.* (2017) 240:473–88. doi: 10.1007/164_2016_2

17. Gaul C, Diener HC, Danesch U; Migravent® Study Group. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. *J Headache Pain.* (2015) 16:516. doi: 10.1186/s10194-015-0516-6

18. Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhäupl KM, Arnold G. High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. *Eur J Neurol.* (2004) 11:475–7. doi: 10.1111/j.1468-1331.2004.00813.x

19. Sazali S, Badrin S, Norhayati MN, Idris NS. Coenzyme Q10 supplementation for prophylaxis in adult patients with migraine-a meta-analysis. *BMJ Open.* (2021) 11:e039358. doi: 10.1136/bmjopen-2020-039358

20. Thompson DF, Saluja HS. Prophylaxis of migraine headaches with riboflavin: a systematic review. *J Clin Pharm Ther.* (2017) 42:394–403. doi: 10.1111/jcpt.12548

21. El-Hattab AW, Zarante AM, Almannai M, Scaglia F. Therapies for mitochondrial diseases and current clinical trials. *Mol Genet Metab.* (2017) 122:1–9. doi: 10.1016/j.ymgme.2017.09.009

22. Yorns WR, Hardison HH. Mitochondrial dysfunction in migraine. *Semin Pediatr Neurol.* (2013) 20:188–93. doi: 10.1016/j.spen.2013.09.002

23. Gross EC, Lisicki M, Fischer D, Sándor PS, Schoenen J. The metabolic face of migraine - from pathophysiology to treatment. *Nat Rev Neurol.* (2019) 15:627–43. doi: 10.1038/s41582-019-0255-4

24. Reyngoudt H, Achten E, Paemeleire K. Magnetic resonance spectroscopy in migraine: what have we learned so far? *Cephalalgia.* (2012) 32:845–59. doi: 10.1177/0333102412452048

25. Bai YX, Fang F, Jiang JL, Xu F. Extrinsic calcitonin gene-related peptide inhibits hyperoxia-induced alveolar epithelial type II cells apoptosis, oxidative stress, and reactive oxygen species (ROS) production by enhancing notch 1 and homocysteine-induced endoplasmic reticulum protein (HERP) expression. *Med Sci Monit.* (2017) 23:5774–82. doi: 10.12659/msm.904549

26. Frank F, Faulhaber M, Messlinger K, Accinelli C, Peball M, Schiefecker A, et al. Migraine and aura triggered by normobaric hypoxia. *Cephalalgia.* (2020) 40:1561–73. doi: 10.1177/0333102420949202

27. Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache.* (2017) 57 (Suppl. 2):47–55. doi: 10.1111/head.13081

28. Dodick DW. CGRP ligand and receptor monoclonal antibodies for migraine prevention: evidence review and clinical implications. *Cephalalgia.* (2019) 39:445–58. doi: 10.1177/0333102418821662

29. Kumar A, Potts JD, DiPette DJ. Protective role of α-Calcitonin gene-related peptide in cardiovascular diseases. *Front Physiol.* (2019) 10:821. doi: 10.3389/fphys.2019.00821

30. Smith TR, Spierings ELH, Cady R, Hirman J, Ettrup A, Shen V. Cardiovascular outcomes in adults with migraine treated with eptinezumab for migraine prevention: pooled data from four randomized, double-blind, placebo-controlled studies. *J Headache Pain.* (2021) 22:143. doi: 10.1186/s10194-021-01360-1

31. Ashina M, Goadsby PJ, Dodick DW, Tepper SJ, Xue F, Zhang F, et al. Assessment of erenumab safety and efficacy in patients with migraine with and without aura: a secondary analysis of randomized clinical trials. *JAMA Neurol.* (2022) 79:159–68. doi: 10.1001/jamaneurol.2021.4678

32. Kudrow D, Pascual J, Winner PK, Dodick DW, Tepper SJ, Reuter U, et al. Vascular safety of erenumab for migraine prevention. *Neurology.* (2020) 94:e497–510. doi: 10.1212/WNL.0000000000008743

33. Di Stefano V, Rispoli MG, Pellegrino N, Graziosi A, Rotondo E, Napoli C, et al. Diagnostic and therapeutic aspects of hemiplegic migraine. *J Neurol Neurosurg Psychiatry.* (2020) 91:764–71. doi: 10.1136/jnnp-2020-322850

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Trigeminal neuralgia caused by cavernoma: A case report with literature review

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Cavernoma is the second most common cerebrovascular lesion. Cavernoma involving the cranial nerves is very rare. Only 15 cases of cavernoma presenting with trigeminal neuralgia (TN) have been previously reported. Here, we report a rare case of cavernoma manifesting with TN. A young female patient with a 15-day history of right-sided lancinating pain in the face, difficulty in opening the mouth, and hearing dysesthesia. Magnetic resonance imaging (MRI) revealed a well-demarcated lesion in the cerebellopontine angle related closely to the root of the trigeminal nerve. The initial impression was that of a neurinoma. The lesion was surgically resected *via* the retrosigmoid approach, postoperative pathological analysis confirmed the diagnosis of cavernoma, and the patient's pain and difficulty in opening the mouth resolved completely. We presented the 16th documented case of cavernoma with TN. Although cavernoma involving the trigeminal nerve is extremely rare, this diagnosis should be taken into consideration when a lesion in the cerebellopontine angle is detected on MRI, and the clinical manifestation is consistent with that of secondary TN. Specialized MRI sequences, such as susceptibility weighted imaging (SWI), gradient echo T2, and constructive interference in steady-state (CISS)-weighted imaging, aid in establishing the diagnosis. Resection *via* craniotomy may be the primary management strategy for cavernoma causing TN. In addition, gamma knife radiosurgery (GKRS) and percutaneous balloon compression (PBC) may ameliorate the pain to some extent.

KEYWORDS

cavernoma, case report, magnetic resonance imaging, trigeminal neuralgia, trigeminal nerve

Introduction

Cavernoma, also known as cavernous malformation, cavernous angioma, or cavernous haemangioma, is the second most common cerebrovascular lesion, with a reported incidence of 0.5% (1, 2). About 40% of cavernoma are asymptomatic, and the typical clinical manifestations include epilepsy, focal deficits, headaches, and intracranial hemorrhage (1, 2). Cavernoma can occur anywhere along the neuraxis; however, cavernoma involving the cranial nerves is very rare (3). The causes of trigeminal neuralgia (TN) include microvascular compression and compression due to

space-occupying lesions, multiple sclerosis, and herpes zoster (4). Only 15 cases of cavernoma presenting with TN have been previously reported (3, 5–18). Here, we report a rare case of cavernoma manifesting with TN.

Case description

A 29-year-old woman with no past medical history presented with a 15-day history of paroxysmal lancinating right facial pain radiating to the jaw, in addition to a difficulty in opening the mouth. Pain attacks were often triggered by chewing. The facial pain lasted for few minutes and occurred three to five times per day. Treatment with carbamazepine was ineffective. Neurological examination revealed mild hearing loss on the right side. Her corneal reflex and facial sensation were normal. Muscle strength and sensation of limbs were normal. No ataxia or pathological reflex was observed. Preoperative brain magnetic resonance imaging (MRI) showed a well-demarcated, oval mass measuring 17 × 11 × 10 mm in the right cerebellopontine angle (Figure 1A). The lesion was closely related to the right trigeminal nerve and appeared slightly hypointense on T1-weighted sequence, slightly hyperintense on T2-weighted sequence, and non-enhanced on T1 contrast sequence. Surgical resection was performed *via* the right retrosigmoid approach. The lesion was dark-red, had an abundant blood supply, and contained vessel-like structures (Figure 2A). In order to avoid stretch injury of posterior cranial nerves and excessive traction of right cerebellar hemisphere which could lead to cerebellar contusion and postoperative edema, the lateral part of pons besides the lesion was not exposed. Eventually, the lesion was resected en bloc (Figure 2B). Sensory root of the right trigeminal nerve could not be preserved because of the obscure boundary between it and the lesion. However, the right trigeminal nerve motor root was carefully preserved (Figure 2C). Following surgery, pain and difficulty in opening the mouth disappeared immediately, but mild hearing loss did not improve. In addition, the patient developed right facial hypoesthesia.

The pathological diagnosis was cavernoma. Microscopically, malformed vascular tissue and hyaline degeneration of the vascular wall were observed (Figure 2D). Postoperative brain MRI showed that the tumor had been completely removed (Figure 1B), and the patient was discharged on the 18th postoperative day. There was no recurrence of pain during the 3-year follow-up period. Her postoperative facial hypoesthesia on the right side was not improved.

Discussion

TN is the most common form of craniofacial neuropathic pain, which can be classified into 3 types, idiopathic, classic, and secondary TN (19). Idiopathic TN is characterized by unapparent causes. Classic TN, the most frequent type clinically, is caused by neurovascular compression in the trigeminal nerve root (19). Microvascular decompression is a particularly effective treatment for classic TN (20). Secondary TN is generally triggered by a major neurologic disease such as multiple sclerosis or the growth of cerebellopontine angle tumors. Tumors that cause TN include meningiomas, acoustic neuromas, epidermoid cysts, and cholesteatomas. These tumors are benign and compress trigeminal root entry zone (19). In both classic and secondary TN, the foremost mechanism is focal demyelination of primary afferents near the trigeminal root entry zone caused by local compression, which may trigger paroxysmal ectopic discharges. In addition, infiltrative tumors could lead to axonal degeneration (19). Zhong (20) proposed that aging would lead cranial nerve root and surrounding vessel get closer mutually and finally the neurovascular conflict happened. The nerve incurs demyelination due to interfacial friction associated with pulse. Once pressure stimulation occur, an impulse or excitability may generate from the axon cranial nerve root. Voltage-gated ion channels and mechanosensitive ion channels are activated subsequently. Thus, they serve as a trigger for a painful attack by ectopic action potential. During the process, inflammation factors like TNF-α and IL-6 may play an indispensable role in mediating the development of transmembrane ion channels (21). This hypothesis could elucidate the clinical phenomenon that secondary TN cases were mostly caused by meningioma or cholesteatoma instead of schwannoma, because the latter could insulate the nerve by providing proliferative sheaths (21–23).

Cavernoma with TN occurs extremely rare. Fehlings et al. (5) reported the first case in 1988, and thus far, only 16 cases, including our case, have been reported (Table 1) (3, 4, 6–18). Among these, 11 were treated with craniotomy, two with pharmacotherapy, one with gamma knife radiosurgery (GKRS), and one with percutaneous balloon compression (PBC); while one case was managed conservatively. Resection *via* craniotomy is the primary management strategy, and most patients have good outcomes after surgery (16–18). Complete resection of cavernoma located in the brainstem is crucial, since incomplete resection could increase the re-bleeding risk by up to 43% (13). In addition, medication and other less invasive treatments including GKRS and PBC can be considered if risk of open surgery is high (8, 9, 16, 18).

In 2014, Adachi et al. (14) reviewed 11 cases and classified them into 4 types according to the origin of cavernoma as follows: type G (within the Gasserian ganglion); type C (between the cisternal and intra-axial portions of the trigeminal nerve root); type P (within the intra-axial trigeminal nerve root in the pons); and type S (within the spinal tract of the trigeminal nerve root). This classification helps in the selection of treatment modality and surgical approach. For instance, five patients with type G or C cavernoma were all treated with surgery without complications, and their pain was relieved. However, the surgical

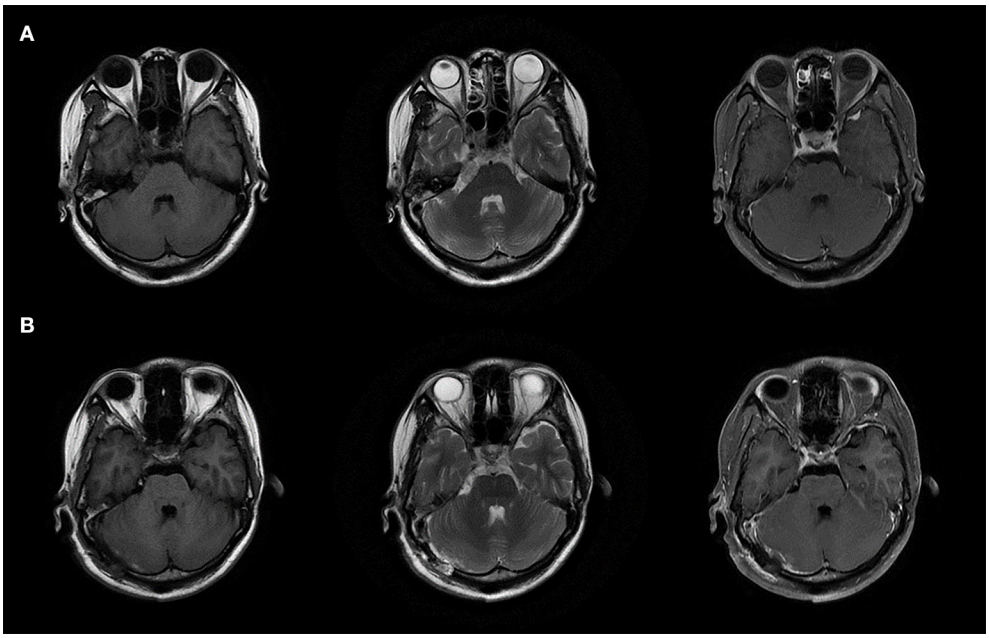

FIGURE 1
MRI images of the lesion. **(A)** Preoperative brain MRI images. **(B)** Postoperative brain MRI images.

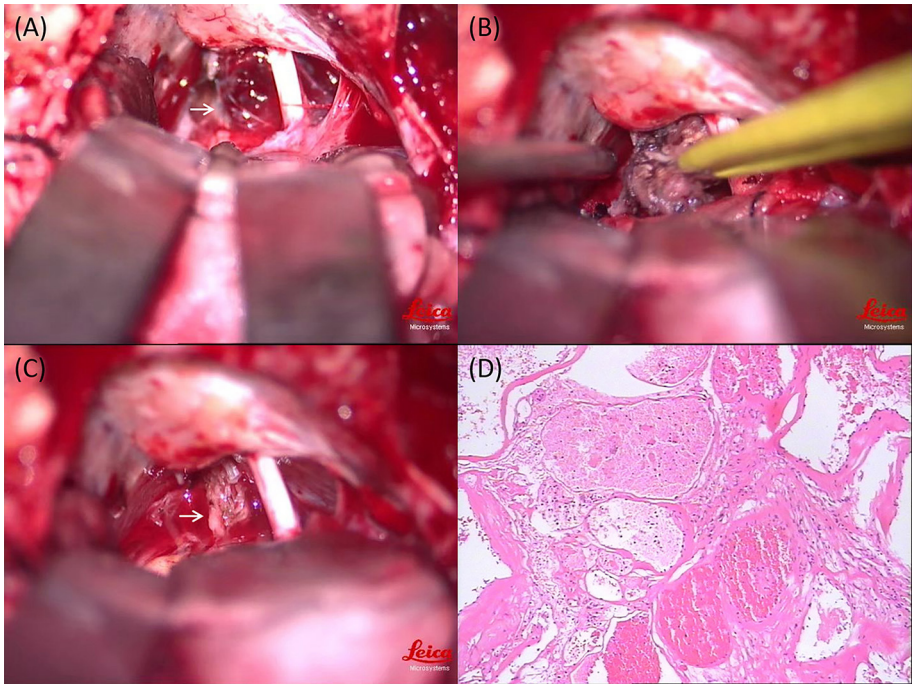

FIGURE 2
Intraoperative photography and histopathological examination of the lesion. **(A)** Intraoperative view: the lesion was dark-red, had an abundant blood supply, and contained vessel-like structures (white arrow). **(B)** Intraoperative view: the lesion was resected en bloc. **(C)** Intraoperative view: the right trigeminal nerve motor root was carefully preserved (white arrow). **(D)** Histopathological examination of the lesion (magnification × 100).

TABLE 1 Reported cases of Cavernous malformation with Trigeminal neuralgia.

References	Patient	Treatment	Efficacy of pain relief according to Brisman's criteria
Fehlings et al. (5)	33 Male	Craniotomy	Cure
Saito et al. (6)	45 Female	Craniotomy	Cure
De Benedittis (7)	62 Male	Craniotomy	Death
Shimpo (8)	67 Male	Pharmacotherapy (carbamazepine)	Effectiveness
Vitek and Tettenborn (9)	61 Male	Pharmacotherapy (gabapentin)	Obvious effectiveness
Deshmukh et al. (3)	52 Female	Craniotomy	Cure
Mascarenhas et al. (10)	54 Male	Craniotomy	Cure
Stellmann et al. (11)	55 Female	Spontaneously disappeared	Cure
Seckin et al. (12)	56 Male	Craniotomy	Cure
Cenzato et al. (13)	45 Male	Craniotomy	Cure
Adachi et al. (14)	62 Male	Craniotomy	Cure
Frossard et al. (15)	56 Female	Craniotomy	Not reported
Pease et al. (16)	80 Female	GKRS	Obvious effectiveness
Scavo et al. (17)	62 Female	Craniotomy	Cure
Zhang et al. (18)	37 Male	PBC	Cure
Present Study	29 Female	Craniotomy	Cure

GKRS, gamma knife radiosurgery; PBC, percutaneous balloon compression.

risk for type P and S was reported to be higher than that for other types (14). One patient with type P cavernoma died of postoperative hemorrhage (7). Therefore, pharmacotherapy could be considered for these two types, and carbamazepine and gabapentin are effective for relieving pain (8, 9). In one case, pain of a patient with type S cavernoma disappeared spontaneously (11). Surgical risk was acceptable in our case as it was type C, and resection *via* the retrosigmoid approach that can expose the lesion sufficiently is the most appropriate strategy for such cases.

Stereotactic radiotherapy is an effective treatment for cavernoma with TN, especially for patients who cannot tolerate surgery. Pease et al. reported the first case of an elderly patient treated with GKRS. After irradiation of the trigeminal nerve, the pain was alleviated significantly without major complications, which confirmed the safety and effectiveness of GKRS (16).

PBC, a traditional therapy for TN and not for cavernoma, is also effective for pain relief. Zhang et al. reported the first case of using PBC to treat TN caused by cavernoma. Considering the surgical risk, the patient refused resection *via* craniotomy. After PBC of the Gasserian ganglion, the patients'pain disappeared completely, which demonstrated that PBC is a reasonable treatment for patients with cavernoma and TN who are reluctant to undergo craniotomy (18).

Cavernoma is most commonly diagnosed using MRI, and it typically appears as a heterogeneous lesion surrounded by a hypointense hemosiderin rim (17). However, preoperative differential diagnosis may be difficult because of atypical imaging findings (10, 12, 15). For example, the most likely preoperative diagnosis in our case was trigeminal neurinoma due to the close relationship between the lesion and right trigeminal nerve observed on MRI, and the signal intensity of the lesion on T1-weighted, T2-weighted, and T1 contrast sequences. The typical symptoms of secondary TN and neurological examination also supported this diagnosis. Susceptibility weighted imaging (SWI) and gradient echo T2 sequence are better able to detect the impressive hemosiderin deposition in the lesion (15, 17, 18). Adachi et al. (14) showed that vague hemosiderin rim and developmental venous anomaly could be observed on constructive interference in steady-state (CISS)-weighted imaging that was helpful in delineating the intracisternal segment of the trigeminal nerve (24). Therefore, specialized MRI sequences may be effective for diagnosing cavernoma with TN.

Conclusions

We presented the 16th documented case of cavernoma with TN. Although cavernoma involving the trigeminal nerve is extremely rare, this diagnosis should be taken into consideration when a lesion in the cerebellopontine angle is detected on MRI, and the clinical manifestation is consistent with that of secondary TN. Specialized MRI sequences, such as SWI, gradient echo T2, and CISS-weighted imaging, aid in establishing the diagnosis. Resection *via* craniotomy may be the primary management strategy for cavernoma causing TN. In addition, GKRS and PBC may ameliorate the pain to some extent.

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 authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HL, CC, and YL collected the data and prepared the manuscript. JL analyzed the data and created the tables and figures. XY and LC designed and supervised the work. All authors agree to be accountable for the content of the work, contributed to the article, and approved the submitted version.

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Conflict of interest

The 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.982503/full#supplementary-material

References

1. Hauck EF, Barnett SL, White JA, Samson D. Symptomatic brainstem cavernomas. *Neurosurgery.* (2009) 64:61–70. doi: 10.1227/01.NEU.0000335158.11692.53

2. Gross BA, Lin N, Du R, Day AL. The natural history of intracranial cavernous malformations. *Neurosurg Focus.* (2011) 30:E24. doi: 10.3171/2011.3.FOCUS1165

3. Deshmukh VR, Hott JS, Tabrizi P, Nakaji P, Feiz-Erfan I, Spetzler RF. Cavernous malformation of the trigeminal nerve manifesting with trigeminal neuralgia: case report. *Neurosurgery.* (2005) 56:E623. doi: 10.1227/01.NEU.0000154063.05728.7E

4. Cruccu G, Finnerup NB, Jensen TS, Scholz J, Sindou M, Svensson P, et al. Trigeminal neuralgia: new classification and diagnostic grading for practice and research. *Neurology.* (2016) 87:220–8. doi: 10.1212/WNL.0000000000002840

5. Fehlings MG, Tucker WS. Cavernous hemangioma of meckel's cave. case report. *J Neurosurg.* (1988) 68:645–7. doi: 10.3171/jns.1988.68.4.0645

6. Saito N, Yamakawa K, Sasaki T, Saito I, Takakura K. Intramedullary cavernous angioma with trigeminal neuralgia: a case report and review of the literature. *Neurosurgery.* (1989) 25:97–101. doi: 10.1227/00006123-198907000-00018

7. De Benedittis G. Sunct syndrome associated with cavernous angioma of the brain stem. *Cephalalgia.* (1996) 16:503–6. doi: 10.1046/j.1468-2982.1996.1607503.x

8. Shimpo T. Trigeminal neuralgia in pontine cavernous angioma. *J Neurol.* (2000) 247:139. doi: 10.1007/PL00007795

9. Vitek L, Tettenborn B. Cavernous angioma in the brachium pontis presenting with trigeminal neuralgia: a case report. *Eur Neurol.* (2002) 48:226–8. doi: 10.1159/000066167

10. Mascarenhas L, Magalhães F, Magalhães Z, Romão H, Resende M, Resende-Pereira J, et al. Cavernous malformation of the trigeminal nerve. *Neurocirugia.* (2006) 17:64–6. doi: 10.1016/S1130-1473(06)70372-4

11. Stellmann JP, Kuhn M, Töpper R. [Chronic facial pain due to a brainstem cavernoma]. *Fortschr Neurol Psychiatr.* (2007) 75:552–4. doi: 10.1055/s-2007-980088

12. Seçkin H, Patel N, Avci E, Dempsey RJ, Başkaya MK. Removal of cavernous malformation of the meckel's cave by extradural pterional approach using heros muscle dissection technique. *Surg Neurol.* (2009) 72:733–6. doi: 10.1016/j.surneu.2009.04.007

13. Cenzato M, Stefini R, Ambrosi C, Latronico N, Milani D. Surgical resolution of trigeminal neuralgia due to intra-axial compression by pontine cavernous angioma. *World Neurosurg.* (2010) 74:544–6. doi: 10.1016/j.wneu.2010.03.035

14. Adachi K, Hasegawa M, Hayashi T, Nagahisa S, Hirose Y. A review of cavernous malformations with trigeminal neuralgia. *Clin Neurol Neurosurg.* (2014) 125:151–4. doi: 10.1016/j.clineuro.2014.07.025

15. Frossard JT, Domingues F, Neves P, Canhedo N, de Souza JM. Cavernous malformation in the trigeminal distribution: a case report of aggressive presentation and management. *World Neurosurg.* (2016) 86:514.e19–22. doi: 10.1016/j.wneu.2015.10.086

16. Pease M, Withrow J, Ozpinar A, Lunsford LD. Gamma knife radiosurgery for trigeminal neuralgia caused by a cavernous malformation: case report and literature review. *Stereotact Funct Neurosurg.* (2018) 96:412–5. doi: 10.1159/000495476

17. Giacobbo Scavo C, Roperto R, Cacciotti G, Mastronardi L. Cystic progression of a cavernous malformation at the level of the trigeminal root entry zone presenting with sudden onset of trigeminal neuralgia. *J Craniofac Surg.* (2018) 29:e728–e30. doi: 10.1097/SCS.0000000000004501

18. Zhang W, Jiang X, Wang Y. Percutaneous balloon compression for trigeminal neuralgia because of pontine cavernous angioma. *World Neurosurg.* (2020) 137:137–9. doi: 10.1016/j.wneu.2019.12.167

19. Cruccu G. Trigeminal neuralgia. *Continuum.* (2017) 23:396–420. doi: 10.1212/CON.0000000000000451

20. Zhong J. The simpler the better: a personal philosophy of microvascular decompression surgery. *Chin Med J.* (2021) 134:410–2. doi: 10.1097/CM9.0000000000001233

21. Liu M, Zhong J. Mechanism underlying cranial nerve rhizopathy. *Med Hypotheses.* (2020) 142:109801. doi: 10.1016/j.mehy.2020.109801

22. Liu MX, Zhong J, Dou NN, Xia L, Li B, Li ST. Management of symptomatic hemifacial spasm or trigeminal neuralgia. *Neurosurg Rev.* (2016) 39:411–8. doi: 10.1007/s10143-016-0702-2

23. Xia L, Zhong J, Zhu J, Wang YN, Dou NN, Liu MX, et al. Cholesteatoma of cerebellopontine angle presented as trigeminal neuralgia. *J Craniofac Surg.* (2014) 25:1540–2. doi: 10.1097/SCS.0000000000000778

24. Yang D, Shen J, Xia X, Lin Y, Yang T, Lin H, et al. Preoperative evaluation of neurovascular relationship in trigeminal neuralgia by three-dimensional fast low angle Shot (3d-Flash) and three-dimensional constructive interference in steady-state (3d-Ciss) mri sequence. *Br J Radiol.* (2018) 91:20170557. doi: 10.1259/bjr.20170557

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Two rare diseases, acute calcific retropharyngeal tendinitis, and crowned dens syndrome, mimicking meningitis: A case report

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We report two rare cases. One involved acute calcific retropharyngeal tendinitis, an inflammatory condition of the longus colli tendon triggered by the deposition of calcium hydroxyapatite crystals. The other involved crowned dens syndrome, caused by pseudogout of the atlantoaxial junction following deposition of calcium pyrophosphate dehydrate or calcium hydroxyapatite. Although these two diseases involve different mechanisms, the common symptoms of neck pain and fever resemble those of meningitis. Accurate diagnosis can thus be difficult without background knowledge of these conditions. Cerebrospinal fluid examination and cervical computed tomography are useful for distinguishing these pathologies from meningitis.

KEYWORDS

neck pain, fever, acute calcific retropharyngeal tendinitis, crowned dens syndrome, cervical computed tomography

Introduction

Meningitis is defined as inflammation of the meninges, usually caused by a central nervous system infection (1, 2). However, on rare occasions, meningitis can be caused by neoplasms, drugs, or autoimmune disease (3–5). The classic triad of meningitis comprises fever, neck stiffness, and altered consciousness. The prevalence of symptoms in meningitis is 87% for headache, 83% for neck stiffness, 77% for fever, and 69% for altered consciousness (6). Only 44% of episodes are characterized by the classic triad of fever, neck stiffness, and altered consciousness (6). At least two of the four signs of the classic triad plus headache are present in 95% of patients with meningitis (6). Acute calcific retropharyngeal tendinitis and crowned dens syndrome are rare pathologies also characterized by an acute onset of neck pain, neck stiffness, and fever (7–10).

Moreover, inflammatory markers such as serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are increased in both these diseases, as in meningitis (7–10). Since the symptoms of these two diseases are similar enough to those of meningitis, diagnosis can be difficult if background knowledge of these two diseases is lacking. Here, we report one case each of acute calcific retropharyngeal tendinitis and crowned dens syndrome and discuss the salient points for identifying each disease.

Case reports

Case 1

A 56-year-old woman presented with a 2-day history of pain in the posterior neck. Neck pain progressively worsened along with limitations to neck movement, and body temperature increased to 38.0°C. Although her body temperature decreased slightly on ice, she visited our hospital's emergency room after neck pain progressed to a headache. Her past medical history was unremarkable, and she had never experienced similar neck pain. On admission, vital signs were blood pressure, 149/79 mmHg; heart rate, 84 beats/min; body temperature, 37.4°C; and respiratory rate, 14 breaths/min. A general physical examination showed no cervical lymphadenopathy. In terms of consciousness, the patient was alert and oriented. A neurological examination showed no abnormalities, with no motor or sensory symptoms or deficits. As for meningeal signs, neck stiffness was present, but both Kernig's and Brudzinski's signs were absent. The patient exhibited odynophagia, tenderness over the posterior neck, and an associated decrease in the range of neck motion in all directions. Laboratory findings were leukocyte count, 9.100/μl (reference: 3.900–9.700/μl); red blood cell count, 4.67 × 10^6/μl (reference: 3.80–5.04 ×10^6/μl); platelet count, 205 ×10^3/μl (reference: 153–346 × 10^3/μl); total protein, 6.3 g/dl (reference: 6.5–8.5 g/dl); and CRP, 0.68 mg/dl (reference: 0.0–0.29 mg/dl). A lumbar puncture was performed due to severe neck stiffness and headache. Cerebrospinal fluid (CSF) examination showed: cell count, 1 cell/μl (reference: <5 cell/μl); protein, 28 mg/dl (reference: 15–45 mg/dl); and glucose, 68 mg/dl (reference: 50–75 mg/dl). CSF cultures yielded no bacterial growth. Cervical computed tomography (CT) identified a nodular calcification in front of the second cervical vertebra (Figures 1A–C), and cervical magnetic resonance imaging (MRI) showed a hyperintense signal in the right longus colli muscle on T2-weighted imaging (Figures 1D,F).

Acute calcific retropharyngeal tendinitis was diagnosed based on the calcification in front of the second cervical vertebra. The patient could not move her body because of neck pain and was unable to eat meals because of pain in swallowing. The following day, serum CRP levels increased to 8.00 mg/dl,

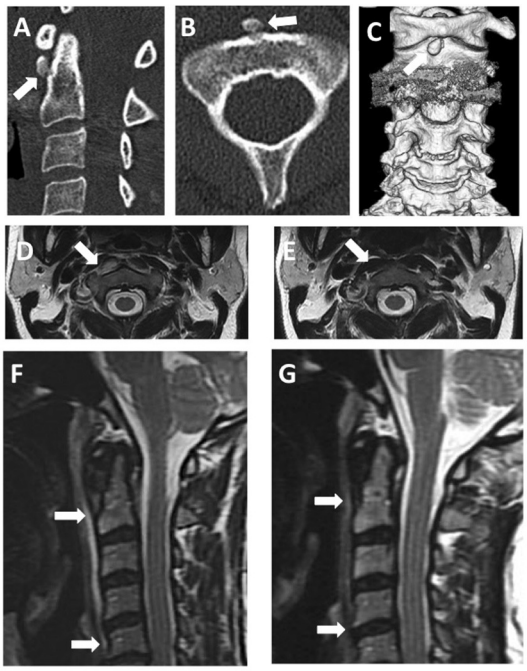

FIGURE 1
Images of acute calcific retropharyngeal tendinitis. **(A)** Sagittal cervical CT. **(B)** Axial cervical CT. **(C)** Three-dimensional reconstruction of cervical CT images. All cervical CT scans reveal nodular calcification in front of the C1–C2 vertebra (arrow). **(D,F)** T2-weighted cervical MRI before treatment. **(E,G)** T2-weighted cervical MRI after treatment. Before treatment, MRI reveals swelling and prevertebral edema (arrows). After treatment, swelling and edema have disappeared.

and intravenous acetaminophen was, therefore, started for pain control. On day three, after symptom onset, neck pain decreased slightly, but she still could not move her neck. Odynophagia decreased, and she became able to swallow both drugs and food. On day five, after symptom onset, the pain subsided to the degree that she could move her neck. The pain completely resolved 10 days after its onset, and she was discharged from the hospital. One month after symptom onset, a cervical spine MRI showed no abnormalities in the longus colli muscle (Figures 1E,G). The follow-up after 2 years showed no recurrence of symptoms and no need for further treatment.

Case 2

A 75-year-old woman visited our emergency department with neck pain and an occipital headache she had never experienced before. The headache was accompanied by a high fever (up to 38.0°C), so she visited the emergency room of our hospital. Her past medical history was unremarkable. On admission, vital signs were blood pressure, 118/70 mmHg; heart

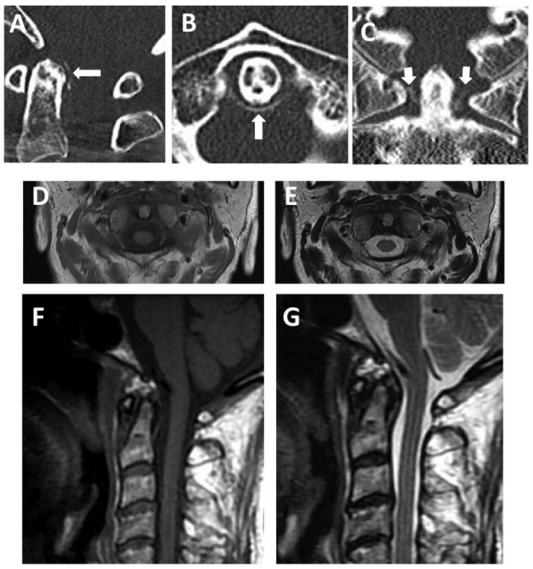

FIGURE 2
Images of crowned dens syndrome. **(A)** Cervical sagittal CT. **(B)** Cervical axial CT. **(C)** Cervical coronal CT. All cervical CT scans reveal calcified lesions around the dens. **(D–G)** Cervical T1-weighted imaging [**(D)** axial; **(F)** sagittal] and T2-weighted imaging [**(E)** axial; **(G)** sagittal] before treatment. A cervical MRI reveals no swelling or prevertebral edema.

rate, 75 beats/min; body temperature, 37.6°C; and respiratory rate, 18 breaths/min. A general physical examination revealed no abnormalities. In terms of consciousness, she was alert and oriented. A neurological examination showed no abnormalities. She had neck stiffness but negative results for both Kernig's and Brudzinski's signs. Laboratory findings included leukocyte count, 5.800/μl (reference: 3.900–9.700/μl); red blood cell count, 3.28 $\times 10^6$/μl (reference: 3.80–5.04 $\times 10^6$/μl); platelet count, 201 $\times 10^3$/μl (reference: 153–346 $\times 10^3$/μl); total protein, 6.6 g/dl (reference: 6.5–8.5 g/dl); and CRP, 9.21 mg/dl (reference: 0.0–0.29 mg/dl). We suspected meningitis based on the severe headache, neck stiffness, and increasing CRP. CSF examination showed cell count, 1 cell/μl (reference: <5 cell/μl); protein, 55.8 mg/dl (reference: 15–45 mg/dl); and glucose, 63 mg/dl (reference: 50–75 mg/dl). CSF cultures yielded no bacterial growth. Despite significant neck pain, laboratory findings did not support the presence of meningitis. Cervical CT showed a curvilinear peri-odontoid calcification in the transverse ligament of the atlas on an axial view (Figures 2A–C). Cervical MRI showed normal signal intensity in the longus colli muscle on T2-weighted imaging (Figures 2D–G). Based on these imaging findings, we diagnosed crowned dens syndrome.

On admission, the patient could not move her body because of neck pain. Oral administration of non-steroidal anti-inflammatory drugs (NSAIDs) was started for pain control. The neck pain decreased 3 days after its onset, and she was able to walk unaided. Nine days after symptom onset, neck pain had almost completely resolved, serum levels of CRP had decreased to 1.17 mg/dl, and the patient was discharged from the hospital. Follow-up after 3 years showed no recurrence of symptoms and no further treatment.

Discussion

Acute calcific retropharyngeal tendinitis is characterized by the sudden onset of acute neck pain, as first reported by Hartly in 1964 (7). This pathology of inflammation in the tendon of the longus colli muscle is triggered by the deposition of calcium hydroxyapatite crystals (11). Although the mechanisms underlying calcification and inflammation remain unclear, ischemic or necrotic changes in the tendons caused by repeated exercise are potential risk factors for calcification (11, 12). This disease is rare, with an estimated incidence of 0.5 cases per 100,000 person-years (13). Acute calcific retropharyngeal tendinitis is most common between the ages of 30 and 60 years, with no obvious sex predominance (8, 14). Previous reports have revealed three major symptoms of neck pain, stiffness, and odynophagia (8, 13–15). Other symptoms that occasionally occur with this disease include shoulder pain, arm pain, back pain, headache, dizziness, nausea, and mild-to-moderate fever (8). In terms of laboratory data, white blood cell counts range from normal to mild leukocytosis, and levels of CRP and ESR are increased in most cases (8, 13–15). As in our case, CSF findings are typically within normal limits (16). Cervical CT is useful for diagnosing acute calcific retropharyngeal tendinitis, showing increased soft-tissue shadows ventral to the cervical spine and calcification anterior to the C1/2 vertebra. Cervical MRI shows diffuse swelling of the longus colli muscle and signals hyperintensity on T2-weighted imaging. Retropharyngeal calcific tendinitis is a self-limiting condition, with symptoms usually resolving spontaneously within 1–2 weeks. Acute calcific retropharyngeal tendinitis responds well to NSAIDs, with or without corticosteroids, and neck pain usually decreases within a few days after starting such treatment (8, 13–15). Immobilization with a soft cervical collar is another useful method to avoid the aggravation of symptoms (11).

Crowned dens syndrome is caused by pseudogout of the atlantoaxial junction due to the deposition of calcium pyrophosphate dehydrate or calcium hydroxyapatite around the dens. This pathology was first described in 1985 by Bouvet et al. (9) and Godfrin-Valnet et al. (17). The incidence of crowned dens syndrome is unclear, although the condition reportedly accounts for 1.9% of outpatients complaining of neck pain (10). Crowned dens syndrome tends to occur in older women, particularly those over 60 (18). Previous reports have revealed three common symptoms: neck pain, neck stiffness, and fever (10). Shoulder pain, occipital pain, pharyngalgia,

TABLE 1 Clinical features of each disease.

	Meningitis	Acute calcific retropharyngeal tendinitis	Crowned dens syndrome
Age/sex	All ages	Middle-age	High age (>60 years old)
	Difference by causes	Men ≒ women	Men < women
Examination	White blood cells ↑	White blood cells ↑	White blood cells ↑
	CRP ↑	ESR, CRP ↑	ESR, CRP↑
	Cerebrospinal fluid cells ↑	Cerebrospinal fluid cells normal	Cerebrospinal fluid cells normal
Symptoms	Headache	Neck pain	Neck pain
	Fever (> 38°C)	Fever	Fever
	Photophobia	Neck stiffness	Neck stiffness
	Vomiting	Odynophagia	Kernig's sign (−)
	Neck stiffness	Kernig's sign (−)	Brudzinski's sign (−)
	Altered consciousness	Brudzinski's sign (−)	
Cervical CT Findings	Normal	Increased soft tissue shadow ventral to cervical spine and calcifications anterior to C1/2 vertebra	Linear calcifications around the dens
Treatment	Acyclovir	NSAIDs	NSAIDs
	Antibiotics	Steroid	Steroid
Prognosis	Varied	Recovery within 1–2 weeks	Recovery within 1–2 weeks

CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; NSAIDs, non-steroidal anti-inflammatory drugs; ↑, increase; (−), absent.

myelopathy, vomiting, and jaw claudication are occasionally seen in this disease. In terms of laboratory data, white blood cell counts range from normal to mild leukocytosis, while levels of CRP and ESR are increased in most cases (10, 18). Findings from CSF are within normal limits (19–21). Cervical CT is useful for diagnosing, showing linear calcification around the dens. These findings represent the "gold standard" for diagnosis, with a diagnosis rate of 97.1% (10). The treatment of crowned dens syndrome involves the administration of NSAIDs, usually leading to symptom resolution within a few days to weeks. Steroids are also effective in severe or recurrent cases (10).

Both acute calcific retropharyngeal tendinitis and crowned dens syndrome commonly present with severe neck pain and fever. The common presence of neck stiffness, fever, and headache in some patients can lead clinicians to misdiagnose meningitis. A few key points distinguish acute calcific retropharyngeal tendinitis and crowned dens syndrome from meningitis. First, according to one report, a limitation of neck rotation to <45° suggests the involvement of the C1/2 joint (21). Crowned dens syndrome is caused by pseudogout of the atlantoaxial junction. On the other hand, the upper part of the longus colli muscle arises from C3–C5 to the atlas and is associated with neck flexion and contralateral rotation. Therefore, both crowned dens syndrome and acute calcific retropharyngeal tendinitis involve the C1/2 joint. When encountering a patient with neck pain and severe limitation of neck movement, clinicians should consider acute calcific retropharyngeal tendinitis and crowned dens syndrome as possibilities and perform cervical CT. Second, altered consciousness is common in cases of meningitis (6) but not in cases of acute calcific retropharyngeal tendinitis or crowned dens syndrome (7–20). When encountering a patient with neck pain and altered consciousness, clinicians should consider the possibility of meningitis and perform a CSF examination. In patients for whom diagnosis proves difficult, CSF examination and cervical CT are useful for distinguishing meningitis from acute calcific retropharyngeal tendinitis or crowned dens syndrome (Table 1).

Differentiating acute calcific retropharyngeal tendinitis from crowned dens syndrome is also important. Crowned dens syndrome tends to be more common among older women, whereas acute calcific retropharyngeal tendinitis most often appears during middle age (Table 1). Odynophagia appears in more than 80% of patients with acute calcific retropharyngeal tendinitis (8), while pharyngalgia appears in only 8.3% of patients with crowned dens syndrome (10). In fact, odynophagia might be relatively specific to acute calcific retropharyngeal tendinitis. As in acute calcific retropharyngeal tendinitis, neck CT is the best tool for diagnosing crowned dens syndrome. Our experience suggests that when examining patients with neck pain and fever, the possibilities of acute calcific retropharyngeal tendinitis and crowned dens syndrome should always be considered, using cervical CT to make a definitive diagnosis. An appropriate diagnosis is needed to avoid unnecessary invasive treatments or inappropriate administration of antibiotics.

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.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EI performed the data research and wrote the manuscript. EI, JF, and KK treated the patients. AF, AN, and HE supported the clinical interpretation. NH and YS were critically involved in the theoretical discussion and composition of the manuscript. All authors read and approved the final version of the manuscript.

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References

1. McGill F, Heyderman RS, Panagiotou S, Tunkel AR, Solomon T. Acute bacterial meningitis in adults. *Lancet.* (2016) 388:3036–47. doi: 10.1016/S0140-6736(16)30654-7

2. Wright WF, Pinto CN, Palisoc K, Baghli S. Viral (aseptic) meningitis: a review. *J Neurol Sci.* (2019) 398:176–83. doi: 10.1016/j.jns.2019.01.050

3. Chamberlain MC. Neoplastic meningitis. *Oncologist.* (2008) 13:967–77. doi: 10.1634/theoncologist.2008-0138

4. Yelehe-Okouma M, Czmil-Garon J, Pape E, Petitpain N, Gillet P. Drug-induced aseptic meningitis: a mini-review. *Fundam Clin Pharmacol.* (2018) 32:252–60. doi: 10.1111/fcp.12349

5. Richie MB. Autoimmune meningitis and encephalitis. *Neurol Clin.* (2022) 40:93–112. doi: 10.1016/j.ncl.2021.08.007

6. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med.* (2004) 351:1849–59. doi: 10.1056/NEJMoa040845

7. Hartley J. Acute cervical pain associated with a retropharyngeal calcium deposit. A case report. *J Bone Joint Surg Am.* (1964) 46:1753–4.

8. Shawky A, Elnady B, El-Morshidy E, Gad W, Ezzati A. Longus colli tendinitis. A review of literature and case series. *Sicot J.* (2017) 3:48. doi: 10.1051/sicotj/2017032

9. Bouvet JP, le Parc JM, Michalski B, Benlahrache C, Auquier L. Acute neck pain due to calcifications surrounding the odontoid process: the crowned dens syndrome. *Arthritis Rheum.* (1985) 28:1417–20. doi: 10.1002/art.1780281215

10. Oka A, Okazaki K, Takeno A, Kumanomido S, Kusunoki R, Sato S, et al. Crowned dens syndrome: report of three cases and a review of the literature. *J Emerg Med.* (2015) 49:e9–13. doi: 10.1016/j.jemermed.2015.02.005

11. Ring D, Vaccaro AR, Scuderi G, Pathria MN, Garfin SR. Acute calcific retropharyngeal tendinitis. Clinical presentation and pathological characterization. *J Bone Joint Surg Am.* (1994) 76:1636–42. doi: 10.2106/00004623-199411000-00006

12. Park R, Halpert DE, Baer A, Kunar D, Holt PA. Retropharyngeal calcific tendinitis: case report and review of the literature. *Semin Arthritis Rheum.* (2010) 39:504–9. doi: 10.1016/j.semarthrit.2009.04.002

13. Horowitz G, Ben-Ari O, Brenner A, Fliss DM, Wasserzug O. Incidence of retropharyngeal calcific tendinitis (longus colli tendinitis) in the general population. *Otolaryngol Head Neck Surg.* (2013) 148:955–8. doi: 10.1177/0194599813482289

14. Kim YJ, Park JY, Choi KY, Moon BJ, Lee JK. Case reports about an overlooked cause of neck pain: calcific tendinitis of the longus colli: case reports. *Medicine (Baltimore).* (2017) 96:e8343. doi: 10.1097/MD.0000000000008343

15. Siag K, Mazzawi S, Paker M, Biener R, Ghanayim R, Lumelsky D. Acute longus colli tendinitis and otolaryngology. *Braz J Otorhinolaryngol.* (2020) 88:351–7. doi: 10.1016/j.bjorl.2020.10.018

16. Wakabayashi Y, Hori Y, Kondoh Y, Asano T, Yamada A, Yamashita M, et al. Acute calcific prevertebral tendonitis mimicking tension-type headache. *Neurol Med Chir (Tokyo).* (2012) 52:631–3. doi: 10.2176/nmc.52.631

17. Godfrin-Valnet M, Godfrin G, Godard J, Prati C, Toussirot E, Michel F, et al. Eighteen cases of crowned dens syndrome: presentation and diagnosis. *Neurochirurgie.* (2013) 59:115–20. doi: 10.1016/j.neuchi.2013.03.003

18. Sato Y, Yasuda T, Konno S, Kuwayama A, Komatsu K. Pseudogout showing meningoencephalitic symptoms: crowned dens syndrome. *Intern Med.* (2004) 43:865–8. doi: 10.2169/internalmedicine.43.865

19. Inoue A, Kohno K, Ninomiya S, Tomita H, Iwata S, Ohue S, et al. Usefulness of cervical computed tomography and magnetic resonance imaging for rapid diagnosis of crowned dens syndrome: a case report and review of the literature. *Int J Surg Case Rep.* (2017) 30:50–4. doi: 10.1016/j.ijscr.2016.11.045

20. Takahashi T, Minakata Y, Tamura M, Takasu T, Murakami M, A. rare case of crowned dens syndrome mimicking aseptic meningitis. *Case Rep Neurol.* (2013) 5:40–6. doi: 10.1159/000348745

21. Dirheimer Y, Wackenheim A. Crowned odontoid apophysis. Apropos of the development mechanism of certain images of axis manifestations. *Sem Hop.* (1974) 50:2077–80.

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Various presentations of the olfactory hallucination in two patients with migraine disease: Case report

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Objectives: To report two different presentations of migraine with the olfactory hallucinations. A case with the typical hallucinatory olfactory symptoms preceding migraine headaches and another case with longstanding olfactory hallucinations.

Background: Migraine prevails in about 12% of the general population, with the migraine aura accountable for at least one-third of these cases. The most common aura is the visual aura, followed by the sensory aura, speech, and motor auras. Olfactory hallucinations preceding the headache phase of migraine are rare. To date, the International Classification of Headache Disorders (ICHD) has not recognized them as a subset of migraine aura.

Results: This report presents a patient with a typical Phantosmia (PO) aura before her migraine headache and a patient who experiences a longstanding PO aura.

Conclusion: The olfactory hallucination may present differently in patients with migraine disease. Based on the clinical significance of migraine with olfactory hallucinations, we propose that the ICHD classify this phenomenon as a subtype of aura in the future. However, larger studies are still required to better assess the pathophysiology of this phenomenon.

KEYWORDS

migraine, migraine aura, olfactory hallucination, Phantosmia, headache

Introduction

The average prevalence of migraines in the population is reported to be around 12% (1). Migraines are painful, recurring headaches that have been traditionally classified into consisting of four phases: prodrome, aura, headache, and postdrome phase (2, 3). However, people's experiences do not always fit these criteria. Many patients who have migraines with aura experience migraines without any aura as well (3), and 4% of patients have aura arise without a headache ever following (4). Aura is a transient sensory disturbance that gradually arises before a migraine headache and can recur (2). About 30% of migraines come about with aura, and the most common symptom associated with migraine aura are visual symptoms, which appear in around 90% of patients (2).

Less typical symptoms of migraine aura are sensory defects, speech or language difficulty, motor weakness, and brainstem or retinal disturbances (2). These symptoms typically last between 5 and 60 min and can occur alone or in succession with one another (3). Olfactory hallucinations or Phantosmia (PO) refers to the perception of an odor that does not exist in the person's environment. PO is a qualitative smell disorder which is often related to quantitative smell disorders (anosmia, hyposmia) in infectious diseases (rhinosinusitis), tumors, schizophrenia, seizures, depression, migraine, and neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease (5–7). Although cases of olfactory hallucinations and their association with migraines have been reported since 1895 (8), PO is not currently classified as a type of migraine aura (9). PO is estimated to occur in about 0.1% of adults who experience migraines (6, 9). However, the prevalence is likely higher because patients do not consider olfaction a pivotal part of migraines. Additionally, the majority of case reports that have explained PO as a noted aura for their patients' migraines have always described their hallucination to occur before the migraine headache. In this report, we explain a similar patient who experiences PO aura before her migraine headache, as well as a patient who experiences PO as a long-standing aura that lasts for several days after the headache resolves.

Case 1

We report a 53-year-old otherwise healthy female with a history of migraine headaches without aura since her early 20s. The patient had her initial consult with headache medicine in July 2017, where she reported to be currently having 12 headache days a month, with pain localized on the left side of the neck and occipital area less commonly as well. She rates the pain on average as a 4–9/10. After a headache arises, the patient is usually pain-free 2 h after taking over-the-counter pain medication (Acetaminophen/Aspirin/Caffeine) and resting. She reports that her headaches used to arise around the time of her menses and have been easy to control, but the severity and frequency of her headaches have been increasing over the past couple of years. The patient experiences photo and phonophobia with her migraine headaches, but no nausea, vomiting, or dizziness with her headaches.

Interestingly, the patient notes that she can smell cigarette smoke from the beginning of her headaches up to 3–7 days after the headaches are gone. She reports that this olfactory hallucination started several years ago and that the smell of smoke is associated with about 30–50% of her headaches. The cigarette smoke smell persisted with her migraines even when she lost her ability to smell in October of 2020 due to COVID-19. Her PO did not get any better or worse during the time she had COVID-19. After starting Topiramate for prophylaxis (August 2021), her headaches have become more well controlled and less severe in pain with only 3–4 headache days a month. She also reports that her PO has gone away with her headaches since October 2021. The patient has no history of seizures, no family history of migraines, and an unremarkable brain MRI.

Case 2

We report a 48-year-old female with a history of migraine without aura, anxiety and depression, and vitamin D deficiency presenting for headache management. The patient's headaches began in her teenage years and started to progress in her mid 30s. The patient describes her headaches as a pressure feeling in the occipital or frontal area lasting up to 3 days and enforces the sensation of a sharp pain on the right or left frontal area lasting a few hours. She has about 15 headache days a month and had about 2–3 headaches a month until a few months ago. She has photo/phono phobia, lightheadedness, and nausea with headache and reports that more of her headaches occur toward the end of the day. The headaches are aggravated by heat/weather changes and alleviated by icepack use. She has a family history of migraine in her mother and maternal grandmother. The patient recently noticed that she started having transient visual disturbances, specifically floaters—a type of visual aura—that can last throughout her headache. Occasionally, the patient will smell burning for about 30 min before her headache. She reports that the burning smell of either cigarette smoke or trash always comes first, followed by visual symptoms and migraine headaches. The patient has no history of seizures, regular menstrual cycles, and has an unremarkable brain MRI.

Discussion

Aura is a recurring transient sensory disturbance reported in 30% of people with migraines (2). The pathophysiology of how migraines with aura arise has been extensively studied in animal models and is strongly believed to involve cortical spreading depression (CSD) of the neurons and glia in the brain. While CSD has mainly modeled how visual aura in migraines comes about, it is believed that the physiology of CSD plays a similar role in all types of migraine aura (10). Therefore, the treatment strategies for migraines, regardless of their aura, are likely similar. In our two patient cases, the second patient had a visual aura that preceded her migraines. In contrast, the first patient did not have any classic presentations of aura with her headaches. However, both patients did experience olfactory hallucinations of cigarette smoke for either some time before or after their migraine headaches. Olfactory hallucinations, involving the smell of cigarette smoke in particular, and their relation to migraines is not a novel discovery. One previous study prospectively followed 11 patients from a tertiary care center who all had olfactory hallucinations that preceded their

migraines. One out of the 11 patients imagined the smell of smoke, eight reported a variety of different unpleasant smells (3/8 smelled gas), and two reported hallucinating pleasant smells. The duration of their pre-migraine smells ranged from 3 to 5 min up to 24 h (9). Another case report from 2020 similarly reported a 51-year-old male who experiences olfactory hallucinations of the smell of gas up to 60–180 min before his migraines (10). In comparison, our second patient had a similar reporting of olfactory hallucinations that preceded her migraines for several minutes before. All of these reported patients, including ours, also had no history of seizures or brain abnormalities, revealing that their olfactory hallucinations are likely influenced by the CSD pathophysiology of their migraine. In contrast, our first patient's olfactory hallucinations consist of a longstanding aura that last up to 3–7 days after her migraines. An olfactory hallucination that occurs for several days after the migraine headache resolves has never been reported in the literature. The reason for this difference in symptoms is unknown and warrants further study on how other longstanding migraine auras physiologically persist. Olfactory hallucinations have been traditionally associated with the temporal lobe (11), and it would be interesting to see if the CSD that occur in these types of migraines also has an association with the temporal lobe or rather other cortical areas. Finally, while our patients offer insight into the different ways olfactory hallucinations can present in patients with migraine disease, more investigation on their formal assessment of olfactory function, differences in family/social history and future response to therapeutic interventions needs to be done.

Olfactory hallucinations and their relation to migraine aura have been reported since 1895 (8), and the number of reports about their association continues to increase. The prevalence of olfactory aura is likely underreported (9) because patients and physicians do not know or expect olfactory aura to be a part of migraine prodrome. Based on the historical significance of this phenomenon, we propose that olfactory hallucinations are considered a subtype of migraine aura in the future. However, larger studies are still required to better assess the pathophysiology and classification of this phenomenon.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Study conception and design, data collection, and analysis and interpretation of results performed by OP and AT. Manuscript draft preparation performed by OP. All authors have reviewed the manuscript and approve the final version.

Conflict of interest

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Publisher's note

References

1. Yeh WZ, Blizzard L, Taylor BV. What is the actual prevalence of migraine? *Brain Behav.* (2018) 8:e00950. doi: 10.1002/brb3.950

2. Lai J, Dilli E. Migraine aura: updates in pathophysiology and management. *Curr Neurol Neurosci Rep.* (2020) 20:17. doi: 10.1007/s11910-020-01037-3

3. Headache classification committee of the international headache society (IHS) the international classification of headache disorders, 3rd edition. *Cephalalgia.* (2018) 38:1–211. doi: 10.1177/0333102417738202

4. Shah DR, Dilwali S, Friedman DI. Current aura without headache. *Curr Pain Headache Rep.* (2018) 22:77. doi: 10.1007/s11916-018-0725-1

5. Fonteyn S, Huart C, Deggouj N, Collet S, Eloy P, Rombaux P. Non-sinonasal-related olfactory dysfunction: a cohort of 496 patients. *Eur Ann Otorhinolaryngol Head Neck Dis.* (2014) 131:87–91. doi: 10.1016/j.anorl.2013.03.006

6. Diamond S, Freitag F G, Prager J, Gandi S. Olfactory aura in migraine. *N Engl J Med.* (1985) 312:1390–1. doi: 10.1056/NEJM198505233122116

7. Sjölund S, Larsson M, Olofsson JK, Seubert J, Laukka EJ. Phantom smells: prevalence and correlates in a population-based sample of older adults. *Chem Senses.* (2017) 42:309–18. doi: 10.1093/chemse/bjx006

8. Fuller GN, Guiloff RJ. Migrainous olfactory hallucinations. *J Neurol Neurosurg Psychiatry.* (1987) 50:1688–90. doi: 10.1136/jnnp.50.12.1688

9. Mainardi F, Rapoport A, Zanchin G, Maggioni F. Scent of aura? Clinical features of olfactory hallucinations during a migraine attack (Ohm). *Cephalalgia.* (2016) 37:154–60. doi: 10.1177/0333102416630580

10. Vgontzas A, Burch R. Episodic migraine with and without aura: key differences and implications for pathophysiology, management, assessing risks. *Curr Pain Headache Rep.* (2018) 22:78. doi: 10.1007/s11916-018-0735-z

11. Tiriticco M, Vanotti A, Mantica D, Coppola A. Migraine with exclusive olfactory aura: case report and literature review. *Headache.* (2020) 60:2544–7. doi: 10.1111/head.14014

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Ramsay Hunt syndrome and mandibular alveolar bone necrosis following herpes zoster: A case report and literature review

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Background: Reactivation of latent varicella-zoster virus (VZV) can induce herpes zoster (HZ). Ramsay Hunt syndrome (RHS) occurs through the reactivation and proliferation of VZV in the geniculate ganglion, which can lead to vesicular rash in the ear or oral mucosa, accompanied by neurological disorders.

Materials and methods: A 50-year-old man sought a remedy for pain in the right ear and face. Within 1 week, all his lower right teeth fell out, and in the following 3 months, his lower right mandibular alveolar bone gradually became necrotic. In the past 20 days, he experienced blister rash, hearing and taste loss, and slight facial paralysis.

Results: After ruling out tumors and other infectious diseases, he was diagnosed with trigeminal HZ and RHS.

Conclusion: Ramsay Hunt syndrome with tooth loss and alveolar osteonecrosis is rare. It requires long-term treatment of pain, and prevention and treatment of tooth loss and alveolar bone necrosis are difficult and warrant further study.

KEYWORDS

herpes zoster, Ramsay Hunt syndrome, pain, teeth exfoliation, jaw osteonecrosis, trigeminal nerve

Introduction

Primary infection with varicella-zoster virus causes chickenpox, followed by viremia with a diffuse rash and latency in the cranial nerve, dorsal root, and autonomic ganglia. Reactivation of latent VZV can induce HZ, which spreads from the cranial nerve or dorsal root ganglia to the dermatome along the sensory nerves. In the USA, >1 million people annually have HZ, with an annual rate of three or four cases per 1,000 persons (1, 2). In China, the prevalence of HZ is 7.7% in hospital patients aged ≥40 years (3). The incidence rate of HZ in the unvaccinated elderly (50 years old) is ~10/1000 person-years (1).

Ramsay Hunt syndrome occurs by the reactivation and multiplication of VZV at the geniculate ganglion, which leads to a vesicular rash on the ear or in the oral mucosa, combined with neurological disturbances (4). Here, we report a rare case of trigeminal HZ combined with RHS, mandibular alveolar bone necrosis, and tooth loss on the same side.

Case report

A 50-year-old man presented to our pain department with a 7-day history of severe acupuncture-like pain in the right prefrontal, temporal, cheek, and mandibular regions and right ear, especially in the mandible, and four right lower teeth fell out within 1 week. In the past 20 days, he experienced blister rash (Figure 1), hearing and taste loss, and slight facial paralysis (Table 1). He had no symptoms of vertigo, tinnitus, nausea, or vomiting. Based on the initial evaluation, the pain intensity was rated as 8 on the visual analogue scale (VAS).

The patient had been smoking for >30 years and smokes at least 20 cigarettes a day. The patient was healthy in the past and had no complications. He did not take any drugs other than those mentioned in Table 1. There was no specific abnormality in his family genetic history.

Intraoral examination revealed severe loosening of the lower right second premolar, and first, second and third molars. The lower right central incisor, lateral incisor, canine, and first premolar had exfoliated, leaving non-healing sockets. The oral hygiene was poor with generalized gingivitis. Extraoral examination demonstrated marked patchy scars of the right facial skin including the forehead, right ear and cheek, angle of the mouth, congestion and swelling of the right external auditory canal, attachment of purulent secretions, and congestion and swelling of the tympanic membrane. His right nasolabial groove is shallower than the opposite, and facial paralysis was classified as House–Brackmann grade II.

There were no obvious abnormalities in renal function and coagulation. Routine blood tests showed a neutrophil percentage of 77.1%, total neutrophil count of 8.06×10^9/L, erythrocyte sedimentation rate of 35.0 mm/h, and inflammatory marker IL-6 of 10.31 pg/ml. Syphilis, HIV, hepatitis B virus, and hepatitis C virus tests were all negative. Anaerobic and aerobic bacterial cultures of skin exudates from ulcerative infection were negative. The following tumor markers were negative: alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen (CA) 153, total and free prostate-specific antigen, CA199, CA24-2, and neuron-specific enolase. Autoimmune anticyclic citrullinated peptide, antikeratin, and antinuclear antibodies were negative. Panoramic radiography showed that the lower right central incisor, lateral incisor, canine, and first premolar had exfoliated (Figure 2A-2). Cranial neck enhanced CT showing osteonecrosis in the right anterior mandible (Figure 3). Electronic fiber otoscopy showed a blistering rash in the external auditory canal.

The rash in our patient was characterized by unilateral aggregated vesicles distributed along the nerves (Figures 1, 2), and the corresponding nerves had different degrees of dysfunction, so we made a diagnosis of HZ. Based on the patient's history of hearing and taste loss and facial paralysis in the early stage, tooth loss and mandibular pain in the late stage, and the distribution of the rash in the right ear canal and on the head and face, we considered that the case involved cranial nerves V, VII, and VIII; therefore, we diagnosed it as RHS.

In terms of treatment, we followed the recommendations of the relevant guidelines (5, 6). When gabapentin measurement reached 0.3 g three times a day for 4 days and the pain could not be relieved, we switched to pregabalin 150 mg two times daily, paracetamol tramadol tablets 362.5 g three times daily, and eperisone hydrochloride 75 mg three times daily, orally for 7 days. As a result of poor relief of jaw pain, we considered that the trigeminal nerve was involved, so we added carbamazepine 0.1 g two times daily orally for 7 days to relieve the pain. Exposed necrotic bone was trimmed periodically; cefixime and metronidazole oral prophylaxis were administered; physiological saline was used for ear canal irrigation and levofloxacin ear drops, two drops three times daily for 10 days. At the time of discharge, the pain score decreased from 8 to 4 on the VAS, and the skin rash healed, leaving a residual scar. The right lower teeth completely fell out (Figure 2).

One month after discharge, the patient underwent a mental foramen nerve block in our outpatient department due to the increased mandibular pain, which reduced the VAS score from 4–6 to 3–4, and after medication, the VAS score gradually decreased to around 2 after 3 months. Since then, we began to gradually reduce the oral drug dose until the pain disappeared (about 6 months later). The right mandible gradually became necrotic, and mandibular debridement was performed regularly in the Department of Stomatology in our hospital until it almost disappeared after 3 months (Figure 2). At the last follow-up visit (6 months later), the pain had disappeared, and the lower right alveolar bone was almost completely necrotic. The facial scar healed and the left teeth were used for chewing.

Discussion

Herpes zoster can occur in anyone who has previously been infected with VZV, through the reactivation of the virus (4). Viral reactivation often occurs in immunocompromised individuals, such as those with physical and psychological trauma, tumor, hematological disease, diabetes, HIV infection, immunosuppressive therapy, malnutrition, aging, emotional stress, smoking, depression, organ transplantation, and some drugs, including but not limited to corticosteroids and

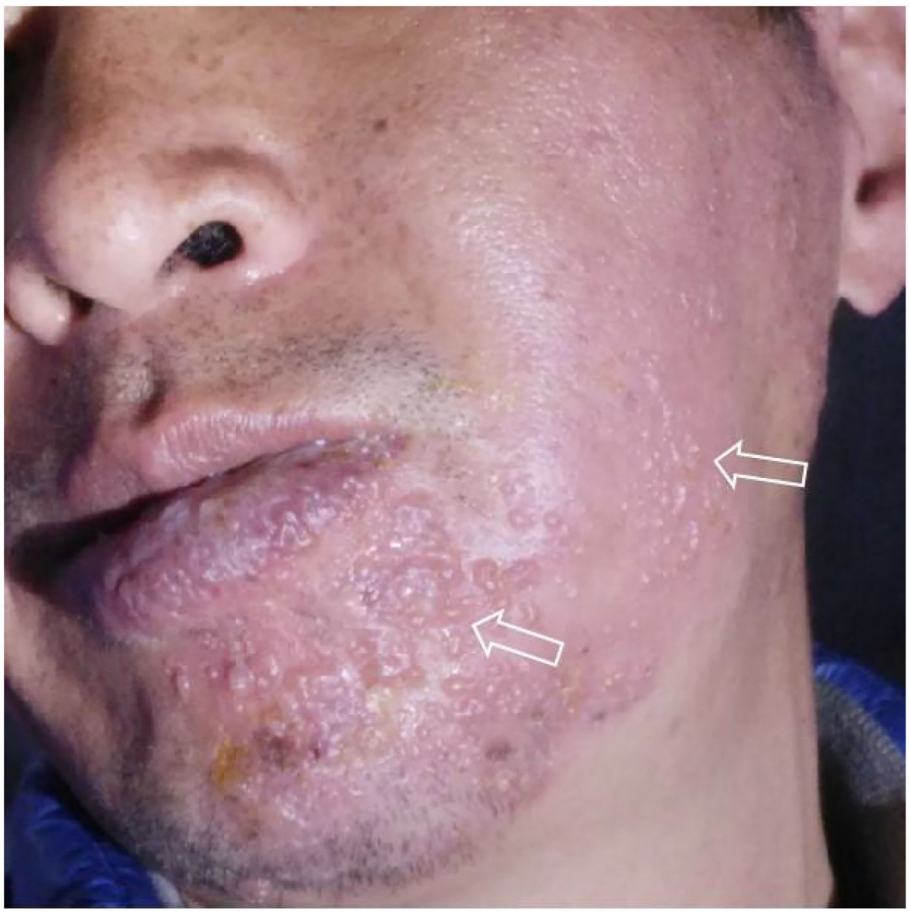

FIGURE 1
Typical unilateral aggregated vesicular rash at the beginning of the disease (2021.4.13), which originated from the patient's self-photography (mirror image).

TABLE 1 Medical history before admission.

Time[a]	Clinical manifestation	Medical institution	Diagnosis	Treatment	Prognosis
20 days before (2021.04.08)	Pain: persistent mild pain in the right lower tooth; VAS:2. Rash: right oral mucosa and gingival blisters and erosion.	Dental clinic	Mouth ulcer	Metronidazole gargle/2 days	No improvement
15 days before (2021.04.13)	Pain: persistent mild pain in right lower tooth; VAS:2. Rash: severe vesicular eruption started from the lower right lip and chin and extended to the face, forehead and ear. Function: right hearing loss, taste loss and facial paralysis (House–Brackman grade III)[b].	Hospital	HZ	Intravenous infusion of methylprednisolone, ceftriaxone and acyclovir/5 days.	Pain: no pain; VAS:0. Rash: gradually scabbed and recovered Function: normal hearing and taste, facial paralysis improved (House–Brackman grade II)[c]
7 days before (2021.04.21)	Pain: severe pain in the right rash area, especially in the mandible; VAS:8. Function: four right lower teeth fell out within 1 week.	None	/	Diclofenac sodium sustained release tablets, 0.1g per day/7 days.	No improvement

[a]Days before visiting our department.
[b]When talking with family members, they need to speak louder; taste was weaker than before; the patient's mouth was tilted to the left and food accumulated on the right side of the mouth when eating (House–Brackmann grade III). [c]Right nasolabial groove was shallower than the opposite groove (House–Brackmann grade II).

FIGURE 2
The **(A–D)** pictures show the rash scar gradually becomes shallow; **(A-1–D-1)** and **(A-2–D-2)** pictures show that the right mandibular teeth gradually fall off and the alveolar bone gradually necrosis.

immunosuppressive agents (4, 7). Our patient was older, had a long history of smoking, and suffered from depression.

Ramsay Hunt syndrome is caused by the reactivation of VZV in the geniculate ganglion, with an incidence of 1% (8). Affected patients can have a blistering rash in the ear (zoster auricularis) or oral mucosa, accompanied by acute peripheral facial paralysis. Other manifestations include pain (face, ears, temporomandibular joint, or teeth); hearing, vision, and taste disorders; tinnitus; vertigo; nausea; ptosis of upper eyelid; increased nasal secretions; fever and discomfort; and abnormal tactile sensation, which are often associated with the involvement of the cranial nerves, such as V, IX, XI, and XII (9).

Recalling the patient's medical history, we speculate that the dentist at the clinic misdiagnosed the oral mucosal herpes as an oral ulcer in the earliest stages. Combined with the clinical manifestations of the patient, the most appropriate description is that HZ was associated with cranial nerve V involvement (mandibular pain and right lower tooth loss), cranial nerve VII involvement (facial paralysis and taste loss), and cranial nerve VIII involvement (hearing loss). The symptoms of cranial nerves VII and VIII involvement improved quickly in the early stage of the disease, which may have been because hormone therapy was used at the initial stage of inflammation.

The pathogenesis of osteonecrosis during HZ was still debated and seems to be multifactorial. Meer et al. (10) suggested that this may be due to the compression of the alveolar artery in the narrow bone canal after edema caused by nerve infection, resulting in arterial ischemia and necrosis of the supply area. Mendieta et al. (11) suggested that the virus spreads directly from adjacent cranial nerves and invades blood vessels, causing segmental granulomatous vasculitis, which seriously affects the growth of the supply area. Judging from the large area of acute skin lesions, our patient's nerves and blood vessels should have been attacked by a large number of viruses, which may have produced the same features as above, leading to tooth loss. Periodontal diseases, such as periodontitis or pulpitis, are common causes of jaw osteonecrosis (12). Badjate et al. (13) explained that tooth exfoliation is an early sign of post-herpetic

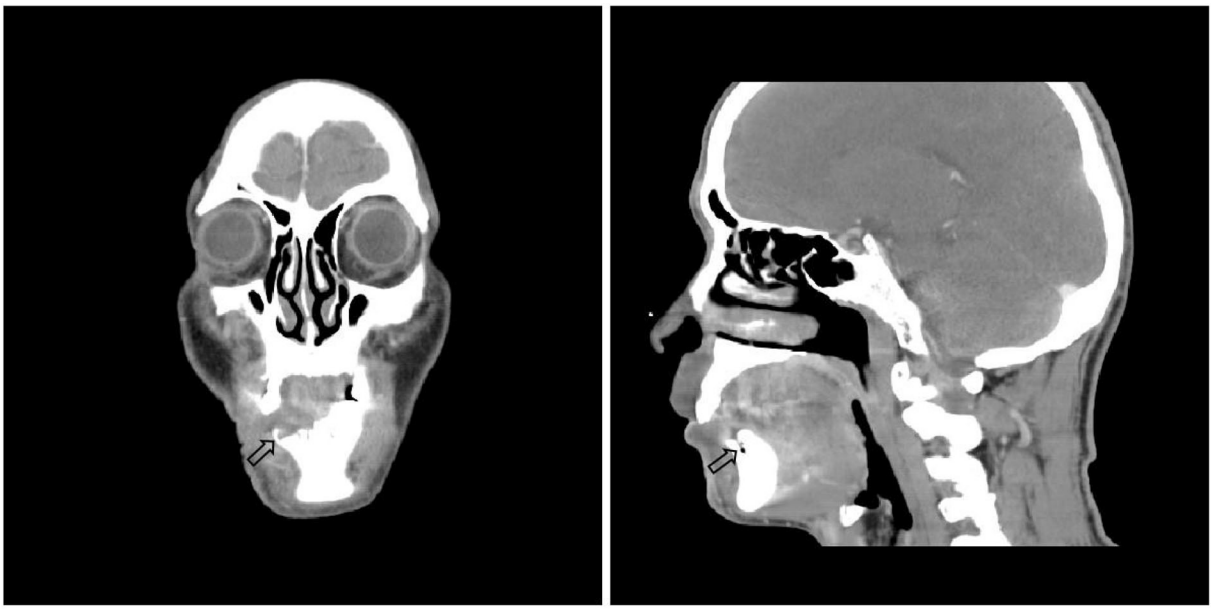

FIGURE 3
Cranial neck enhanced CT(2021-4-30) showed the right side of the lower alveolar bone is partially absorbed, and there is no corresponding tooth. No tumor or other suspicious lesions.

osteonecrosis. The loss of dental proprioception caused by damage to periosteal blood flow leads to periodontal membrane necrosis before alveolar osteonecrosis. Similarly, our patient's hygiene was poor, and he had generalized gingivitis, which may also be one of the reasons for tooth loss and alveolar bone necrosis. Also, the vasoconstriction caused by sympathetic excitation should not be ignored (14). The sympathetic nervous system has a vasoconstrictive effect on the peripheral vascular bed, which is regulated by the local vascular nerve signaling mechanism. When the blood vessels or sympathetic nerves are invaded by the virus, they are stimulated to produce a vasoconstrictive response, which can lead to the obstruction of blood supply to local tissues. It has also been suggested that some neural mechanisms may be involved. Some studies have shown genetic, neuroanatomical, and physiological evidence that leptin regulates bone mass by regulating sympathetic nerve tension (15).

Early application of antiviral drugs and antibiotics combined with aggressive debridement of necrotic bone is considered to improve wound healing to the greatest extent (16). Some scholars have recommended that low-dose hormones combined with antiviral treatment in the early stage of the disease can improve the symptoms associated with viral invasion of the nerves (17). However, mandibular necrosis occurred in a 30-year-old female patient with lupus erythematosus who took prednisone (5 and 7.5 mg, alternately) for 9 years and a 50-year-old male patient with psoriatic arthritis who took prednisone (7.5 mg/day) for 2 years (18, 19). We believe that the key to mandibular necrosis caused by hormone application is long-term use, and we do not use hormone treatment anymore. In recent studies, complementary treatment, including platelet concentrates in solid and liquid form, has been developed to prevent jaw osteonecrosis and improve healing after surgical treatment of bone lesions (19). During treatment, we should pay attention to screening for occult malignancies, immunodeficiency, and other systemic conditions, so as to make the treatment more comprehensive (20). To enhance immunoprotection, Cunningham et al. have recommended the administration of two doses of recombinant virus and adjuvant varicella-zoster vaccine, 2 months apart, beginning at age 60 years (21). Thus, vaccination is an important way to avoid the occurrence of herpes zoster.

Conclusion

Herpes zoster is characterized by pain and neurological impairment in addition to rashes. We need to pay close attention to its medical history when treating such patients to better identify the involved nerves. Our patient had a rare case of RHS with tooth loss and jaw necrosis. There are many references in the literature to the treatment of pain and rash. However, the treatment of tooth loss and jaw necrosis is limited to symptomatic treatment. It is hoped that more cases can be seen to investigate the pathogenetic mechanism and to find timely preventive methods to improve the prognosis of patients.

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 Ethics Committee of PLA Army Characteristic Medical Center; Army Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The 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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References

1. Tseng HF, Bruxvoort K, Ackerson B, Luo Y, Tanenbaum H, Tian Y, et al. The Epidemiology of herpes zoster in immunocompetent, unvaccinated adults ≥50 Years Old: incidence, complications, hospitalization, mortality, and recurrence. *J Infect Dis.* (2020) 222:798–806. doi: 10.1093/infdis/jiz652

2. Rimland D, Moanna A. Increasing incidence of herpes zoster among Veterans. *Clin Infect Dis.* (2010) 50:1000–5. doi: 10.1086/651078

3. Yang F, Yu S, Fan B, Liu Y, Chen YX, Kudel I, et al. The epidemiology of herpes zoster and postherpetic neuralgia in china: results from a cross-sectional study. *Pain Ther.* (2019) 8:249–59. doi: 10.1007/s40122-019-0127-z

4. Werner RN, Nikkels AF, Marinović B, Schäfer M, Czarnecka-Operacz M, Agius AM, et al. European consensus-based (S2k) Guideline on the management of herpes zoster - guided by the european dermatology forum (EDF) in cooperation with the European academy of dermatology and venereology (EADV), part 2: treatment. *J Eur Acad Dermatol Venereol.* (2017) 31:20–9. doi: 10.1111/jdv.13957

5. Liu BT, Xue K, Fan BF, Cui Y. Interpretation of the expert consensus on the whole-process management of herpes zoster-associated pain. *Zhonghua Yi Xue Za Zhi.* (2022) 102:3156–9.

6. Jonsson L, Tien R, Engström M, Thuomas KA. Gd-DPTA enhanced MRI in Bell's palsy and herpes zoster oticus: an overview and implications for future studies. *Acta Otolaryngol.* (1995) 115:577–84. doi: 10.3109/00016489509139371

7. Irwin M, Costlow C, Williams H, Artin KH, Chan CY, Stinson DL, et al. Cellular immunity to varicella-zoster virus in patients with major depression. *J Infect Dis.* (1998) 178:S104–8. doi: 10.1086/514272

8. Demir UL, Basut O. Ramsay Hunt syndrome and current approaches. *Kulak Burun Bogaz Ihtis Derg.* (2012) 22:59–63. doi: 10.5606/kbbihtisas.2012.012

9. Sweeney CJ, Gilden DH. Ramsay-Hunt syndrome. *J Infect.* (2011) 62:180–1. doi: 10.1016/j.jinf.2010.12.005

10. Meer S, Coleman H, Altini M, Alexander T. Mandibular osteomyelitis and tooth exfoliation following zoster-CMV co-infection. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* (2006) 101:70–5. doi: 10.1016/j.tripleo.2005.06.022

11. Mendieta C, Miranda J, Brunet LI, Gargallo J, Berini L. Alveolar bone necrosis and tooth exfoliation following herpes zoster infection: a review of the literature and case report. *J Periodontol.* (2005) 76:148–53. doi: 10.1902/jop.2005.76.1.148

12. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res.* (2015) 30:3–23. doi: 10.1002/jbmr.2405

13. Badjate SJ, Cariappa KM, Shenoi SR, Nakhate S. Ramsay-Hunt syndrome complicating osteonecrosis of edentulous maxilla and mandible: report of a rare case. *J Maxillofac Oral Surg.* (2009) 8:188–91. doi: 10.1007/s12663-009-0046-3

14. van Heerden WF, McEachen SE, Boy SC. Alveolar bone necrosis and tooth exfoliation secondary to herpes zoster in the setting of HIV/AIDS. *AIDS.* (2005) 19:2183–4. doi: 10.1097/01.aids.0000194803.89540.a8

15. Takeda S, Karsenty G. Molecular bases of the sympathetic regulation of bone mass. *Bone.* (2008) 42:837–40. doi: 10.1016/j.bone.2008.01.005

16. Lambade P, Lambade D, Saha TK, Dolas RS, Pandilwar PK. Maxillary osteonecrosis and spontaneous teeth exfoliation following herpes zoster. *Oral Maxillofac Surg.* (2012) 16:369–72. doi: 10.1007/s10006-011-0303-8

17. Francis M, Subramanian K, Sankari SL, Potluri VL, Prabakaran A. Herpes zoster with post herpetic neuralgia involving the right maxillary branch of trigeminal nerve: a case report and review of literature. *J Clin Diagn Res.* (2017) 11:ZD40–2. doi: 10.7860/JCDR/2017/22590.9237

18. Wong LS, Tay KK, Chieng YL. Osteonecrosis of mandible: a rare complication of long-term steroid use. *J Oral Maxillo Surg Med Path.* (2015) 27:255–7. doi: 10.1016/j.ajoms.2014.05.009

19. Nisi M, Ferla F, Graziani F. Osteonecrosis of the jaws related to corticosteroids therapy: a case report. *Ann Stomatol.* (2014) 5:29–30.

20. Cotton SJ, Belcher J, Rose PK, Jagadeesan S, Neal RD. The risk of a subsequent cancer diagnosis after herpes zoster infection: primary care database study. *Br J Cancer.* (2013) 108:721–6. doi: 10.1038/bjc.2013.13

21. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Díez-Domingo J. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med.* (2016) 375:1019–32. doi: 10.1056/NEJMoa1603800

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Can aura migraine be elicited by isolated pulmonary arteriovenous fistula?—A case report

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A pulmonary arteriovenous fistula (PAVM) is an abnormal blood vessel that creates a direct connection between a pulmonary artery and its tributary vein bypassing capillary filter, establishing as a consequence of a low-resistance right-to-left shunting (RLS). The vast majority of PAVMs are congenital appearing more often in females than in males. A great number of patients with PAVMs is suffering concurrently from hereditary hemorrhagic telangiectasia (HHT) whose incidence is around 1 in 5,000. Very few cases of acquired PAVMs have been described in the literature. Paradoxical embolism through PAVMs can cause systemic desaturation, cyanosis, and serious cerebrovascular ischemic events (transient ischemic attacks, strokes, and intracranial abscess), even when the abnormal blood vessel is small (diameter <3 mm). Notably, it has been reported a high prevalence of aura migraine (MHA) symptoms in patients with PAVMs and concomitant HHT. We described in this study the case of a young aura migraineur female patient without HHT in whom isolated PAVM below the detection limit of pulmonary angiography and chest computed tomography angiography (CTA) has been documented by contrast Transthoracic and Transesophageal Echocardiography (cTTE/TEE) showing a delayed (>17 s) RLS coming from left pulmonary veins to left atrium while a patent foramen ovale (PFO), small atrial septal defects or septum primum fenestration could not be detected despite several attempts. Contrast Transcranial Doppler (cTCD) confirmed a delayed (>16 s) RLS with two short "shower" patterns corroborating the diagnosis of an extra-cardiac RLS. During the right heart catheterization and pulmonary angiography, it was impossible to cross the interatrial septum with a multipurpose catheter. The patient was finally discharged with off-label thienopyridine agents (clopidogrel 75 mg die) in terms of primary prophylaxis for paradoxical right-to-left embolization of thrombotic material ultimately. Aura migraine symptoms were nearly abolished by P2Y12 platelet inhibition, suggesting a platelet-based mechanism. During 2 years of clinical follow-up on thienopyridine therapy, the resolution of aura migraine episodes was definitively accomplished with significant improvement in her quality of life.

KEYWORDS

pulmonary arteriovenous malformations, migraine aura, hereditary hemorrhagic telangiectasia, right-to-left shunt, patent foramen ovale, Transcranial Doppler

Introduction

A pulmonary arteriovenous fistula (PAVM) is defined as a congenital abnormal communication between the pulmonary artery and its tributary vein creating a low-resistance, high-flow right-to-left shunting (RLS) bypassing the capillary bed (1, 2). The vast majority of PAVMs are congenital. Isolated PAVMs are uncommon. Their incidence has been reported as high as 1 in 2,600 (3) and occur in about one-third of all patients with hereditary hemorrhagic telangiectasia (HHT) also known as Rendu–Osler–Weber disease, an autosomal dominant disorder caused by a mutation of endoglin gene (HHT type 1) or activin receptor-like kinase 1 (HHT type 2) and characterized by abnormalities of vascular structures involving multiple organs (4, 5). A third gene, the one that codes for the transcription factor SMAD4, is responsible for the HHT associated with Juvenile Polyposis (6, 7). PAVMs may be present with a variety of clinical manifestations such as dyspnea, hypoxemia, chest pain, and pulmonary hypertension. Cryptogenic strokes from isolated PAVMs have been described but they are rare (8, 9). Migraines linked to intrapulmonary RLS have been described (10–12) and are sometimes the presenting clinical manifestation of PAVMs. We reported such a case of isolated intrapulmonary RLS below the detection limit of pulmonary angiography and computed tomography angiography in a patient presenting with severe aura migraine successfully treated with P2Y12 platelet inhibition.

Case

A 38-year-old woman without cardiovascular risk factors was suffering since the age of 14 from endometriosis refractory to non-steroidal anti-inflammatory drugs. At the age of 25, progesterone replacement therapy (PRT) was prescribed with a significant decrease in pain and cramps around menstruations, but worsening episodes of migraine with aura concomitantly occurred. She reported no neurologic symptoms. On neurological examination, strength, skin sensation, visual field, reflexes, and coordination were normal.

She was suffering since childhood from prodromal symptoms (sensitivity to light) preceding recurrent attacks of unilateral reversible visual aura and sensory symptoms (numbness) that were usually followed by intensive headache lasting up to 24 h occurring two times a week with nausea often followed by emesis with aggravation of the headaches, meeting International Classification of Headache Disorders—3rd edition for migraine aura. Tryptans did not ameliorate her headaches. T1-, T2-, T2-FLAIR, and diffusion-weighted brain magnetic resonance imaging (MRI) showed scanty focal bilateral supratentorial white matter hyperintensities (WMHs).

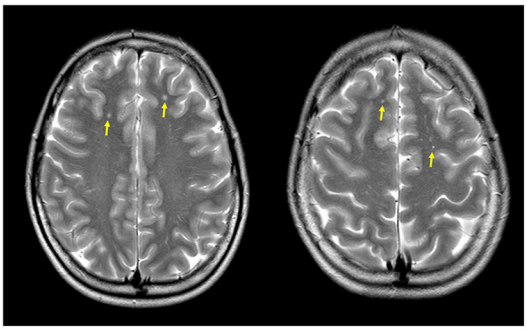

FIGURE 1
Magnetic resonance (MR) axial T2-weighted-FLAIR images showing multiple focal bilateral supratentorial white matter hyperintensities (yellow arrows).

Pregnancy was planned and HRT was suspended. After an uneventful delivery, HRT was re-started and a severe migraine aura occurred thereafter.

Diagnostic assessment

On control MRI 1 year later, WMHs of the same size and number were identified (Figure 1) as it has been reported in shunt-associated migraine (SAM) patients (13).

Electrocardiogram showed persistent sinus rhythm and incomplete right bundle branch block. Chest X-ray, computed tomography angiography (CTA), and 2D TTE/TEE color Doppler were performed resulting within normal limits. Contrast TTE/TEE using agitated saline solution showed no RLS across the interatrial septum (Figure 2, Supplementary Videos 1, 2) but conversely demonstrated bubbles arriving from left pulmonary veins to the left atrium and left ventricle *via* a pulmonary arteriovenous fistula (Supplementary Figure 1) in basal conditions. Contrast-enhanced Transcranial Doppler (cTCD) raised the suspicion of an extracardiac RLS by showing in basal conditions high-intensity transient signals passing through the middle cerebral artery with a delayed (17 s) "shower" pattern (Figure 3, Supplementary Video 2). Of note, aura migraine symptoms occurred 4 min after agitated saline injection ("bubble migraine positive" patient) (14). According to the protocol of the Venice 1999 Consensus conference, the bubble count was performed twice, during normal breathing and after Valsalva strain (15). It is worth to mention that no evidence or family history of HHT was documented in her past medical history.

The decision was made by our multidisciplinary heart and brain team to offer a clinical re-evaluation in order to stratify the risk of paradoxical embolism and consequently to perform possibly a catheter-based embolization using detachable coils or vascular plugs of the isolated intrapulmonary RLS.

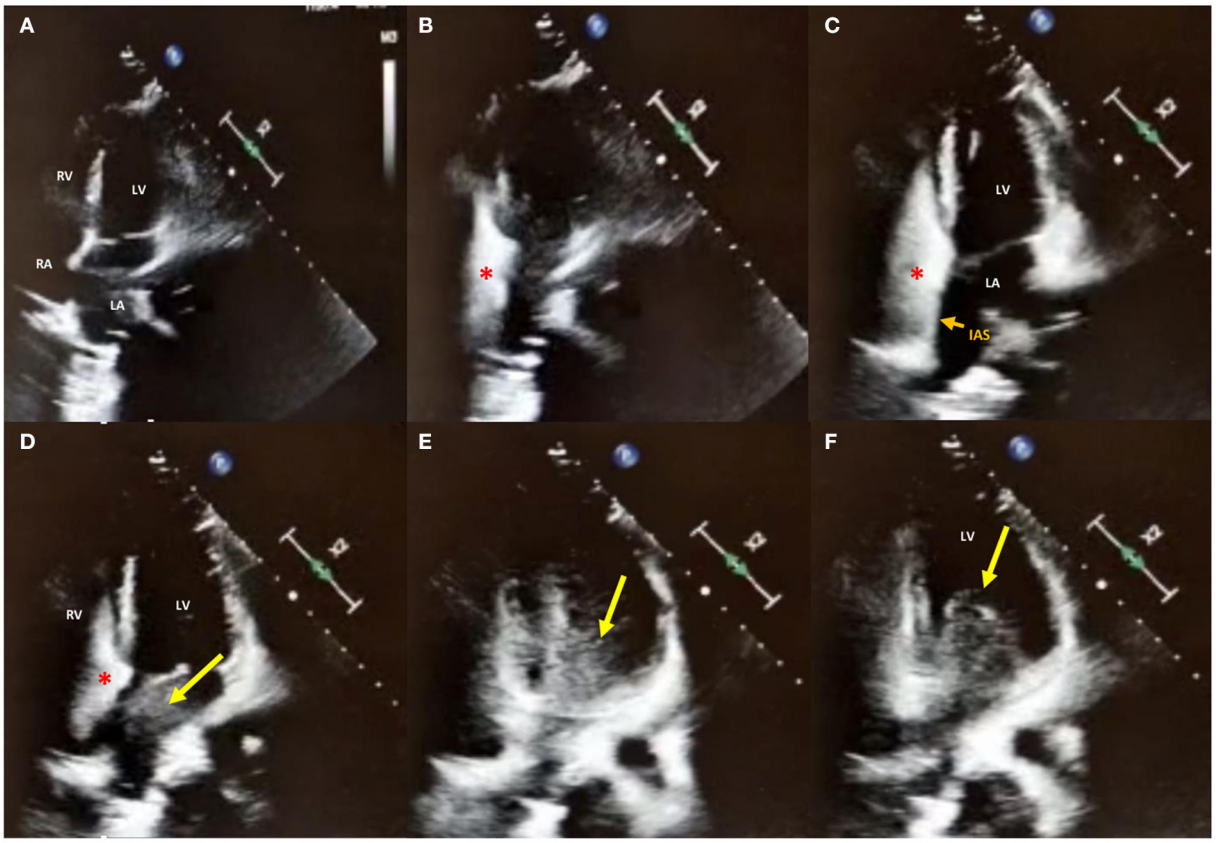

FIGURE 2
2D contrast-Transthoracic Echocardiography in apical 4-chambers view in basal conditions. **(A–C)** Agitated saline injection (red asterisk) from the right antecubital vein showed no right-to-left shunt (RLS) across the interatrial septum (IAS; small orange arrow); **(D–F)** While still no bubbles were crossing the interatrial septum, a delayed (17 s) RLS coming from left pulmonary veins to LA and LV through the mitral valve is shown, confirming the diagnosis of extra-cardiac RLS. LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle.

Written informed consent, after explanation, was obtained from the patient. During the hospital stay, she was monitored for vital parameters without any abnormalities except for a slight reduction in arterial oxygen saturation (SaO_2) of 94%. Continuous ECG ruled out atrial fibrillation. Right heart catheterization to evaluate hemodynamic parameters and selective pulmonary angiograms were performed in order to definitively check for an isolated PAVM and to search for accompanying malformations. Right atrial pressure, pulmonary artery pressure, pulmonary vascular resistance, and pulmonary to systemic flow ratio (QP/QS) were within normal limits. It has been impossible to cross the interatrial septum with a multipurpose catheter despite multiple attempts. Oddly, selective right and left pulmonary arteriograms did not show abnormalities of the pulmonary vasculature or arteriovenous shunts (Figure 4, Supplementary Video 3). Brachiocephalic vein angiogram ruled out the presence of persistent left superior vena cava draining into the left atrium, another possible rare cause of RLS and paradoxical embolism (Supplementary Video 4) (16).

The Heart and Brain team then decided to discharge the patient on off-label thienopyridine agents (clopidogrel 75 mg die) in terms of primary prophylaxis for paradoxical embolization of thrombotic material that could bypass the pulmonary capillary filter. Surprisingly, a substantial reduction in aura migraine symptoms in our patient was achieved using P2Y12 platelet inhibition, suggesting a platelet-based trigger. HRT was advantageously resumed without migraine attacks. During 2 years of follow-up on thienopyridine therapy, the resolution of migraine aura episodes was accomplished.

Discussion

Increased prevalence of migraines has been described in patients with HHT, the most common cause of PAVMs (1–4) as well in patients with intrapulmonary RLS shunts (11, 17, 18). Thenganatt et al. pointed out that PAVMs were significantly associated with migraine (OR = 2.4, 95% CI = 1.1–5.5, $p = 0.04$), after adjustment for age and sex, using logistic regression (10).

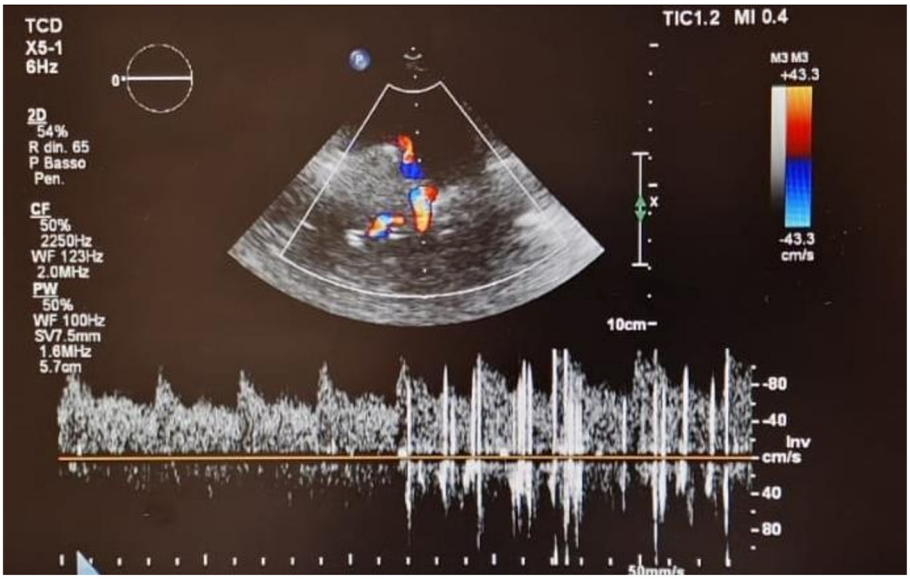

FIGURE 3
Contrast Transcranial Doppler in basal conditions showing high-intensity transient signals passing through the middle cerebral artery with a delayed (17 s) "shower" pattern.

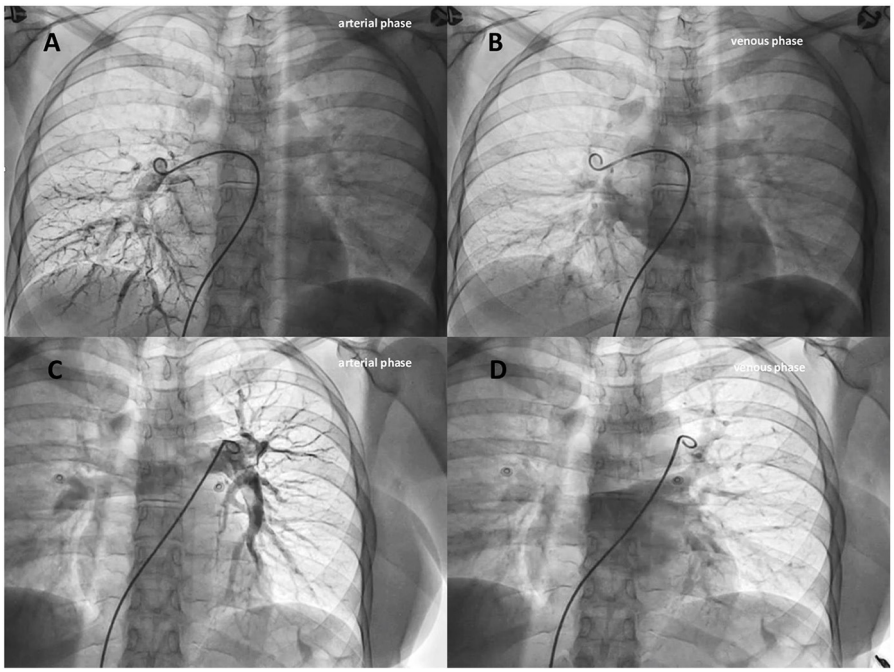

FIGURE 4
Selective right **(A,B)** and left **(C,D)** pulmonary angiograms (arterial and venous phases) didn't show abnormalities of the pulmonary vasculature or arteriovenous shunts.

Our patient had no personal evidence or family history of HHT and was diagnosed with isolated congenital PAVM. The frequency of migraine headaches in patients with isolated PAVM is unknown. A causal relationship between the presence of an RLS and migraines has been suggested but remains unproven until now. Several hypotheses have been suggested. Firstly, being HHT and some subtypes of migraines autosomal-dominant disorders, it might be that a particular genetic substrate

determining intrapulmonary RLS in patients with HHT may also activate migraines (19). Secondly, trigger substances such as micro embolic particles or vasoactive chemicals (serotonin) might enter directly the systemic circulation through the RLS instead of being inactivated in the pulmonary capillary bed. These vasoactive substances might induce instability or increased excitability of central nervous system, causing aura migraine attacks (20). Thirdly, micro embolic air load could act as a trigger of migraine attack provoking a sudden decrease of oxygen saturation in cerebral circulation triggering cortical spreading depression and as a result migraine attack (14).

A further mechanism strictly interacting with those mentioned could be identified in cerebral hemodynamics of MHA patients. Evidence support the role of increased cerebral vasomotor reactivity in MHA patients with large right-to-left shunt and an altered cerebral autoregulation in aura migraineurs (21, 22).

Furthermore, a high prevalence of migraines (up to 59%) has been shown in patients who were admitted for transcatheter closure of large PAVMs (9, 23). However, the effects of embolization on the prevalence of migraines have not been confirmed. Only one study has reported a significant reduction in migraine episodes after embolization of PAVMs (24).

Based on the Second International Guidelines for the diagnosis and management of HHT (25), confirmation of intrapulmonary shunts should be performed by CTA with thin-cut reconstructions, in order to evaluate the necessity for endovascular embolization. Nevertheless, additional chest CTA with thin-cut reconstructions should not be performed in cases with only an isolated intrapulmonary RLS documented by cTTE/TEE and cTCD, as these shunts may be too small for subsequent transcatheter embolization procedure.

Of note, the availability of simple diagnostic techniques such as cTCD and cTTE/TEE to assess RLS undoubtedly contributed a great deal of knowledge and understanding of this rare clinical entity.

Historically, progressive expansion of the PAVMs and paradoxical embolism are the main two indications for surgical ligation and resection (26). Technological improvements have made endovascular embolization the treatment of choice for most patients (27, 28), and this represents a clear advantage in comparison to surgical ligation and resection. The exact number, size, and location of PAVMs confirmed by pulmonary angiography can be very helpful guidance to tailor the percutaneous treatment to each patient's clinical condition and anatomical characteristics. Noteworthy, while transcatheter embolization is considered first-choice treatment for PAVMs, a significant amount of patients successfully treated may experience recurrences in the follow-up.

Based on observational series, Sommer et al. (29) demonstrated that in the PFO-MHA population treatment with thienopyridines (platelet P2Y12 receptor inhibitors) substantially reduced or eliminated migraine symptoms in up to two-thirds of patients. Platelet aggregation or platelet activation byproducts from the venous circulation, rather than being filtered in the lungs, might cross the PFO or an extra-cardiac source like an intrapulmonary fistula as in our case to reach the brain in exceeding levels, triggering the MHA. That assumption was substantiated by the observation that the MHA response to P2Y12 platelet inhibition correlated nearly perfectly with the MHA response to subsequent PFO closure.

More recently, laboratory analysis of platelet function in patients with PFO and MHA demonstrated that there is a hyperactive platelet state resulting in an increased endogenous thrombin potential and an altered oxidative stress status documented by increased platelet reactive oxygen species production and blood oxidized glutathione/reduced glutathione ratio. Concomitantly, the markers of platelet hyperactivity returned to control levels and coincided with MHA cessation with the administration of clopidogrel or with subsequent catheter-based PFO closure (30). Accordingly, with Sommer and more recent literature, this platelet prothrombotic phenotype was better controlled by P2Y12 antagonist while aspirin had little effect on it (31).

In summary, we report a case of a patient with isolated intrapulmonary RLS below the detection limit of pulmonary angiography and CTA whose aura migraine symptoms resolved following P2Y12 platelet inhibition with a considerable improvement in her quality of life. Further studies are needed to determine the association between intrapulmonary RLS and migraine and whether MHA symptoms can be elicited by isolated pulmonary arteriovenous fistula.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

EO, JS, and TC contributed to the conception and design of the study. EO, JS, MB, and GA contributed to drafting the text or preparing the figures. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1079959/full#supplementary-material

SUPPLEMENTARY FIGURE 1
2D contrast-Transthoracic Echocardiography (cTTE) showing agitated saline solution (yellow arrow) coming from left superior pulmonary vein draining into the left atrium. LAA, left atrial appendage; LSPV, left superior pulmonary vein.

SUPPLEMENTARY VIDEO 1
2D contrast-Transthoracic Echocardiography (cTTE) after Valsalva maneuver showed a delayed (16 s) RLS coming from left superior pulmonary vein to LA (extra-cardiac RLS).

SUPPLEMENTARY VIDEO 2
2D contrast-Transesophageal Echocardiography (cTEE) in basal conditions **(A)** and after Valsalva maneuver **(B)** showing non bubbles crossing the interatrial septum.

SUPPLEMENTARY VIDEO 3
Selective right **(A)** and left **(B)** pulmonary angiograms in the anteroposterior projection showing no abnormalities of the pulmonary vasculature or intrapulmonary arteriovenous malformations.

SUPPLEMENTARY VIDEO 4
Brachiocephalic vein angiogram showed a remnant of the persistent left superior vena cava but ruled out its draining into the left atrium.

References

1. Shovlin CL, Condliffe R, Donaldson JW, Kiely DG, Wort SJ. British Thoracic Society clinical statement on pulmonary arteriovenous malformations. *Thorax.* (2017) 72:1154–63. doi: 10.1136/thoraxjnl-2017-210764

2. Post MC, Majumdar S, McWilliams JP. Approach to pulmonary arteriovenous malformations: a comprehensive update. *J Clin Med.* (2020) 9:1927. doi: 10.3390/jcm9061927

3. Nakayama M, Nawa T, Chonan T, Endo K, Morikawa S, Bando M, et al. Prevalence of pulmonary arteriovenous malformations as estimated by low-dose thoracic CT screening. *Intern Med.* (2012) 51:1677–81. doi: 10.2169/internalmedicine.51.7305

4. Khurshid I, Downie GH. Pulmonary arteriovenous malformation. *Postgrad Med J.* (2002) 78:191–7. doi: 10.1136/pmj.78.918.191

5. Müller-Hülsbeck S, Marques L, Maleux G, Osuga K, Pelage J-P, Wohlgemuth WA, et al. CIRSE standards of practice on diagnosis and treatment of pulmonary arteriovenous malformations. *Cardiovasc Intervent Radiol.* (2020) 43:353–61. doi: 10.1007/s00270-019-02396-2

6. Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet.* (2004) 363:852–9. doi: 10.1016/S0140-6736(04)15732-2

7. Cichy W, Klincewicz B, Plawski A. Juvenile polyposis syndrome. *Arch Med Sci.* (2014) 10:570–7. doi: 10.5114/aoms.2014.43750

8. Husain Z, Vuppali M, Hussain K, Khan MN, Patel K, Forbes T, et al. An isolated fistula between the right pulmonary artery and the right pulmonary vein: an unusual cause of stroke in a young female. *Cardiol J.* (2011) 18:73–6.

9. Veeram Reddy SR, Patel VG, Gualano SK. Amplatzer vascular plug IV for occlusion of pulmonary arteriovenous malformations in a patient with cryptogenic stroke. *Ann Pediatr Cardiol.* (2014) 7:145–7. doi: 10.4103/0974-2069.132498

10. Thenganatt J, Schneiderman J, Hyland RH, Edmeads J, Mandzia JL, Faughnan ME, et al. Migraines linked to intrapulmonary right-to-left shunt. *Headache.* (2006) 46:439–43. doi: 10.1111/j.1526-4610.2006.00291.x

11. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. *Chest.* (2005) 128:2485–9. doi: 10.1378/chest.128.4.2485

12. Marziniak M, Jung A, Guralnik V, Evers V, Prudlo J, Geisthoff UW, et al. An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary right-to-left shunts. *Cephalalgia.* (2009) 29:76–81. doi: 10.1111/j.1468-2982.2008.01703.x

13. Anzola GP, Meneghetti G, Zanferrari C, Adami A, Dinia L, Del Sette M, et al. Is migraine associated with right-to-left shunt a separate disease? Results of the SAM study. *Cephalalgia.* (2008) 28:360–6. doi: 10.1111/j.1468-2982.2008.01539.x

14. Caputi L, Usai S, Carriero MR, Grazzi L, D'Amico D, Falcone C, et al. Microembolic air load during contrast-Transcranial Doppler: a trigger for migraine with aura? *Headache.* (2010) 50:1320–7. doi: 10.1111/j.1526-4610.2010.01621.x

15. Jauss M, Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. *Cerebrovasc Dis.* (2000) 10:490–6. doi: 10.1159/000016119

16. Butera G, Salvia J, Carminati M. When side matters: contrast echocardiography with injection from he left antecubital vein to detect a persistent left superior vena cava draining to the left atrium in a patient with cerebral stroke *Circulation.* (2012) 125:e1. doi: 10.1161/CIRCULATIONAHA.110.013318

17. Post MC, van Gent MW, Plokker HW, Wetsremann CJJ, Kelder JC, Mager JJ, et al. Pulmonary arteriovenous malformations associated with migraine with aura. *Eur Respir J.* (2009) 34:882–8. doi: 10.1183/09031936.00179008

18. Steele JG, Nath PU, Burn J, Porteous ME. An association between migrainous aura and hereditary haemorrhagic telangiectasia. *Headache.* (1993) 33:145–8. doi: 10.1111/j.1526-4610.1993.hed3303145.x

19. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. *Clin Sci.* (2001) 100:215–20. doi: 10.1042/cs1000215

20. Wilmshurst P, Nightingale S. The role of cardiac and pulmonary pathology in migraine: a hypothesis. *Headache.* (2006) 46:429–34. doi: 10.1111/j.1526-4610.2006.00374.x

21. Vernieri F, Tibuzzi F, Pasqualetti P, Altamura C, Palazzo P, Rossini PM, et al. Increased cerebral vasomotor reactivity in migraine with aura: an autoregulation disorder? A Transcranial Doppler and near-infrared spectroscopy study. *Cephalalgia.* (2008) 28:689–95. doi: 10.1111/j.1468-2982.2008.01579.x

22. Altamura C, Paolucci M, Brunelli N, Cascio Rizzo A, Cecchi G, Assenza F, et al. Right-to-left shunts and hormonal therapy influence cerebral vasomotor reactivity in patients with migraine with aura. *PLoS ONE.* (2019) 14:e0220637. doi: 10.1371/journal.pone.0220637

23. Na SJ, Min Cho H, Par JSA. Case of successful surgical treatment of migraine headaches in a patient with sporadic pulmonary arteriovenous malformations. *J Korean Med Sci.* (2009) 24:330–2. doi: 10.3346/jkms.2009.24.2.330

24. Post MC, Thijs V, Schonewille WJ, Budts W, Snijder RJ, Plokker HW, et al. Embolization of pulmonary arteriovenous malformations

and decrease in prevalence of migraine. *Neurology.* (2006) 66:202–5. doi: 10.1212/01.wnl.0000194257.75559.b0

25. Faughnan ME, Mager JJ, Hetts S, Palda VA, Lang-Robertson K, Buscarini E, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *Ann Intern Med.* (2020) 173:989–1001. doi: 10.7326/M20-1443

26. White RI, Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, et al. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. *Radiology.* (1988) 169:663–9. doi: 10.1148/radiology.169.3.3186989

27. James RG, Ghassan K. Pulmonary arteriovenous malformations. A state of the art review. *Am J Respir Crit Care Med.* (1998) 158:643–61. doi: 10.1164/ajrccm.158.2.9711041

28. Terry PB, Barth KH, Kaufman SL, White RI. Balloon embolization for treatment of pulmonary arteriovenous fistulas. *N Engl J Med.* (1980) 302:1189–90. doi: 10.1056/NEJM198005223022107

29. Sommer RJ, Nazif T, Privitera L, Robbins BT. Retrospective review of thienopyridine therapy in migraineurs with patent foramen ovale. *Neurology.* (2018) 91:1010–7. doi: 10.1212/WNL.0000000000006573

30. Trabattoni D, Brambilla M, Canzano P, Becchetti A, Teruzzi G, Porro B, et al. Migraine in patients undergoing PFO closure: characterization of a platelet-associated pathophysiological mechanism: the LEARNER study. *J Am Coll Cardiol Basic Trans Science.* (2022) 6:525–40. doi: 10.1016/j.jacbts.2022.02.002

31. Wang F, Cao Y, Liu Y, Ren Z, Li F. Platelet P2Y12 inhibitor in the treatment and prevention of migraine: a systematic review and meta-analysis. *Behav Neurol.* (2022) 2022:2118740. doi: 10.1155/2022/2118740

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Case report: Paralysis after epidural analgesia due to a hemorrhage of pure epidural venous hemangioma

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Purpose: To report a case of sudden paralysis after epidural analgesia to raise awareness of the condition and the importance of early identification and appropriate treatment of extradural venous angiomas.

Clinical features: A 28-year-old man with myofascial pain syndrome experienced paraplegia after receiving an epidural block for pain relief, which was later discovered to be caused by hemorrhage from extradural venous angiomas. Decompression surgery was performed immediately and successfully. A follow-up examination was performed 5 months after surgery. The patient reported improvement in urinary retention. The muscle strength in both his lower extremities had recovered to 4 out of 5 but still exhibited considerable residual spasticity.

Conclusions: Before administering epidural analgesia to relieve undetermined pain, it is prudent to carefully weigh potential benefits against potential risks to patient health to minimize the likelihood of complications.

KEYWORDS

extradural venous angiomas, epidural analgesia, myofascial pain syndrome, paralysis, pain

Spinal vascular malformations can be divided into four types: capillary, cavernous, arteriovenous, and venous. Extradural venous angiomas are a rare type of spinal vascular malformation but a serious cause of neurological deterioration, which includes sensory disturbance accompanied by radicular pain and/or paraparesis (1). In this study, we report on a spinal epidural venous angioma case in an adult who received epidural analgesia to relieve his progressive chest and abdominal pain but developed symptoms of bilateral rigidity and paralysis in the lower extremities after an operation. This case indicates that, for patients with chest and abdominal pain, we must immediately identify signs of rupture and bleeding of hemangiomas in the spinal canal and use epidural analgesia with caution.

Case report

A 20-year-old man who had received epidural analgesia at the T6–7 position to relieve progressive chest and abdominal pain described the pain as a tense and discontinuous ache, especially when he laid down, and rated its severity as 9 out of

10. He had no history of using medications or having surgery and was not regularly taking any prescribed drugs. No deformity was found upon physical examination, but several tenderness points were found in the T3–T12 paraspinal muscles. The results of the chest and abdominal computed tomography (CT), routine blood studies, diastasimetry, four coagulation tests, and renal and liver function tests were normal. Myofascial pain syndrome was considered after the exclusion of organic disease. He was prescribed over-the-counter pain medication, but it did not relieve the pain. Based on previous treatment experience, trigger point injection is an effective therapeutic method for patients with mild myofascial syndrome, except for those suffering from acute pain. Considering the need for silver needle treatment under epidural anesthesia after the relevant examinations, the patient was administered epidural analgesia in advance to relieve the unbearable pain.

After assisting the patient in the knee-to-chest position, we monitored his vital signs through SpO2 and an electrocardiogram, and non-invasive blood pressure (NIBP) measurements were obtained every 5 min. After disinfection, a needle with 3 ml of 2% lidocaine was inserted. We performed puncture at the T6–T7 space *via* a median approach using an 18 G Tuohy epidural needle (TUORen Medical Instrument Group Co., Ltd., China). The loss-of-resistance to air technique was applied to confirm correct entry into the epidural space. A 4-cm epidural catheter was inserted into the back of the patient with the puncture needle facing the head and in a fixed position. After confirming the absence of the reflux of CSF and blood, we injected a test dose of 1% lidocaine (5 mL). An initial dose of 5 mL of lidocaine 1% and a continuous infusion of lidocaine 0.02% were programmed to be administered at a rate of 5 mL/h. After 15 min, the patient declared that the pain had been relieved. His vital signs were continuously monitored using SpO2 and an electrocardiogram and NIBP every 20 min after he returned to the ward. The sensation and motor function of his lower limbs were normal at the time.

However, 4 h after epidural analgesia, the patient suddenly developed bilateral rigidity and paralysis in the lower extremities. A physical examination revealed numbness below the level of T6, grade I strength, and hyperactive deep tendon reflexes were noted in the bilateral lower extremities, while Babinski's response was also positive. The patient also reported difficulty with bowel or urinary retention or incontinence, and superficial sensations were abnormal in bilateral lower extremities. Gadolinium-enhanced magnetic resonance imaging (MRI) showed an epidural mass measuring 11 × 16 × 11 mm with a distinct border, which intensified at the T7–T8 extradural level. An iso-intense area was detected on the T1-weighted images (T1WI) and mixed-signal intensity on the T2-weighted images (T2WI). The T1-weighted transverse plane showed that the lesion occupied more than half of the T7–8 canal (Figure 1). Laminectomy, intravertebral mass removal, and spinal canal decompression were performed immediately and successfully. Multiple dilated, thin-walled vessels with hemorrhage and hematoma formation were observed through the histopathology of the extradural lesions. It also showed that CD31 was positively expressed in the epithelial cells of the cyst walls (Supplementary Figure 1). The extradural lesion was determined to be an extradural venous angioma. In patients with spinal epidural venous hemangiomas, a significant expansion of intralesional hemorrhage led to acute neurological deterioration. After 8 days of surgery, the sensory effect in both his lower extremities had recovered, and muscle strength was at 3 out of 5. Babinski's response was negative, and superficial sensations were normal in the bilateral lower extremities. However, no significant improvement in bowel and urinary retention was observed. A follow-up examination was performed 5 months after the surgery. The patient reported an improvement in urinary retention. Muscle strength in both his lower extremities had recovered to 4 out of 5, but the patitent still showed considerable residual spasticity.

Discussion

Extradural venous angiomas are the most uncommon subtype of spinal vascular malformations (2, 3). Damage to the movement and differentiation of the primitive mesoderm is widely recognized as the cause of spinal vascular malformations. However, the etiology of spinal vascular malformations remains unclear (4). Only six cases of purely extradural spinal venous angiomas have been reported since 1978 during which the first case was reported by Decker et al. A review of these six cases showed that almost all patients presented with somatic pain, numbness, or limb weakness (2, 3). During the early stage, the patient's symptoms were fairly insidious, leading doctors to ignore them until the enlargement of the intralesional hemorrhage caused other symptoms (5). Spinal vascular malformations are difficult to diagnose preoperatively. During surgery, histopathology samples can be obtained to make a definitive diagnosis. Compressive epidural hemangiomas are best treated with surgical resection (4). The main differential diagnoses are epidural hematoma, spinal cord injury, neuroma, lymphoma, schwannomas, or meningioma. Compared with other common epidural spinal cord tumors, radiculopathy is the only clinical manifestation of epidural venous hemangiomas. Unfortunately, the MRI features of pure epidural venous hemangioma do not differ significantly from those of other space-occupying spinal cord lesions (6). Therefore, we may erroneously identify an epidural lesion as a spinal epidural hematoma preoperatively and thus fail to predict intraoperative bleeding in advance due to this misdiagnosis.

Myofascial pain syndrome lacks clear diagnostic criteria, and a characteristic symptom is a regional pain originating from a tender point located within the taut band of skeletal muscles (7). In this case, chest and abdominal CT, physical examination,

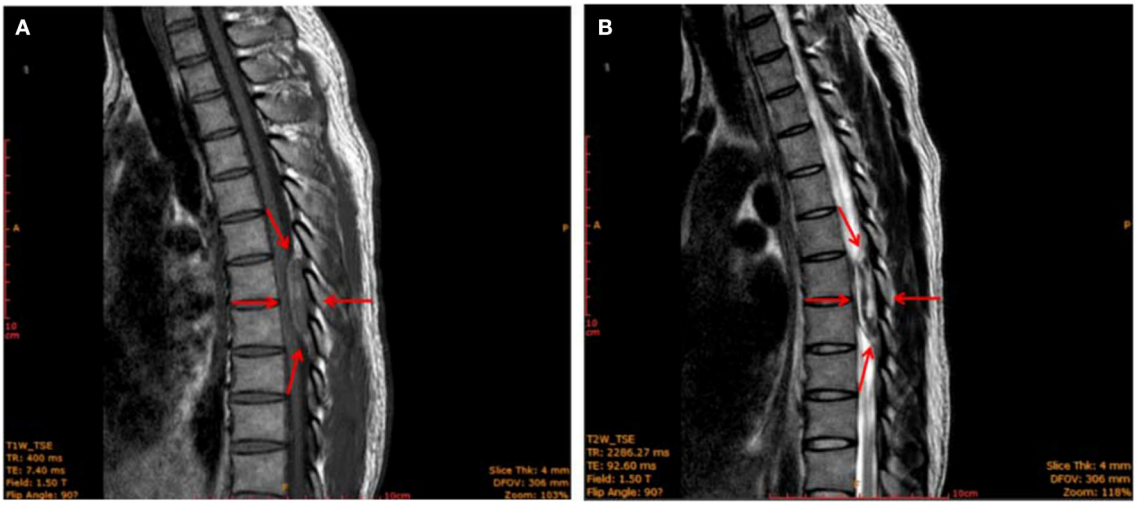

FIGURE 1
MRI image of the thoracic spine (sagittal plane) showing an epidural mass (red arrows) with a clear border measuring 11 × 16 × 11 mm located at the level of 2 thoracic vertebrae (T7–T8). The mass was iso-intense on T1-weighted images **(A)** and showed mixed-signal intensity on T2-weighted images **(B)**.

and laboratory tests provide a normal result except for multiple tenderness points in the T3–T12 paravertebral muscles, which are classic symptoms of myofascial syndrome. On reflection, we aimed to determine whether radiculopathy and myofascial syndrome caused progressive xiphoid process pain and chest back pain in patients. The symptoms of radiculopathy, in this case, were related to chronic haemangioma, which is an atypical symptom and so insidious that the doctors ignored it.

Epidural analgesia has been shown to be a safe procedure that can produce equal or better pain relief than systemic opioids. However, some risks are still associated, including infection, intravascular or subdural medication injections, hematoma, air embolism, and direct nerve trauma. As epidural analgesia has become more standardized, major complications are now rare after surgery, especially the surgery that do not involve infection or bleeding resolve within 6 months (8, 9). According to statistical information available, the occurrence rate of spinal epidural hematoma after epidural anesthesia was 1/150,000 cases in patients who did not receive thromboprophylaxis (10). Some of the risk factors include coagulopathy, trauma, and vascular malformations (11, 12).

Our case is unique because the sudden paralysis after epidural analgesia is correlated with a purely extradural spinal venous angioma. This is the first report of a purely extradural spinal venous angioma with atypical symptoms that are difficult to distinguish from myofascial pain syndrome. Patients' perceptions of pain are highly subjective and have many functional implications and functional effects that cannot be detected through radiography. Radicular pain radiating from the trigger point is similar to myofascial pain syndrome. We should carefully perform differential diagnosis and conservative treatment until improvements are observed in relevant imaging examinations (13). To relieve undetermined pain, health physicians should weigh the potential benefits against potential risks to the patient's health to reduce the likelihood of complications before epidural analgesia.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Ethics Committee of Guangdong Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Ethics approval number: YJLW2022005.

Author contributions

JL and DL conceived the idea for this paper. XL and PX performed the literature search. JT and JL identified and/or managed the case. JL wrote the article. JT took responsibility

for the veracity of the information mentioned in this report. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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Supplementary material

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References

1. Krings T. Vascular malformations of the spine and spinal cord*: anatomy, classification, treatment. *Clin Neuroradiol.* (2010) 20:5–24. doi: 10.1007/s00062-010-9036-6

2. Nsir AB, Hadhri R, Kilani M, Chabaane M, Darmoul M, Hattab N. Epidural venous angioma presenting with spinal cord compression in a 42-year-old woman with previous history of ovarian malignancy. *World Neurosurg.* (2016) 93:488e5–7. doi: 10.1016/j.wneu.2016.06.090

3. Baykara E, Korucu M, Ozdemir M, Gok S. Spinal epidural venous angioma presenting symtomps of lumbar disc herniation: a case report. *Turk Neurosurg.* (2019) 29:607–10. doi: 10.5137/1019-5149.JTN.23081-18.2

4. Nowak DA, Widenka DC. Spinal intradural capillary haemangioma: a review. *Eur Spine J.* (2001) 10:464–72. doi: 10.1007/s005860100296

5. Hemalatha AL, Ravikumar T, Chamarthy NP. Puri K. A pure epidural spinal cavernous hemangioma - with an innocuous face but a perilous behaviour! *J Clin Diagn Res.* (2013) 7:1434–5. doi: 10.7860/JCDR/2013/6030.3159

6. Wu L, Yang T, Deng X, Yang C, Xu Y. Spinal epidural venous angioma: a case report and review of the literature. *Childs Nerv Syst.* (2014) 30:1601–5. doi: 10.1007/s00381-014-2397-4

7. Desai MJ, Saini V, Saini S. Myofascial pain syndrome: a treatment review. *Pain Ther.* (2013) 2:21–36. doi: 10.1007/s40122-013-0006-y

8. Maddali P, Moisi M, Page J, Chamiraju P, Fisahn C, Oskouian R, et al. Anatomical complications of epidural anesthesia: a comprehensive review. *Clin Anat.* (2017) 30:342–46. doi: 10.1002/ca.22831

9. Hoelzler MG, Harvey RC, Lidbetter DA, Millis DL. Comparison of perioperative analgesic protocols for dogs undergoing tibial plateau leveling osteotomy. *Vet Surg.* (2005) 34:337–44. doi: 10.1111/j.1532-950X.2005.00052.x

10. Makito K, Mouri H, Matsui H, Michihata N, Fushimi K, Yasunaga H. Spinal epidural hematoma and abscess after neuraxial anesthesia: a historical cohort study using the Japanese diagnosis procedure combination database. *Can J Anaesth.* (2021) 68:42–52. doi: 10.1007/s12630-020-01827-w

11. Tryba M. Epidural regional anesthesia and low molecular heparin: Pro. *Anasthesiol Intensivmed Notfallmed Schmerzther.* (1993) 28:179–81. doi: 10.1055/s-2007-998902

12. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American society of regional anesthesia and pain medicine evidence-based guidelines (Fourth Edition). *Reg Anesth Pain Med.* (2018) 43:263–309. doi: 10.1097/AAP.0000000000000763

13. Facco E, Ceccherelli F. Myofascial pain mimicking radicular syndromes. *Acta Neurochir Suppl.* (2005) 92:147–50. doi: 10.1007/3-211-27458-8_32

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Case report: Fully endoscopic microvascular decompression for trigeminal neuralgia

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Microvascular decompression is safe, effective, and micro-invasive. Due to these advantages, it has become the mainstream treatment for trigeminal neuralgia, glossopharyngeal neuralgia, and hemifacial spasm. Initially, microvascular decompression was performed under a microscope, which limited the light source and visualization capabilities. With the development of endoscopic technology, the endoscope has been used in microvascular decompression, which further improved the visualization range and light source properties. The purpose of the present study was to investigate the efficacy of fully endoscopic microvascular decompression for the treatment of trigeminal neuralgia. In total, three patients with trigeminal neuralgia who underwent fully endoscopic microvascular decompression were evaluated. After surgery, the facial pain of all patients was significantly relieved. In addition, there were no obvious postoperative complications and no recurrence after 6 months of follow-up. These excellent surgical outcomes indicate that fully endoscopic microvascular decompression is an effective and safe method for the treatment of trigeminal neuralgia. Furthermore, it also shows that the endoscope presents advantages for use in microvascular decompression.

KEYWORDS

endoscopy, microvascular decompression, trigeminal neuralgia, suboccipito-retrosigmoid approach, functional neurosurgery

Introduction

Trigeminal neuralgia (TN) is a common chronic neuropathic pain condition that presents with characteristic pain in one or more branches of the fifth cranial nerve (1). This condition is usually characterized by paroxysmal, transient, and intense pain and is described as a "shock" or "electric sensation" (2–5). Coughing, chewing, swallowing, gargling, or blowing may induce TN, which seriously affects the patient's quality of life. TN is more common in women than in men and its incidence rate increases with age (6). TN is divided into three types: classic, secondary, and special. Intracranial vascular compression of the trigeminal nerve root is the most common cause of classic TN (1). At present, drug therapy is the primary treatment for TN, and anticonvulsant carbamazepine is considered to be the first drug of choice (7, 8). Oxcarbazepine, lamotrigine, gabapentin, and pregabalin are also commonly used. However, drugs are not always effective for each patient and drug intolerance may occur.

In these cases, surgical treatment may be considered. The mainstream surgical treatments include radiculotomy, radiofrequency thermocoagulation, glycerol rhizolysis, balloon compression, gamma-knife stereotactic radiosurgery, and microvascular decompression (MVD) (9–13). Among them, MVD is currently considered the most effective surgical treatment for classic TN. It has many advantages, as it is effective, minimally invasive, safe, and low-cost and has no recurrence (1, 2, 14, 15). Most MVD procedures are performed under a microscope, but not all offending vessels can be detected due to the microscope's limited field of vision. In contrast, the endoscope can provide brighter illumination and a panoramic view, which is more conducive to identifying the vessels of interest and evaluating the decompression effect (16–18). The present report describes three patients with TN who were successfully treated with fully endoscopic MVD. All patients had classical TN and a history of paroxysmal facial pain. The preoperative head MRI showed vascular compression of the trigeminal nerve. The case outcomes demonstrated that fully endoscopic MVD is an effective method for treating TN and that endoscopy presents significant advantages for use in MVD.

Case report

Case 1

Case 1 was a 78-year-old woman who was admitted to the hospital in May 2020. The main clinical symptom was paroxysmal pain on the right side of the face over the course of 7 years, which was induced when brushing teeth and chewing. Each attack lasted for about 5 s. Hearing loss was present in the right ear. Neurological examination results were normal and pathological signs were negative. All physical examinations, including routine blood tests, assessments of liver and kidney, and evaluation of immune and blood coagulation functions, were within normal limits. The patient had no history of trauma or any family history of genetic disorders. She was treated at the departments of stomatology, otolaryngology, and neurology many times and was provided symptomatic treatment, such as analgesia and carbamazepine. However, the symptoms were not significantly relieved and continued to recur. The preoperative cranial MRI indicated that the right trigeminal nerve was compressed by small vessels (Figure 1A). Finally, the patient underwent fully endoscopic MVD *via* the suboccipito-retrosigmoid approach.

Case 2

Case 2 was a 60-year-old woman who was admitted to the hospital in November 2020. The main clinical symptom was paroxysmal discharge-like pain on the right side of the face over the course of 1 year, which was induced when brushing teeth and washing the face. Neurological examination was normal, and pathological signs were negative. The routine blood test outcomes, liver and kidney, and immune and blood coagulation functions were comprehensively examined, and the results showed that they were within the normal limits. The patient had no history of trauma or any family history of genetic disorders. The patient was diagnosed with right trigeminal neuralgia and was treated with carbamazepine and gabapentin without a positive effect. Preoperative cranial MRI showed that the right trigeminal nerve was compressed by blood vessels (Figure 2A). Finally, the patient underwent fully endoscopic MVD *via* the suboccipito-retrosigmoid approach.

Case 3

Case 3 patient was a 75-year-old woman who was admitted to the hospital in January 2021 due to the paroxysmal shock-like pain in the left side of the face over the course of 1 year. The pain was induced by drinking and eating. She received a comprehensive examination, which showed that the neurological examination results were normal and the pathological signs were negative. All laboratory tests, including routine blood tests, assessments of liver and kidney, and immune and blood coagulation functions, were within normal limits. The patient had no unambiguous history of trauma or any family history of genetic disorders. At first, the pain was relieved slightly after the oral carbamazepine treatment. However, the effect did not last and the pain became aggravated and recurred. In addition, the patient admitted to taking traditional Chinese medicine, which was also ineffective. Preoperative cranial MRI showed that the left trigeminal nerve was compressed by blood vessels (Figure 3A). Finally, the patient received fully endoscopic MVD *via* the suboccipito-retrosigmoid approach.

Surgical procedure

All three patients underwent fully endoscopic MVD *via* the suboccipito-retrosigmoid approach. After general anesthesia, the patient was placed in a lateral decubitus position with the head drooping at 15° and rotated at 10° to the contralateral side. The neck was positioned slightly forward. The jaw was located about two transverse fingers away from the sternum, and the mastoid process on the surgical side was roughly parallel to the operating table at the highest position. First, a long transverse incision about 5 cm in length was made 1 cm below the star point behind the ear. The skin was cut, the muscle was dissected, and the bleeding was stopped. A bone window of about 3 cm × 3 cm was created using a grinding drill, and the transverse and sigmoid sinuses were fully exposed. Then, the dura mater was cut in an "X" shape, the arachnoid membrane was cut,

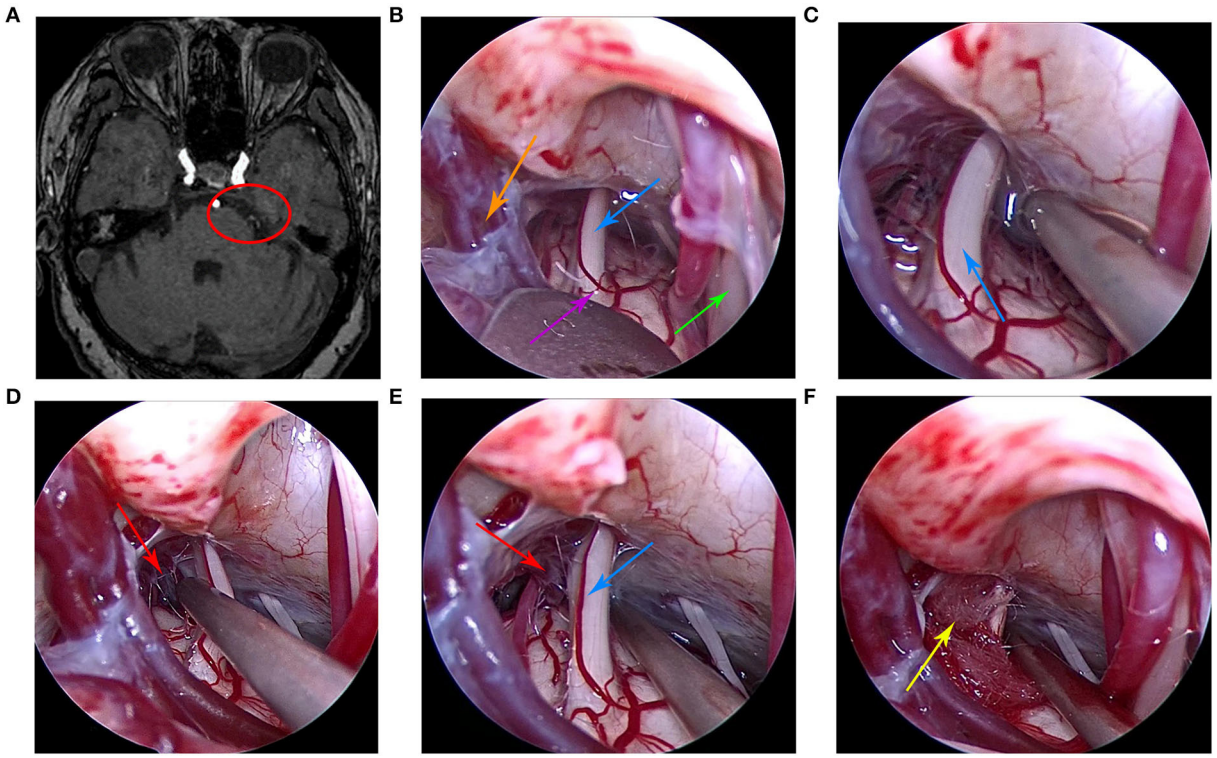

FIGURE 1
(A) Preoperative head magnetic resonance imaging of the patient. **(B)** Under the endoscope, the arachnoid was explored along the outer and upper margins of the cerebellum and subsequently cut to fully expose the trigeminal nerve. **(C)** At first, no obvious offending vessels were found. **(D)** After careful exploration, we found the offending small vein and arachnoid adhesions. **(E)** The petrosal vein branch and trigeminal nerve were clearly visible under the endoscopic view. **(F)** The Teflon pad was placed between the trigeminal nerve and the petrosal vein branch under the endoscopic view. The red circle indicates that the trigeminal nerve was compressed by the petrosal vein branch, the purple arrow indicates the brainstem, the orange arrow indicates petrosal vein, the red arrow indicates the petrosal vein branch, the blue arrow indicates the trigeminal nerve, the green arrow indicates the facial nerve, and the yellow arrow indicates the Teflon pad.

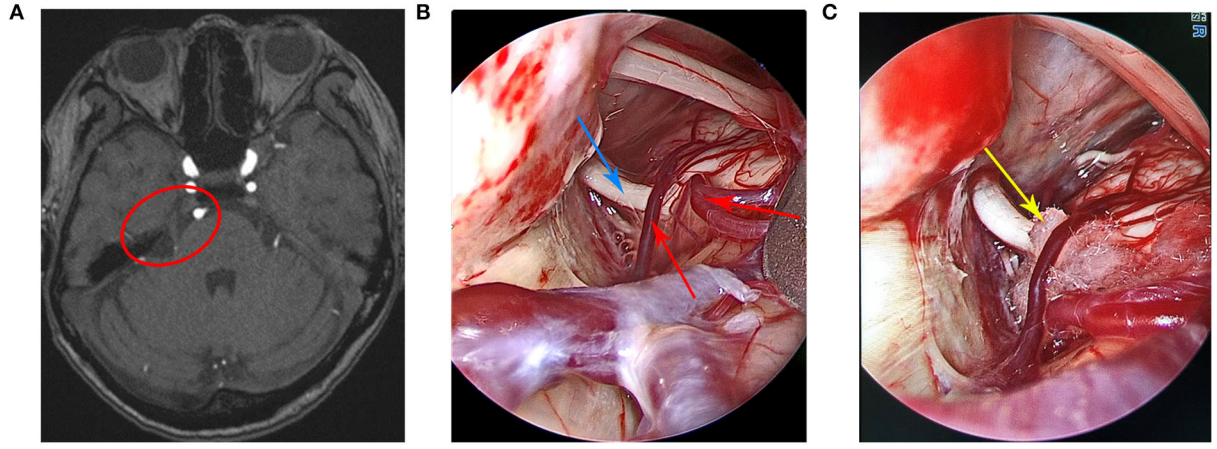

FIGURE 2
(A) Preoperative head magnetic resonance imaging of the patient. **(B)** A small artery, a vein that spanned the right trigeminal nerve, and the trigeminal nerve were clearly visible under the endoscopic view. **(C)** The Teflon pad was placed between the trigeminal nerve and the offending vessels under the endoscopic view. The red circle indicates trigeminal nerve compression by the offending vessels, the red arrow indicates the offending vessels, the blue arrow indicates the trigeminal nerve, and the yellow arrow indicates the Teflon pad.

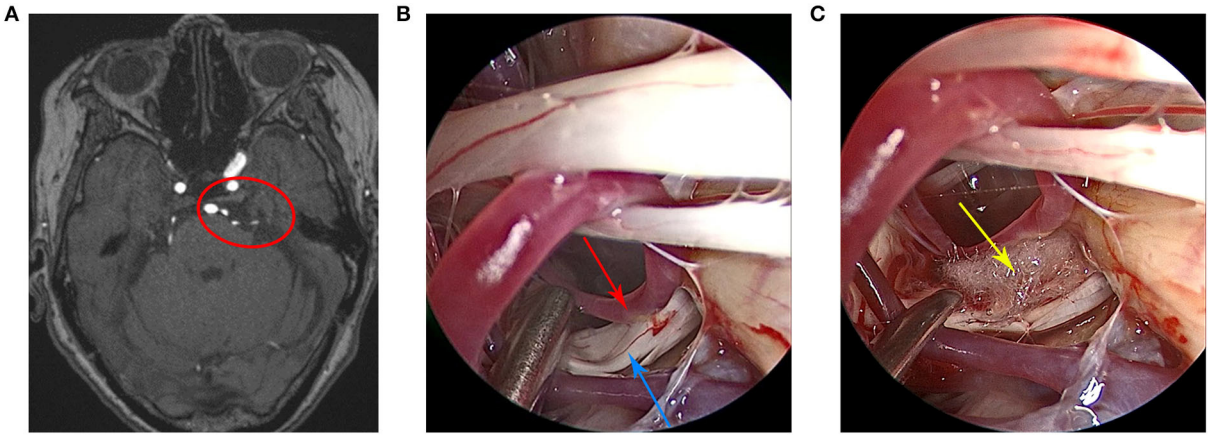

FIGURE 3
(A) Preoperative head magnetic resonance imaging of the patient. **(B)** The trigeminal nerve and the anterior cerebellar artery were clearly visible under the endoscopic view. **(C)** The Teflon pad was placed between the trigeminal nerve and the anterior cerebellar artery under the endoscopic view. The red circle indicates that the trigeminal nerve was compressed by the anterior cerebellar artery, the red arrow indicates the anterior cerebellar artery, the blue arrow indicates the trigeminal nerve, and the yellow arrow indicates the Teflon pad.

and the cistern release was opened to release the cerebrospinal fluid to achieve full decompression. Under the endoscope, the arachnoid was explored along the outer and upper margins of the cerebellum and subsequently cut to fully expose the trigeminal nerve. Benefiting from the panoramic view provided by the endoscope, the compression of the trigeminal nerve by blood vessels was clearly observed. Then, the blood vessels in contact with the trigeminal nerve were separated and shifted, and a Teflon pad was placed between the offending blood vessels and the trigeminal nerve. In order to check for the complete separation of the offending vessels, decompression sufficiency, Teflon pad size and location suitability, and nerve and blood vessel damage, the endoscopy procedure was performed again. Finally, the dura mater and the edge of the bone window were suspended, the dura mater was repaired with a double layer of artificial dura mater to prevent cerebrospinal fluid leakage, the skull defect was repaired with four titanium plates and screws, and the muscle, subcutaneous tissue, and skin were sutured layer by layer.

Results

Overall results

Figures 1–3 show the intraoperative images of three patients, where the offending vessels can be clearly observed. The clinical symptoms of all patients were significantly relieved after the operation. The effectiveness rate was up to 100%. There were no subsequent medication requirements for the patients. Moreover, there were no obvious postoperative complications and no recurrence during the follow-up period in all cases. These surgical outcomes suggest that endoscopic MVD is a safe and effective method for the treatment of TN and that the endoscope has certain advantages and important application prospects for MVD.

Individual case results

Case 1

Intraoperative endoscopy showed that the petrosal vein branch was adjacent to the right trigeminal nerve root. No arterial compression was observed around the trigeminal nerve. A Teflon pad was placed between the petrosal vein branch and the right trigeminal nerve. Postoperative facial pain symptoms were basically relieved, and hearing loss symptoms were slightly improved. There were no postoperative complications and no evidence of recurrence after 6 months of follow-up.

Case 2

During the operation, it was found that the root of the right trigeminal nerve was compressed by a small artery, and a vein spanned the right trigeminal nerve. Then, a Teflon pad was placed between the offending vessels and the right trigeminal nerve. After surgery, the patient's facial pain was completely relieved and there were no postoperative complications. There was no evidence of recurrence after 6 months of follow-up.

Case 3

Intraoperative endoscopy revealed that the left trigeminal nerve was compressed and deformed by the left anterior cerebellar artery. A Teflon pad was placed between the left

anterior cerebellar artery and the left trigeminal nerve to separate them. As a result, the patient's facial pain was completely relieved without postoperative complications. There was no evidence of recurrence during the 6 months of follow-up.

Discussion

Trigeminal neuralgia is a common chronic neuropathic pain condition that mainly manifests as paroxysmal, transient, and severe pain in the distribution area of the fifth cranial nerve, which seriously affects patient's quality of life. A description of TN was first recorded in the first century AD. Nicolas André first fully described the clinical symptoms of TN in 1756 and called it "tic douloureux" (19, 20). TN is also known as a "suicide disease" due to its severity and incidence rate (21). In 1773, John Fothergill first reported 14 patients with TN at the meeting of the London Medical Association (22). Since 1858, neurosurgeons have begun to explore a variety of surgical methods to treat TN. The early operation methods included neurectomy and neurolytic injection procedures (20). In 1901, Spiller and Frazier performed nerve root resection for patients with TN *via* the infratemporal approach. As a result, the pain was relieved but facial paralysis occurred (23). Later, Dandy cuts off the trigeminal nerve root using the cerebellar approach for TN treatment, which did not only achieve the good surgical results, but also significantly reduced the incidence of facial paralysis (24, 25). Dandy also suggested that most cases of TN were caused by compression of the trigeminal nerve by blood vessels, which is of great significance for the treatment of TN. In 1951, Taarnhøj was the first to perform a decompression operation on the trigeminal nerve root of a patient with TN instead of nerve root resection (26). In 1967, Jannetta was the first to come up with the most successful surgical method for TN-MVD and reported a case series of TN treated by MVD (27). Since then, MVD has been considered the most effective surgical method for the treatment of TN, especially classic TN, where the intracranial blood vessels compress the trigeminal nerve. Broggi et al. reviewed 250 patients with TN who underwent the MVD treatment. Approximately 75% of these patients experienced complete pain relief after surgery, and 15% relapsed during the long-term follow-up (28). Similarly, Mizobuchi et al. observed 166 patients with TN who received the MVD treatment. Their research results showed that after surgery, the complete pain relief rate was 79%, and the recurrence rate was about 20% over the course of a long-term follow-up (29). The above MVD procedure was performed under a microscope, and the surgical results showed that microscopic MVD was a relatively effective and safe treatment for these patients with TN. However, due to the light source and visualization capability limitations of the microscope, not all of the vessels of interest could be accurately located. To fully identify the offending blood vessels *via* a microscope, larger wounds and greater cerebellar contraction were required, which increases the possibility of postoperative complications. Due to the advantages of the wide field of vision, bright light source, the lack of obstruction in the field of vision, and operation flexibility, the endoscope has been widely used in various neurosurgery operations as well as MVD with good results (30, 31). Compared to the microscope, the biggest advantage of the endoscope is that it can accurately locate all of the vessels of interest. Chen et al. (17) found that about 14.74% of the offending vessels in 167 patients with TN were missed under a microscope and were only located when using an endoscope. Teo et al. (32) stated that the offending vessels of about 33% of patients with TN were difficult to see under a microscope, but easy to visualize under an endoscope. These findings suggest that an endoscope can increase the likelihood of identifying the offending vessels. Eby et al. (33) first treated TN with fully endoscopic MVD in 2002 and achieved good results. Bohman et al. reported that 47 patients with TN received a fully endoscopic MVD treatment. As a result, 94% of patients with TN experienced facial pain relief after surgery, and only one patient suffered from hearing loss (34). Sun et al. carried out fully endoscopic MVD in 20 patients with TN. All patients experienced pain relief after the operation. A total 16 patients had obvious pain relief, and four patients experienced good pain relief. None of the patients had complications (35). Meta-analysis by Zagzoog et al. compared the efficacy of MVD under both an endoscope and a microscope in the treatment of TN (16). The results showed that the remission and recurrence rates of the endoscopic and microscopic groups were similar. These values were 88 and 9%, as well as 81 and 14%, respectively. However, the endoscope group had significantly fewer postoperative complications than the microscope group, and the incidence rates were 8 and 19%, respectively. Lee et al. found that endoscopic MVD used for TN treatment had a lower incidence of complications compared to microscopic MVD, especially headaches. The incidence rates were 7 and 21%, respectively (36). Moreover, Lee et al. also found that endoscopic MVD was unlikely to cause complications after the TN treatment, especially headaches. The present study reported that three patients with TN were treated with fully endoscopic MVD. All of the offending blood vessels were clearly identified during the operation that was assisted by an endoscope, which significantly improved the surgery effect. After the operation, the patients' facial pain was significantly relieved without obvious postoperative complications. There was also no evidence of recurrence after 6 months of follow-up. These results indicate that fully endoscopic MVD was an effective and safe surgical method for TN in these patients. The following is a summary of the main reasons why endoscopic MVD can successfully treat TN. First, the endoscope provides good lighting, adequate visual angle, and wide field of vision during the operation, which does not only greatly improve the identification of blood vessels of interest and reduces the possibility of missing them, but also avoids

damaging the surrounding brain tissues, blood vessels, and nerves and reduces postoperative complications. Second, after decompression, the endoscope can be used to evaluate whether the Teflon pad was correctly placed from multiple angles, whether the decompression was sufficient, and whether the surrounding tissues, nerves, and blood vessels were damaged. Finally, endoscopic MVD requires a relatively short surgical incision with less traction on brain tissue and cranial nerves and no significant cerebellar contraction, which means that the incidence of cerebellar contraction-related complications, such as cerebellar hemorrhage, infarction, swelling, and hearing loss, is relatively low (37). However, endoscopic surgery presents certain challenges for surgeons and requires a period of learning to be comfortable with this type of procedure. Sufficient training, experience, and up-to-date equipment can help to successfully master this technology. It should be noted that the present study had limitations due to a small number of patients included and a relatively short-term follow-up. In addition, it was designed as a non-randomized retrospective study and does not completely rule out potential selection bias.

Conclusions

The present study described three TN cases that were successfully treated with fully endoscopic MVD. The surgical outcomes, including postoperative symptom relief, postoperative complications, and recurrence rate, indicate that fully endoscopic MVD may be a safe and effective method for TN treatment. Furthermore, the endoscope presents some advantages for use in MVD.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Committee Ethics of Chongqing General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Study conception and design were contributed by HJ, DZ, PW, and LZ. Material preparation, data collection, and analysis were performed by HJ, JL, CT, GZ, XT, and NW. The first draft of the manuscript was written by HJ. All authors commented on the previous versions of the manuscript, read, and approved the final manuscript

Conflict of interest

The 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.

Publisher's note

References

1. Cruccu G, Di Stefano G, Truini A. Trigeminal neuralgia. *N Engl J Med.* (2020) 383:754–62. doi: 10.1056/NEJMra1914484

2. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. *BMJ.* (2015) 350:h1238. doi: 10.1136/bmj.h1238

3. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain.* (2019) 160:53–9. doi: 10.1097/j.pain.0000000000001365

4. Di Stefano G, Maarbjerg S, Nurmikko T, Truini A, Cruccu G. Triggering trigeminal neuralgia. *Cephalalgia.* (2018) 38:1049–56. doi: 10.1177/0333102417721677

5. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia—a prospective systematic study of clinical characteristics in 158 patients. *Headache.* (2014) 54:1574–82. doi: 10.1111/head.12441

6. Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. *Ann Neurol.* (1990) 27:89–95. doi: 10.1002/ana.410270114

7. Centre for Clinical Practice at NICE (UK). *Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-specialist Settings*. London: National Institute for Health and Care Excellence (2013).

8. Bendtsen L, Zakrzewska JM, Abbott JA, Braschinsky M, Di Stefano G, Donnet A, et al. European Academy of Neurology guideline on trigeminal neuralgia. *Eur J Neurol.* (2019) 26:831–49. doi: 10.1111/ene.13950

9. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. *BMJ.* (2014) 348:g474. doi: 10.1136/bmj.g474

10. Tuleasca C, Carron R, Resseguier N, Donnet A, Roussel P, Gaudart J, et al. Repeat Gamma Knife surgery for recurrent trigeminal neuralgia: long-term outcomes and systematic review. *J Neurosurg.* (2014) 121 Suppl:210–21. doi: 10.3171/2014.8.GKS141487

11. Sweet WH, Wepsic JG. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1 Trigeminal neuralgia. *J Neurosurg.* (1974) 40:143–56. doi: 10.3171/jns.1974.40.2.0143

12. Håkanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. *Neurosurgery.* (1981) 9:638–46. doi: 10.1227/00006123-198112000-00005

13. Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. *Cochrane Database Syst Rev.* (2011) 2011:CD007312. doi: 10.1002/14651858.CD007312.pub2

14. Kabatas S, Albayrak SB, Cansever T, Hepgul KT. Microvascular decompression as a surgical management for trigeminal neuralgia: a critical review of the literature. *Neurol India.* (2009) 57:134–8. doi: 10.4103/0028-3886.51279

15. Bendtsen L, Zakrzewska JM, Heinskou TB, Hodaie M, Leal PR, Nurmikko T, et al. Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. *Lancet Neurol.* (2020) 19:784–96. doi: 10.1016/S1474-4422(20)30233-7

16. Zagzoog N, Attar A, Takroni R, Alotaibi MB, Reddy K. Endoscopic versus open microvascular decompression for trigeminal neuralgia: a systematic review and comparative meta-analysis. *J Neurosurg.* (2018) 2018:1–9. doi: 10.3171/2018.6.JNS172690

17. Chen MJ, Zhang WJ, Yang C, Wu YQ, Zhang ZY, Wang Y. Endoscopic neurovascular perspective in microvascular decompression of trigeminal neuralgia. *J Craniomaxillofac Surg.* (2008) 36:456–61. doi: 10.1016/j.jcms.2008.05.002

18. Takemura Y, Inoue T, Morishita T, Rhoton AL Jr. Comparison of microscopic and endoscopic approaches to the cerebellopontine angle. *World Neurosurg.* (2014) 82:427–41. doi: 10.1016/j.wneu.2013.07.013

19. Cole CD, Liu JK, Apfelbaum RI. Historical perspectives on the diagnosis and treatment of trigeminal neuralgia. *Neurosurg Focus.* (2005) 18:E4. doi: 10.3171/foc.2005.18.5.5

20. Patel SK, Markosian C, Choudhry OJ, Keller JT, Liu JK. The historical evolution of microvascular decompression for trigeminal neuralgia: from Dandy's discovery to Jannetta's legacy. *Acta Neurochir (Wien).* (2020) 162:2773–82. doi: 10.1007/s00701-020-04405-7

21. Tai AX, Nayar VV. Update on trigeminal neuralgia. *Curr Treat Options Neurol.* (2019) 21:42. doi: 10.1007/s11940-019-0583-0

22. Fothergill J. Of a pain affliction of the face. *Med Obs.* (1773) 5:129–42.

23. Spiller WG, Frazier CH. The division of the sensory root of the trigeminus for relief of tic douloureux: an experimental pathological and clinical study with a preliminary report of one surgical successful case. *Philadelphia Med J.* (1901) 8:1039–49.

24. Dandy WE. An operation for the cure of tic douloureux: partial section of the sensory root at the pons. *Arch Surg.* (1929) 18:687–734. doi: 10.1001/archsurg.1929.04420030081005

25. Dandy WE. The treatment of trigeminal neuralgia by the cerebellar route. *Ann Surg.* (1932) 96:787–95. doi: 10.1097/00000658-193210000-00026

26. Taarnhøj P. Decompression of the trigeminal root and the posterior part of the ganglion as treatment in trigeminal neuralgia; preliminary communication. *J Neurosurg.* (1952) 9:288–90. doi: 10.3171/jns.1952.9.3.0288

27. Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. *J Neurosurg.* (1967) 26:159–62. doi: 10.3171/jns.1967.26.1part2.0159

28. Broggi G, Ferroli P, Franzini A, Servello D, Dones I. Microvascular decompression for trigeminal neuralgia: comments on a series of 250 cases, including 10 patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* (2000) 68:59–64. doi: 10.1136/jnnp.68.1.59

29. Mizobuchi Y, Nagahiro S, Kondo A, Arita K, Date I, Fujii Y, et al. Microvascular decompression for trigeminal neuralgia: a prospective, multicenter study. *Neurosurgery.* (2021) 89:557–64. doi: 10.1093/neuros/nyab229

30. Jho HD, Carrau RL. Endoscopy assisted transsphenoidal surgery for pituitary adenoma. Technical note. *Acta Neurochir (Wien).* (1996) 138:1416–25. doi: 10.1007/BF01411120

31. Nagata Y, Watanabe T, Nagatani T, Takeuchi K, Chu J, Wakabayashi T. The multiscope technique for microvascular decompression. *World Neurosurg.* (2017) 103:310–4. doi: 10.1016/j.wneu.2017.04.059

32. Teo C, Nakaji P, Mobbs RJ. Endoscope-assisted microvascular decompression for trigeminal neuralgia: technical case report. *Neurosurgery.* (2006) 59(4 Suppl 2):ONSE489–90. doi: 10.1227/01.NEU.0000232768.47615.82

33. Jarrahy R, Eby JB, Cha ST, Shahinian HK. Fully endoscopic vascular decompression of the trigeminal nerve. *Minim Invasive Neurosurg.* (2002) 45:32–5. doi: 10.1055/s-2002-23586

34. Bohman LE, Pierce J, Stephen JH, Sandhu S, Lee JY. Fully endoscopic microvascular decompression for trigeminal neuralgia: technique review and early outcomes. *Neurosurg Focus.* (2014) 37:E18. doi: 10.3171/2014.7.FOCUS14318

35. Sun Z, Wang Y, Cai X, Xie S, Jiang Z. Endoscopic vascular decompression for the treatment of trigeminal neuralgia: clinical outcomes and technical note. *J Pain Res.* (2020) 13:2205–11. doi: 10.2147/JPR.S268441

36. Lee JYK, Pierce JT, Sandhu SK, Petrov D, Yang AI. Endoscopic versus microscopic microvascular decompression for trigeminal neuralgia: equivalent pain outcomes with possibly decreased postoperative headache after endoscopic surgery. *J Neurosurg.* (2017) 126:1676–84. doi: 10.3171/2016.5.JNS1621

37. Jiang HT, Wang P, Zhou W, Zeng LW, Lin B, Wu N. Fully endoscopic microvascular decompression for hemifacial spasm. *Exp Ther Med.* (2022) 24:483. doi: 10.3892/etm.2022.11410

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Life changing response to successive surgical interventions on cranial venous outflow: A case report on chronic fatigue syndrome

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Recognition of similarities between chronic fatigue syndrome and idiopathic intracranial hypertension (IIH) has raised suggestions that they might be connected, with chronic fatigue syndrome representing a mild version of IIH, sharing many of its symptoms, but without the signature features of elevated intracranial pressure that characterize the complete syndrome. A further development of this idea factors in the effects of a cerebrospinal fluid leak, a known complication of IIH, to explain cases where symptoms seem out of proportion to the apparent physiological disturbance. Cranial venous outflow obstruction has been proposed as the pathological substrate. We describe a patient with multiple symptoms, including headache and disabling fatigue, in which this model guided investigation and treatment. Specifically, CT and catheter venography identified focal narrowings of both jugular and the left brachiocephalic veins. Treatment of brachiocephalic obstruction was not feasible. However, in separate surgical procedures, relief of jugular venous obstruction produced incremental and significant clinical improvements which have proven durable over the length of follow-up. We suggest that investigating chronic fatigue syndrome under this model might not only bring benefit to individual patients but also will provide new insights into IIH and its relationship with spontaneous intracranial hypotension.

KEYWORDS

chronic fatigue syndrome, fibromyalgia, idiopathic intracranial hypertension, spontaneous intracranial hypotension, cranial venous outflow obstruction

Introduction

The recognition of similarities between chronic fatigue syndrome and idiopathic intracranial hypertension (IIH) has raised suggestions that they might be connected, with chronic fatigue syndrome perhaps representing a mild version of IIH, sharing many of its symptoms, but without the signature features of increased intracranial pressure that characterize the complete syndrome (1). One group has shown that patients with chronic fatigue syndrome, on average, have intracranial pressures in the high normal range but with some unequivocally passing the threshold for IIH (2, 3). Another group has reported similar findings in fibromyalgia (4). Both found that reducing intracranial pressure by withdrawing cerebrospinal fluid (CSF) gave symptomatic improvement even when pressure was within

normal limits. A third group has found MRI evidence of raised intracranial pressure in many patients with chronic fatigue syndrome (5).

This relatively simple hypothesis, however, does not explain instances of chronic fatigue syndrome in which the level of disability seems far out of proportion to any conceivable notion of a "forme fruste" version of IIH, even if the risk of visual loss is absent. IIH, however, can be complicated by a CSF leak (6–8). Indeed, it is probable that many cases of spontaneous CSF leaks, manifesting as the syndrome of spontaneous intracranial hypotension, have IIH as their underlying condition (6–8). As pertains to IIH without papilloedema, most cases of spontaneous intracranial hypotension also present no clinical signs. Moreover, the distinctive radiological features of low intracranial pressure may be absent, and the debilitating symptoms that can accompany this syndrome might not include the characteristic orthostatic headache (9, 10).

Many of the complex symptoms described in spontaneous intracranial hypotension are also seen in severe cases of chronic fatigue syndrome (11, 12), and recently, a modification of the IIH/chronic fatigue hypothesis has been published to allow for the possibility of a CSF leak (13). In this modification, chronic fatigue syndrome represents a form of IIH that may be mild because the underlying pathology is mild, or a form in which the underlying pathology is more severe, but whose outward manifestation is modified, for better or worse, by the presence of a CSF leak. In either case, papilloedema would be absent.

Intracranial venous hypertension has been proposed as the final common pathway in the development of IIH (14, 15). We describe a patient with disabling chronic fatigue syndrome in whom this disease model guided investigation and treatment.

Case history

A 46-year-old woman, a partner in a medical practice, with a long history of headache, dizziness, and fatigue had been unable to work for 3 years since waking up one morning with florid positional vertigo and an inability to hold objects steady in her visual field during movement (later diagnosed as oscillopsia). Since that time, she had suffered daily bouts of dizziness, loss of balance, light-headedness, nausea, bowel disturbance, noise and light sensitivity, increased headaches, and often overwhelming fatigue. Other idiosyncratic symptoms were episodes of daytime confusion and sudden feelings of intense thirst. She had two young children and recalled that she had been unable to work during either of her pregnancies mainly because of vomiting.

Her only significant history was of a bicycle accident 25 years previously. She was told that she had a seizure at the scene but was not admitted to hospital until a week later, by that time suffering with headaches, drowsiness, and confusion. A CT scan revealed a left temporal lobe contusion which was treated conservatively. Anticonvulsants were not prescribed. Ever since, however, she had experienced frequent dizzy spells, light-headedness on standing, and episodes of nausea, as well as vague neurological symptoms such as problems with orientation, making it difficult for her to find her way around buildings. She had a single further seizure 3 years later. Again, anticonvulsant medication was not prescribed.

Over the years, she had sought advice from multiple medical specialists. She had received diagnoses of vestibular migraine and mild autonomic dysfunction, with the latter following a tilt table test. MRI brain was normal. Treatments included amitriptyline, topiramate, propranolol, verapamil, botulinum toxin, venlafaxine, pizotifen, vitamin B2, and magnesium and also physiotherapy, cognitive behavioral therapy, exercise therapy, and dietary and lifestyle adjustment.

Clinical examination was normal; her body mass index value was 23 (normal 18–25). There was no papilloedema. All laboratory investigations were normal. Therefore, satisfying the clinical criteria, she was diagnosed with chronic fatigue syndrome and, in accordance with protocols being developed at the time at our institution (2, 3), was put forward for investigation of intracranial pressure.

Investigation of intracranial pressure and cranial venous outflow

CT and CT venography

CT brain was normal. CT venography revealed normal intracranial venous sinuses. However, there was striking narrowing of both internal jugular veins anterior to the transverse processes of the C1 vertebra and marked narrowing of the left brachiocephalic vein between the sternum and the origins of the left common carotid and right brachiocephalic arteries (Figure 1).

Catheter venography and venoplasty

Through a microcatheter, with the patient awake, contrast injections were used to assess the pattern of cranial venous outflow and intraluminal pressure recordings of the significance of any venous narrowing. Venoplasty was used to assess the clinical significance of extracranial venous narrowings by dilating the narrowed segment and monitoring any change in symptoms. These procedures in patients with chronic fatigue syndrome have been described previously (16).

There was mild intracranial venous hypertension (midsagittal sinus pressure = 20 cm H_2O), with an 8 cm H_2O pressure gradient between the midsagittal sinus and the superior vena cava, including a 3 cm H_2O focal gradient across the right jugular narrowing and a 6 cm H_2O gradient across the tandem narrowings in the left brachiocephalic vein. There was no appreciable gradient across the narrowing of the left upper jugular vein (Figure 2).

The right jugular narrowing was dilated to 8 mm. There was no immediate change but for a week afterward, headache and dizziness were absent, and noise and light intolerance were improved.

She came back subsequently for left brachiocephalic venoplasty, having no symptoms at the time of the procedure but still describing an immediate "clearing" of her head, this benefit lasting until the evening, and then wearing off completely over the next 2 days.

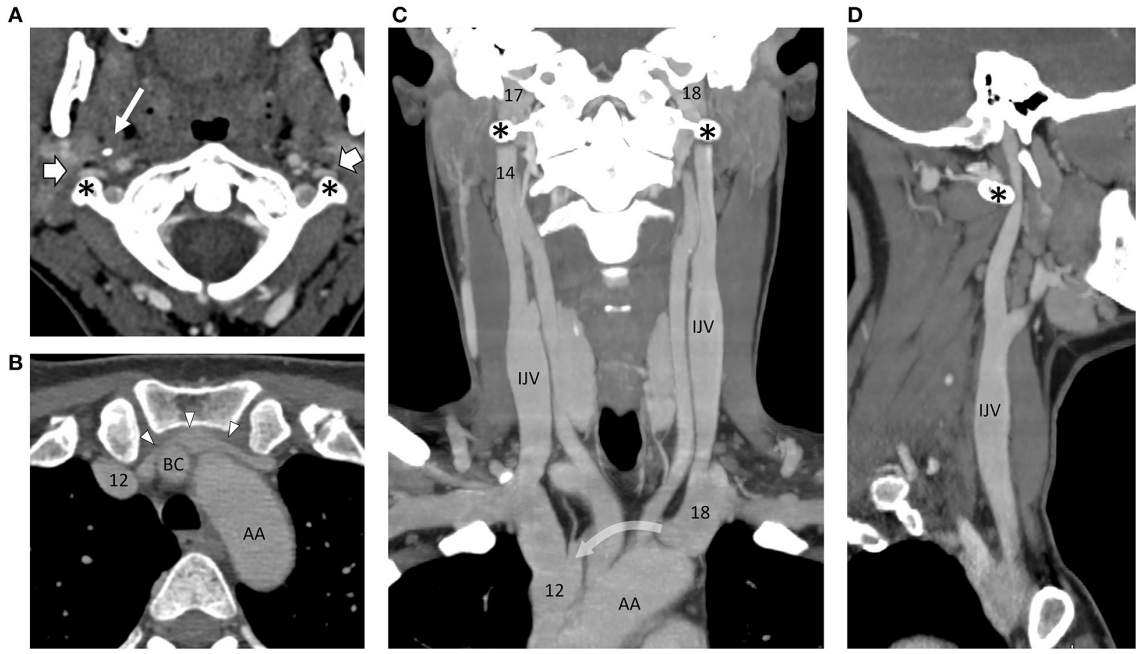

FIGURE 1
Montage of CT images following intravenous contrast, outlining the arterial and venous angioarchitecture of the neck. **(A)** Axial slice through the C1 vertebra and odontoid peg show the narrowing and flattening of both internal jugular veins (block arrows) as they pass in front of the transverse processes of C1 (asterisks) on either side. The styloid process of the skull (thin arrow) can be seen on the right side. The internal carotid arteries are round in cross-section and situated more medially. **(B)** Axial slice through the thoracic inlet at the level of the left brachiocephalic vein (arrowheads) showing marked narrowing in front of the right brachiocephalic artery (BC, right brachiocephalic artery; AA, aortic arch). **(C)** In this coronal reconstruction, the internal jugular veins (IJVs) lie on the lateral side of the carotid arteries. They are out of the plane as they pass over the C1 transverse processes, but on the sagittal reconstruction **(D)**, the distortion produced on the left side is evident (curved arrow = path of the left brachiocephalic vein, out of the plane in front of the left common carotid and right brachiocephalic arteries.). Numbers are transposed from pressures (cm H_2O) recorded on catheter venography.

Lumbar puncture

One month later, lumbar puncture revealed an opening pressure of 14 cm H_2O. She was not particularly symptomatic at the time, and withdrawal of 17 ml of CSF had no immediate effect, and over the next few days, she had quite severe postural headaches, although commented that when she lay flat in bed, she felt unusually well. As her postural headaches receded, she had 2 days when fatigue and headache were absent, before her usual symptoms returned.

Diagnostic formulation and first surgery—Right jugular decompression

On the strength of these investigations, she was diagnosed with cranial venous outflow obstruction, with the key lesions being the narrowing of the right jugular vein at the C1 level and of the left brachiocephalic vein anterior to the origins of the great vessels. The significance of left jugular narrowing was uncertain, given the severity of brachiocephalic narrowing downstream.

She was offered decompression of the right jugular vein by the styloidectomy and resection of the right transverse process of C1. Decompression of the brachiocephalic vein was ruled out by the expected difficulty of the procedure, given the uncertainty of the outcome. She was counseled that even if the diagnostic formulation was correct, this surgery would leave the other sites of venous compromise untreated and, therefore, might only be a partial solution to her clinical problem. She had the surgery 16 months after her first consultation. The surgical technique has been described previously (17, 18).

Progress

Immediately after surgery, her oscillopsia resolved and has not returned. Fatigue, headaches, noise sensitivity, and brain fog were improved. Once home, for example, she found that she was able to do light gardening for 40 min instead of 20. Though she still needed to rest afterward, she was able to finish a full supermarket shop, where previously headache and vertigo routinely forced her to give up halfway, leaving her ill for the rest of the day. She had no further episodes of unexpected thirst.

With symptoms stable 12 months post-surgery, repeat CT venography confirmed wide expansion of the right jugular vein at the site of surgical resection. On the left side, jugular and brachiocephalic vein narrowings were unchanged (Figure 3). Limited catheter venography on this occasion revealed a 1 cm H_2O pressure gradient across the left jugular narrowing and a 4 cm H_2O gradient along the left brachiocephalic vein. She had left

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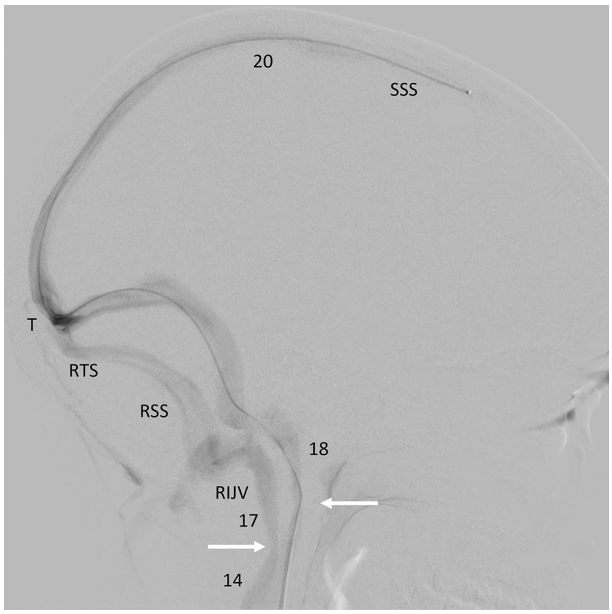

FIGURE 2
Catheter venogram. Background-subtracted, oblique lateral view of the head and upper neck. Radiographic contrast injected through a catheter passed up through the left lateral sinus into the sagittal sinus outlines the sagittal, both lateral sinuses and upper jugular veins. There is a narrowing of both internal jugular veins (arrows) where they pass over the transverse processes of C1 (SSS, superior sagittal sinus; T, torcula; RTS, right transverse sinus; RSS, right sigmoid sinus; RIJV, right internal jugular vein) (Numbers = pressure recordings in cm H_2O).

jugular venoplasty, following which her head felt generally better for about 90 min.

Second surgery—Left jugular decompression

The nature of the brachiocephalic narrowing still precluded surgery. However, her response to venoplasty suggested that there might yet be a benefit in relieving left jugular narrowing, and 2 years following her first surgical procedure she had the second, specifically, decompression of the left jugular vein by resection of the left C1 transverse process, leaving the styloid intact (Figure 3).

Further progress

There was no change at first, but over the following weeks, her symptoms gradually improved. Fatigue was greatly improved: she could be more active during the day, needing to sleep only one or two afternoons in the week instead of five. She no longer suffered from nausea or diarrhea. Noise sensitivity was improved. Her head was clearer. Headaches were fewer and less severe. She mentioned that previously she had struggled sitting or standing for long periods and that this was greatly improved. She noticed that her resting pulse rate, which had been in the 90 s before treatment, had fallen into the 80 s after her first procedure and was down into the 70 s after her second procedure. Prior to treatment, she had noticed her heart rate increasing in the upright position (confirmed as 18 beats per minute in the tilt table test). Later, she was able to record this increase as consistently reduced to six beats per minute. At 10 months post second surgery, she has been planning a return to work.

Discussion

The volume and complexity of symptoms experienced by patients with chronic fatigue syndrome, the complete absence of physical signs of ill health, and the complete absence of confirmatory diagnostic tests have placed this condition firmly in the realms of psychological illness in the minds of the majority of medical practitioners (19). Yet similarities with IIH abound, the latter an unequivocally organic condition, the presence of which is only betrayed by signs of raised intracranial pressure, usually papilloedema. Thus, headache and fatigue are usual in both, along with multiple other symptoms, including anxiety, dizziness, depression, body pains, and cognitive and memory disturbance (20–22). Papilloedema, however, is not inevitable, and some patients with IIH do not have any signs of raised intracranial pressure at all (23). These cases are thought to be rare, but in reality, the correct diagnosis depends on clinical suspicion precipitating a diagnostic lumbar puncture, and clinical suspicion is low in the absence of papilloedema (1). Their diagnoses, therefore, if they are given one, will depend on the relative prominence of any one of the multiple other symptoms seen in IIH, and the underlying fact of raised intracranial pressure will be missed.

This idea has been taken up by two independent research groups, one with respect to chronic fatigue syndrome, the other with respect to fibromyalgia, each reporting similar results, specifically that a significant minority of these patients have intracranial pressures above the threshold for IIH and that the majority of those who do not, respond to CSF withdrawal in exactly the same way as those who do (2–4). This implies not only that IIH is being missed but also that the different conditions are connected, with chronic fatigue or fibromyalgia essentially representing IIH in mild form.

If this is correct, then debate regarding the etiology of IIH is relevant to chronic fatigue, and, concerning this, three distinct etiopathological mechanisms have been proposed for IIH: idiopathic brain swelling, a CSF production/absorption mismatch, and cranial venous outflow obstruction (24). Among these, obstruction to cranial venous outflow has received the most attention, venous sinus thrombosis, for example, being a well-known mimic (25), and recently, it has become clear that stenotic lesions on both transverse sinuses in this condition are usual (26, 27). Yet, the extent to which these lesions represent the cause or effect of raised intracranial pressure is uncertain, even if stenting them seems to bring clinical benefit (28–30). Pertinent to the case we describe, however, instances of intracranial hypertension have now been reported, clinically indistinguishable from IIH, which seem to be caused by obstruction to cranial venous outflow in the neck. In these cases, such ambiguity over cause and effect is absent (17, 31–33).

Extracranial venous outflow obstruction has also been implicated in cases of spontaneous intracranial hypotension (18, 34). This condition, caused by a CSF leak, appears to develop

spontaneously or following minimal trauma, giving symptoms that cover a spectrum of severity from postural headache, fatigue, dizziness, nausea, vomiting, blurred vision, and light and noise sensitivity, to enforced recumbency, cognitive disturbance, dementia, and even coma (9). The cause of these multiple symptoms is thought to rest largely in the distortion of brain structures that occur as a result of CSF depletion. Spontaneous intracranial hypotension, however, also has its perplexing features:

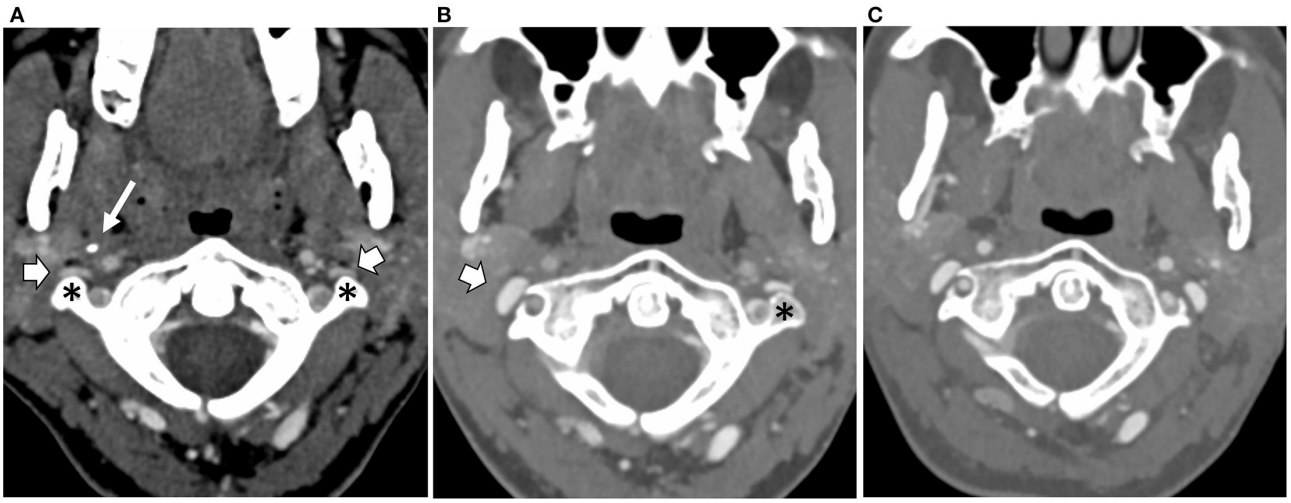

FIGURE 3
Axial CT scans at the level of the C1 vertebra and odontoid peg following intravenous contrast injection, **(A)** at the baseline, **(B)** following resection of the right styloid and C1 transverse processes, and **(C)** following resection of the left C1 transverse process. The baseline scan **(A)** shows narrowing and flattening of both internal jugular veins (block arrows) as they pass in front of the transverse processes of C1 (asterisk) on either side. The styloid process of the skull (thin arrow) can be seen on the right side. **(B)** Following the right transverse process and styloid resections, the right internal jugular vein (block arrow) has expanded into the space created by the surgery. **(C)** Following left transverse process resection, the left internal jugular vein has now also expanded.

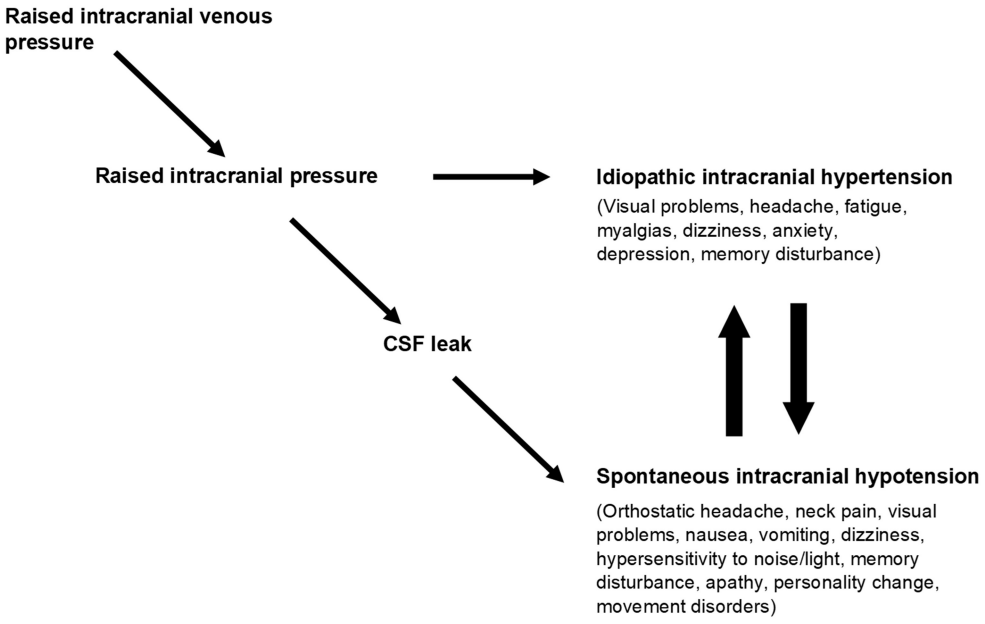

FIGURE 4
Obstruction to cranial venous outflow causes a rise in intracranial venous pressures leading to a rise in intracranial pressure and the syndrome of IIH. If a CSF leak develops before IIH becomes evident, then the physiological disturbance manifests as spontaneous intracranial hypotension (SIH). IIH and SIH have multiple overlapping symptoms, and patients may reach an equilibrium position between them or may cycle between one and the other, reflecting opposing forces on intracranial pressure. Taken from "A paradigm for chronic fatigue syndrome: caught between idiopathic intracranial hypertension and spontaneous intracranial hypotension; caused by cranial venous outflow obstruction" by J Nicholas P. Higgins & John D. Pickard. Fatigue: Biomedicine, Health & Behavior 2021, 9:3, copyright © 2021 ACFS/ME reprinted by permission of Informa UK Limited, trading as Taylor & Francis Group https://www.tandfonline.com on behalf of ACFS/ME.

the typical phenotype may not be accompanied by any radiological abnormality, and in some patients, intracranial pressure may be normal or even elevated (8–10).

This last observation, in particular, is difficult to reconcile with the historical view of spontaneous intracranial hypotension, defined partly by intracranial pressures less than 6 cm H_20. However, the observation that the closure of a leak in spontaneous intracranial hypotension can lead to rebound intracranial hypertension (35, 36) and the knowledge that CSF leaks may accompany IIH (6–8) imply that spontaneous intracranial hypotension can often represent a complication of IIH, developing when the dura gives way to a weak point under the stress of prolonged elevation of intracranial pressure. In these circumstances, it might not be expected that CSF pressures would fall to very low levels.

This concept, however, while establishing a plausible connection between IIH and spontaneous intracranial hypotension, does not fit well with the idea that IIH is caused by a mismatch between CSF production and CSF absorption since, in this situation, one would expect the complication to effect a cure. On the other hand, it is an encouragement to return to the idea of an external force, such as venous hypertension, acting to elevate intracranial pressure and, recently, two cases of spontaneous intracranial hypotension have been published, caused by narrowing of the jugular veins (18, 34). In both cases, the clinical syndrome was severe, and the radiological findings were striking. In one CSF, the pressure was shown to be in the high normal range (34). Both responded to relief of jugular obstruction with complete resolution of symptoms. Similar syndromes and responses to treatment have been recorded after iatrogenic occlusion of the sigmoid sinus during posterior fossa surgery (37).

Thus, extracranial venous outflow obstruction can give rise to syndromes in which intracranial pressure may be high, normal, or low, depending on the severity of venous obstruction and the presence or absence of a CSF leak. The clinical manifestation of these syndromes is likely to be complex, reflecting the effect of venous obstruction on cerebral perfusion, the effect of abnormal intracranial pressure on brain function and pain-sensitive structures, and the product of distortion of intracranial contents if there is CSF depletion. Importantly, the absolute value of intracranial pressure in these circumstances may be an unreliable indicator of the level of physiological disturbance (16) (Figure 4).

The case we described here conformed to this template. CSF opening pressure was in the normal range (14 cm H_2O). Her response to CSF drainage was complex, but there were features that suggested that she gained benefit when CSF pressure was reduced. There was mild intracranial venous hypertension, with sagittal sinus pressures of 20 cm H_2O, this implying a reversal of the normal pressure gradient between CSF and the venous sinuses, seen only when there is a CSF leak or a functioning CSF shunt. She responded positively to venoplasty of the narrowed segments identified on CT and catheter venography, demonstrating the potential reversibility of her clinical syndrome and suggesting targets for treatment. The treatment, itself, while by no means affecting a cure, has been transforming.

What does this mean? Observer bias cannot be discounted in a report without a control group, nor can the effect of placebo, especially when the treatment offered is based on an organic model of disease sympathetic to the widely held view among these patients that they have an illness with a physical cause. Nevertheless, the subtle clinical response to the diagnostic investigations witnessed in this case, the nuanced and incremental response to successive interventions (reminiscent of the response in other similar cases) (18, 34), durable over the course of long follow-up, and easily reconciled with the limited success of the interventions themselves, would require a degree of sophistication and consistency in placebo effect that would be hard to credit.

Equally, it should not be surprising that whatever pathological process is behind IIH, creating a spectrum of increasing clinical severity above a threshold value of 25 cm H_2O, should also furnish a population of patients with an equivalent illness that does not make the threshold. The requirement for a threshold declares the presence of symptoms in these patients. The key questions are what form these symptoms would take and what diagnostic label might be attached to them. In answer to the first, the form will be contributed from the multiple symptoms seen in IIH, outside those attributed to papilloedema but including those that might be attributable to a CSF leak. In answer to the second, the prevalence of fatigue among these symptoms should make a diagnosis of chronic fatigue syndrome prominent.

The outcome reported here, therefore, which is consistent with another reported previously (38) and with results emerging from recent research (2–5), suggests that investigating patients with chronic fatigue syndrome as if they had a disorder of intracranial pressure might not only bring clinical benefit to individual patients but also contribute to a better understanding of IIH itself and its relationship with spontaneous intracranial hypotension.

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.

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. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JH advocated the management approach, directed the diagnostic procedures, and wrote the first draft of the manuscript. PA performed the surgical procedures. AL conducted the

preliminary clinical assessments and follow-up. All authors reviewed and contributed to the final draft of the manuscript.

Conflict of interest

The 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.

Publisher's note

References

1. Higgins JNP, Pickard JD, Lever AML. Chronic fatigue syndrome and idiopathic intracranial hypertension: different manifestations of the same disorder of intracranial pressure? *Med Hypotheses.* (2017) 105:6–9. doi: 10.1016/j.mehy.2017.06.014

2. Higgins N, Pickard J, Lever A. Looking for idiopathic intracranial hypertension in patients with chronic fatigue syndrome. *J Obs Pain Med.* (2013) 1:28–35.

3. Higgins N, Pickard J, Lever A. Lumbar puncture, chronic fatigue syndrome and idiopathic intracranial hypertension: a cross-sectional study. *JRSM Short Rep.* (2013) 4:2042533313507920. doi: 10.1177/2042533313507920

4. Hulens M, Rasschaert R, Dankaerts W, Stalmans I, Vansant G, Bruyninckx F. Spinal fluid evacuation may provide temporary relief for patients with unexplained widespread pain and fibromyalgia. *Med Hypotheses.* (2018) 118:55–8. doi: 10.1016/j.mehy.2018.06.017

5. Bragée B, Michos A, Drum B, Fahlgren M, Szulkin R, Bertilson BC. Signs of intracranial hypertension, hypermobility, and craniocervical obstructions in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Front Neurol.* (2020) 11:828. doi: 10.3389/fneur.2020.00828

6. Schlosser RJ, Woodworth BA, Wilensky EM, Grady MS, Bolger WE. Spontaneous cerebrospinal fluid leaks: a variant of benign intracranial hypertension. *Ann Otol Rhinol Laryngol.* (2006) 115:495–500. doi: 10.1177/000348940611500703

7. Pérez MA, Bialer OY, Bruce BB, Newman NJ, Biousse V. Primary spontaneous cerebrospinal fluid leaks and idiopathic intracranial hypertension. *J Neuroophthalmol.* (2013) 33:330–7. doi: 10.1097/WNO.0b013e318299c292

8. Bidot S, Levy JM, Saindane AM, Oyesiku NM, Newman NJ, Biousse V. Do most patients with a spontaneous cerebrospinal fluid leak have idiopathic intracranial hypertension? *J Neuroophthalmol.* (2019) 39:487–95. doi: 10.1097/WNO.0000000000000761

9. Mokri B. Spontaneous low pressure, low CSF volume headaches: spontaneous CSF leaks. *Headache.* (2013) 53:1034–53. doi: 10.1111/head.12149

10. Schievink WI. Misdiagnosis of spontaneous intracranial hypotension. *Arch Neurol.* (2003) 60:1713–8. doi: 10.1001/archneur.60.12.1713

11. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study. *Group Ann Intern Med.* (1994) 121:953–9. doi: 10.7326/0003-4819-121-12-199412150-00009

12. Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: international consensus criteria. *J Intern Med.* (2011) 270:327–38. doi: 10.1111/j.1365-2796.2011.02428.x

13. Higgins JNP, Pickard JD. A paradigm for chronic fatigue syndrome: caught between idiopathic intracranial hypertension and spontaneous intracranial hypotension; caused by cranial venous outflow obstruction. *Fatigue.* (2021) 9:139–47. doi: 10.1080/21641846.2021.1956223

14. King JO, Mitchell PJ, Thomson KR, Tress BM. Cerebral venography and manometry in idiopathic intracranial hypertension. *Neurology.* (1995) 45:224–8. doi: 10.1212/WNL.45.12.2224

15. Karahalios DG, Rekate HL, Khayata MH, Apostalides PJ. Elevated intracranial venous pressure as a universal mechanism in pseudotumor cerebri of varying etiologies. *Neurology.* (1996) 46:198–202. doi: 10.1212/WNL.46.1.198

16. Higgins N, Pickard JD, Lever AM. What do lumbar puncture and jugular venoplasty say about a connection between chronic fatigue syndrome and idiopathic intracranial hypertension? *EJMINT.* (2014) 2014:1443000223.

17. Higgins JN, Garnett MR, Pickard JD, Axon PR. An evaluation of styloidectomy as an adjunct or alternative to jugular stenting in idiopathic intracranial hypertension and disturbances of cranial venous outflow. *J Neurol Surg B Skull Base.* (2017) 78:158–63. doi: 10.1055/s-0036-1594238

18. Higgins JN, Axon PR, Macfarlane R. Spontaneous intracranial hypotension complicated by subdural effusions treated by surgical relief of cranial venous outflow obstruction. *J Neurol Surg Rep.* (2020) 81:e59–65. doi: 10.1055/s-0040-1722268

19. Wojcik W, Armstrong D, Kanaan R. Is chronic fatigue syndrome a neurological condition? A survey of UK neurologists. *J Psychosom Res.* (2011) 70:573–4. doi: 10.1016/j.jpsychores.2011.02.007

20. Round R, Keane JR. The minor symptoms of increased intracranial pressure: 101 patients with benign intracranial hypertension. *Neurology.* (1988) 38:1461–4. doi: 10.1212/WNL.38.9.1461

21. Kleinschmidt JJ, Digre KB, Hanover R. Idiopathic intracranial hypertension: relationship to depression, anxiety, and quality of life. *Neurology.* (2000) 54:319–24. doi: 10.1212/WNL.54.2.319

22. Hulens M, Rasschaert R, Vansant G, Stalmans I, Bruyninckx F, Dankaerts W. The link between idiopathic intracranial hypertension, fibromyalgia, and chronic fatigue syndrome: exploration of a shared pathophysiology. *J Pain Res.* (2018) 11:3129–40. doi: 10.2147/JPR.S186878

23. Marcelis J, Silberstein SD. Idiopathic intracranial hypertension without papilledema. *Arch Neurol.* (1991) 48:392–9. doi: 10.1001/archneur.1991.00530160060014

24. Sussman JD, Sarkies N, Pickard JD. Benign intracranial hypertension. Pseudotumour cerebri: idiopathic intracranial hypertension. *Adv Tech Stand Neurosurg.* (1998) 24:261–305. doi: 10.1007/978-3-7091-6504-1_6

25. Ray BS, Dunbar HS. Thrombosis of the dural venous sinuses as a cause of "pseudotumor cerebri". *Ann Surg.* (1951) 134:376–86. doi: 10.1097/00000658-195113430-00009

26. Farb RI, Vanek I, Scott JN, Mikulis DJ, Willinsky RA, Tomlinson G, et al. Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. *Neurology.* (2003) 60:1418–24. doi: 10.1212/01.WNL.0000066683.34093.E2

27. Higgins JN, Gillard JH, Owler BK, Harkness K, Pickard JD. MR venography in idiopathic intracranial hypertension: unappreciated and misunderstood. *J Neurol Neurosurg Psychiatry.* (2004) 75:621–5. doi: 10.1136/jnnp.2003.021006

28. Higgins JNP, Owler BK, Cousins C, Pickard JD. Venous sinus stenting for refractory benign intracranial hypertension. *Lancet.* (2002) 359:228–30. doi: 10.1016/S0140-6736(02)07440-8

29. Higgins JNP, Cousins C, Owler BK, Sarkies N, Pickard JD. Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting. *J Neurol Neurosurg Psychiatry.* (2003) 74:1662–6. doi: 10.1136/jnnp.74.12.1662

30. Nia AM, Srinivasan VM, Lall R, Kan P. Dural venous sinus stenting in idiopathic intracranial hypertension: a national database study of 541 patients. *World Neurosurg.* (2022) 2022:S1878–8750(22)01135-4. doi: 10.1016/j.wneu.2022.08.035

31. Dashti SR, Nakaji P, Hu YC, Frei DF, Abla AA, Yao T, et al. Styloidogenic jugular venous compression syndrome: diagnosis and treatment: case report. *Neurosurgery.* (2012) 70:E795–9. doi: 10.1227/NEU.0b013e3182333859

32. Zhou D, Meng R, Zhang X, Guo L, Li S, Wu W, et al. Intracranial hypertension induced by internal jugular vein stenosis can be resolved by stenting. *Eur J Neurol.* (2018) 25:365–e13. doi: 10.1111/ene.13512

33. Li M, Sun Y, Chan CC, Fan C, Ji X, Meng R. Internal jugular vein stenosis associated with elongated styloid process: five case reports and literature review. *BMC Neurol.* (2019) 19:112. doi: 10.1186/s12883-019-1344-0

34. Higgins N, Trivedi R, Greenwood R, Pickard J. Brain slump caused by jugular venous stenoses treated by stenting: a hypothesis to link spontaneous intracranial hypotension with idiopathic intracranial hypertension. *J Neurol Surg Rep.* (2015) 76:e188–93. doi: 10.1055/s-0035-1555015

35. Mokri B. Intracranial hypertension after treatment of spontaneous cerebrospinal fluid leaks. *Mayo Clin Proc.* (2002) 77:1241–6. doi: 10.4065/77.11.1241

36. Schievink WI, Maya MM, Jean-Pierre S, Moser FG, Nuño M, Pressman BD. Rebound high-pressure headache after treatment of spontaneous intracranial hypotension: MRV study. *Neurol Clin Pract.* (2019) 9:93–100. doi: 10.1212/CPJ.0000000000000550

37. Higgins JN, Macfarlane R, Axon PR, Mannion RA, Tysome JR, Donnelly N, et al. Headache, cerebrospinal fluid leaks, and pseudomeningoceles after resection of vestibular schwannomas: efficacy of venous sinus stenting suggests cranial venous outflow compromise as a unifying pathophysiological mechanism. *J Neurol Surg B Skull Base.* (2019) 80:640–7. doi: 10.1055/s-0039-1677706

38. Higgins N, Pickard J, Lever A. Borderline intracranial hypertension manifesting as chronic fatigue syndrome treated by venous sinus stenting. *J Neurol Surg Rep.* (2015) 76:e244–7. doi: 10.1055/s-0035-1564060

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Enhanced acupuncture therapy for radiotherapy-related neuropathic pain in patients with gynecologic cancer: a report of two cases and brief review

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As radiation therapy is increasingly utilized in the treatment of cancer, neuropathic pain (NP) is a common radiotherapy-related adverse effect and has a significant impact on clinical outcomes negatively. However, despite an improved understanding of neuropathic pain management, pain is often undertreated in patients with cancer. Herein, we reported two cases with radiotherapy-related neuropathic pain (RRNP) who presented a positive reaction to acupuncture. Patient 1 (a 73-year-old woman) with gynecologic cancer complained of burning and electric shock-like pain in the lower limb after radiotherapy. With the accepted combination of acupuncture and drugs, the pain was alleviated completely in 8 weeks. Patient 2 (a 64-year-old woman) accepted acupuncture in the absence of medication because of her inability to tolerate the adverse events of anticonvulsant drugs. She achieved remission of pain 4 weeks later. The results of this study showed that acupuncture might be promising for controlling the RRNP in patients with cancer, especially who were intolerant or unresponsive to medications.

KEYWORDS

neuropathic pain, radiotherapy, acupuncture, cancer, case report

1. Introduction

Neuropathic pain (NP) is defined as "pain caused by a lesion or disease affecting the somatosensory system" (1), which is different from nociceptive pain due to damage to the non-neural tissue and activation of nociceptors. In patients with cancer, it had been reported that NP affects ~20–40% of populations (2) and severely interferes with emotional and physical function, influences the quality of life negatively, as well as is associated with the clinical outcome directly (3, 4). In etiology, cancer-related NP could be subdivided into tumor-related (caused by tumor *per se*) and treatment-related NP (caused by treatments, such as chemotherapy or radiotherapy) (5). At present, pain secondary to tumor have been universally appreciated, and the neurotoxicity of chemotherapy is increasingly recognized as well. In comparison, there exists a sparsity of direct data focused on radiotherapy-related neuropathic pain (RRNP) (6) despite the increased utilization of radiotherapy in cancer care and the overall increase in cancer survivorship.

Current analgesic approaches are pharmaceutical (including antidepressants, anticonvulsants, and opioids) and non-pharmaceutical. Despite an improved understanding of pain management and many approaches, pain is often under-treated in patients with cancer (7). A system review revealed that approximately one-third of patients with cancer do not receive appropriate analgesia proportional to their pain intensity (8). Therefore, for optimal pain control, a multimodal approach of medications and non-pharmaceutical therapy could be applied in conjunction with disease-directed treatment (9), especially for patients who show no positive response to these conventional treatments.

As a therapy of traditional Chinese medicine, acupuncture is widely used for palliative and supportive care for cancer patients, and evidence is increasing over the years (10). Some studies suggested that acupuncture might be effective for chemotherapy-induced neuropathic pain (CINP) (11–14). Based on the similar concept of acupuncture, acupuncture might have potential in the pain management of RRNP. Herein, we report the successful application of acupuncture for the management of RRNP in patients with gynecologic cancer. The article follows the CARE guidelines (15).

2. Case presentation

2.1. Case 1

A 73-year-old woman who presented with postmenopausal bleeding for 20 years was admitted to the gynecology department at the Third Affiliated Hospital of Sun Yat-Sen University. Her past medical history revealed type 2 diabetes mellitus with regular hypoglycemic drugs. On admission, the test of serum tumor markers showed that carbohydrate antigen-125 was 90.4 U/ml, carbohydrate antigen-199 was 41.6 U/ml, and human epididymal protein 4 was 153 mmol/L. Considering the results of the pathological morphology examination (Figure 1) comprehensively, she was diagnosed with endometrial carcinoma. On the 10th day after admission, the gynecologist performed a hysterectomy plus lymph node dissection for her. After 1 week of surgery, she accepted chemotherapy (docetaxel 100 mg, carboplatin 500 mg, 1 day) and was discharged. The pelvic magnetic resonance imaging (Figure 2) at 1 month after surgery showed no residual tumor tissue, or metastasis was detected. Hence, she started to accept radiotherapy (IMRT PTV:50Gy/2Gy/25F). Approximately 3 months after surgery, she was back to the hospital because of the burning, electric shock-like pain, and pitting edema of the left lower limb that got an outbreak. Other complaints included constipation, frequent micturition, and insomnia. Neoplasm metastasis, recurrence, and deep venous thrombosis were excluded through a series of examinations like pelvic imaging and ultrasonic testing (Figure 3). She accepted oral pain relief drugs (pregabalin 75 mg Bid and mecobalamin 0.5 mg Tid) for 2 weeks but her symptoms did not improve. Therefore, she sought the aid of acupuncture in the outpatient department ~4 months after surgery. Physical examination showed hyperalgesia in the medial side of the lower limb, pressing pain (++) in the left groin area, and weakness of muscle strength of the left lower extremity. The pain intensity score evaluated by the numerical rating scale (NRS) was as high as 7 points. To control the pain better, we applied enhanced acupuncture therapy, accompanied by adjusting the dosage of medication (pregabalin 75 mg 8 am/150 mg 8 pm). The acupuncture treatment procedure was composed of manual acupuncture and electro-acupuncture, which was given 3 times per week, a total of 20 sessions of treatments within 8 weeks and implemented by an experienced and certified acupuncturist who had over 5 years of experience. The details of acupuncture based on the theory of traditional Chinese medicine, such as the acupoints, we chose and needling methods are demonstrated in Supplementary material 1.

After five times of performing therapies, the patient claimed that the pain had relief significantly, and the NRS scores decreased from 7 to 3. Subsequently, accompanied by acupuncture therapy and the improvement of pain, the dose of pregabalin was reduced gradually until it was discontinued (Figure 4). After 20 times of therapy, the patient felt relieved of the pain completely, but the edema of the lower limb was not improved. No side effect or adverse event was observed in association with the treatment methods described. During a telephone follow-up, 6 months after the end of treatment, the patient reported no recurrences of neuropathic pain.

2.2. Case 2

Patient 2 was a 64-year-old woman who visited our acupuncture and moxibustion department due to pain and weakness in her right lower limbs. 4 months before her first visit to our acupuncture department, she had suffered from irregulate postmenopausal bleeding, at which she was diagnosed with endometrial carcinoma and had accepted the surgery, combined with chemotherapy and radiotherapy in the hospital. After the comprehensive treatment above, she had got severe neuropathic pain in her right lower limb. Her symptoms occurred with no residual tumor tissue, local tumor recurrence, or metastasis illustrated by pelvic MRI. She began to receive pregabalin (75 mg bid), and pain had got partly controlled. However, she started to complain of dizziness and gait disturbance after taking the medicine. Therefore, she decided to stop taking the medicine due to intolerance to the adverse events of pregabalin. After withdrawal, the pain recurred but the intensity was less than before. She started to visit our department and accepted acupuncture without medication. On her first visit at outpatient, pain intensity evaluation (NRS) was 4 points out of 10.

Subsequently, we performed enhanced acupuncture therapy three times per week, which was composed of two forms of acupuncture. After 10 times of therapy, the pain in the right limb was relieved completely. At 6 months after acupuncture therapy, the pain occurred occasionally but the degree was slight. Since the patient only had minor complaints with respect to occasional pain, we decided to observe her symptoms without any management.

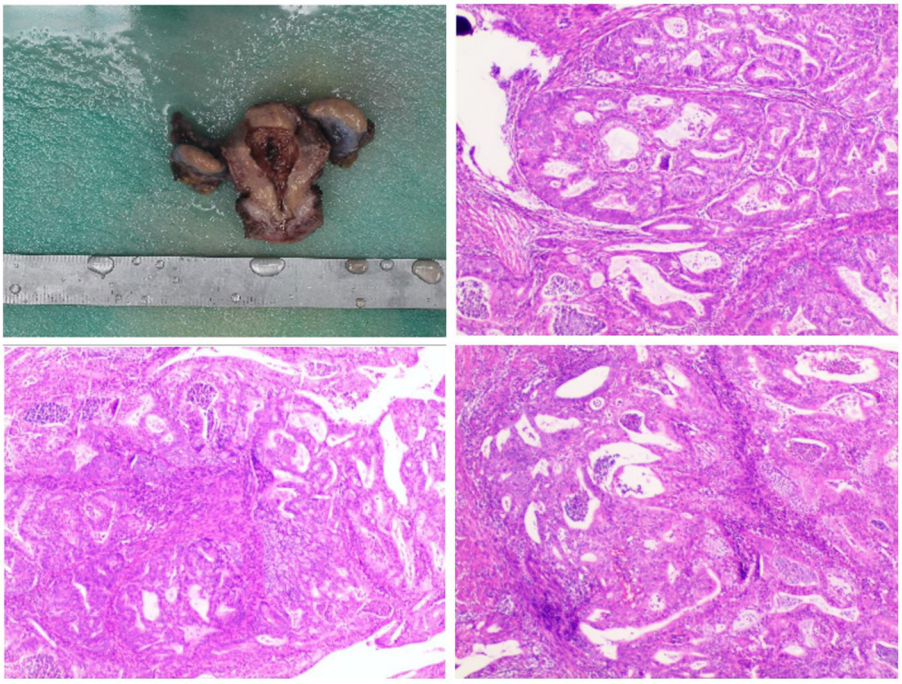

FIGURE 1
Pathological morphology examination.

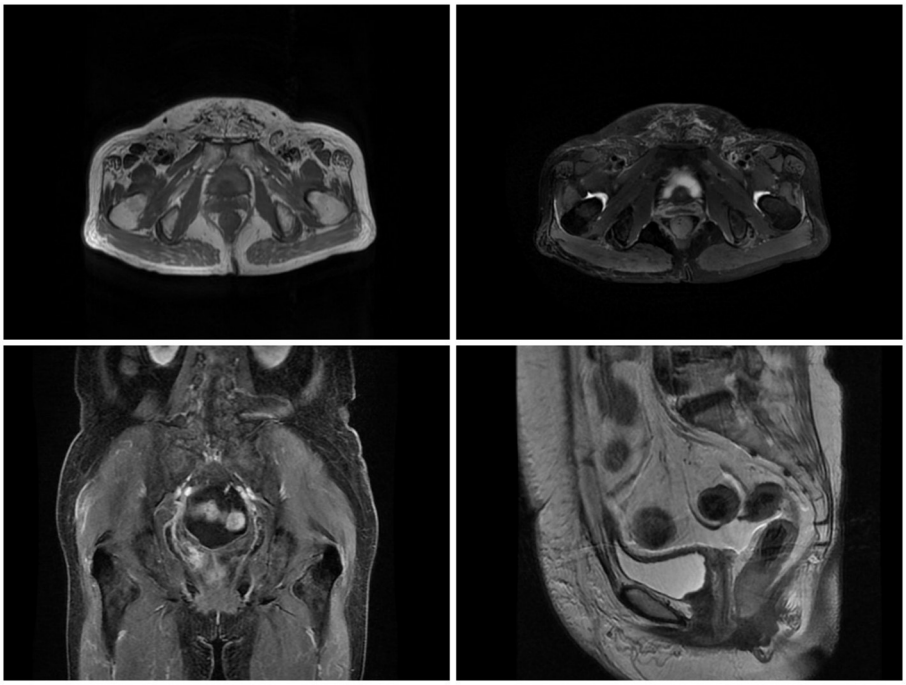

FIGURE 2
The pelvic MRI on 1 month after surgery showed no residual tumor tissue or metastasis.

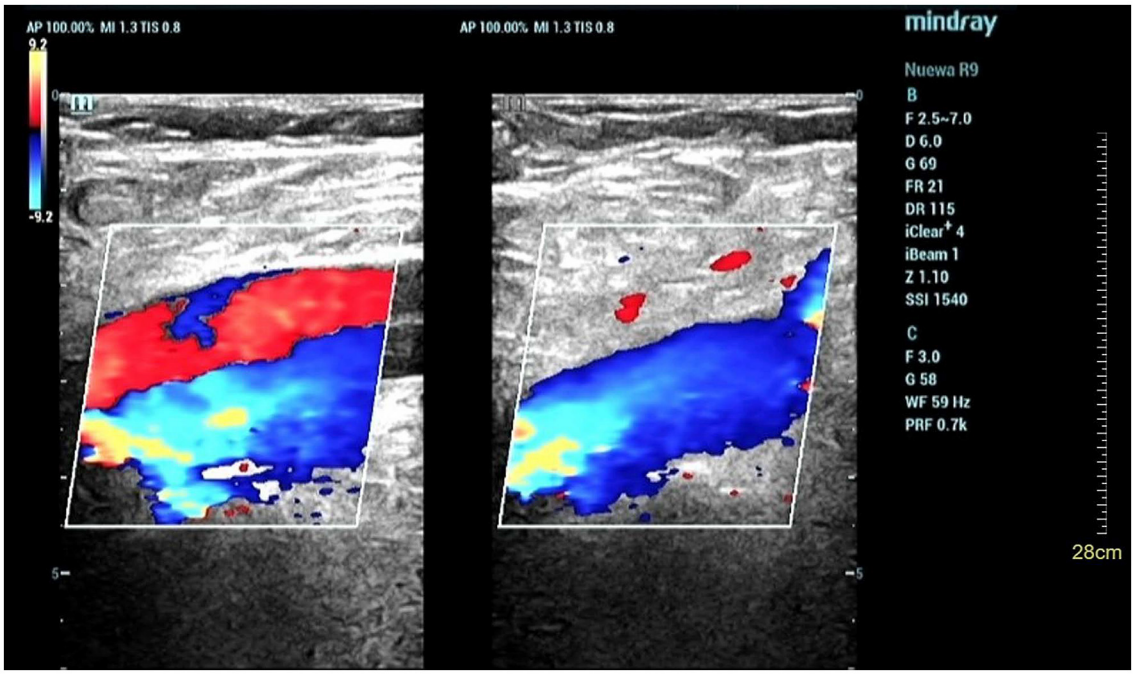

FIGURE 3
Ultrasonic testing showed venous blood flow in the lower extremities is smooth.

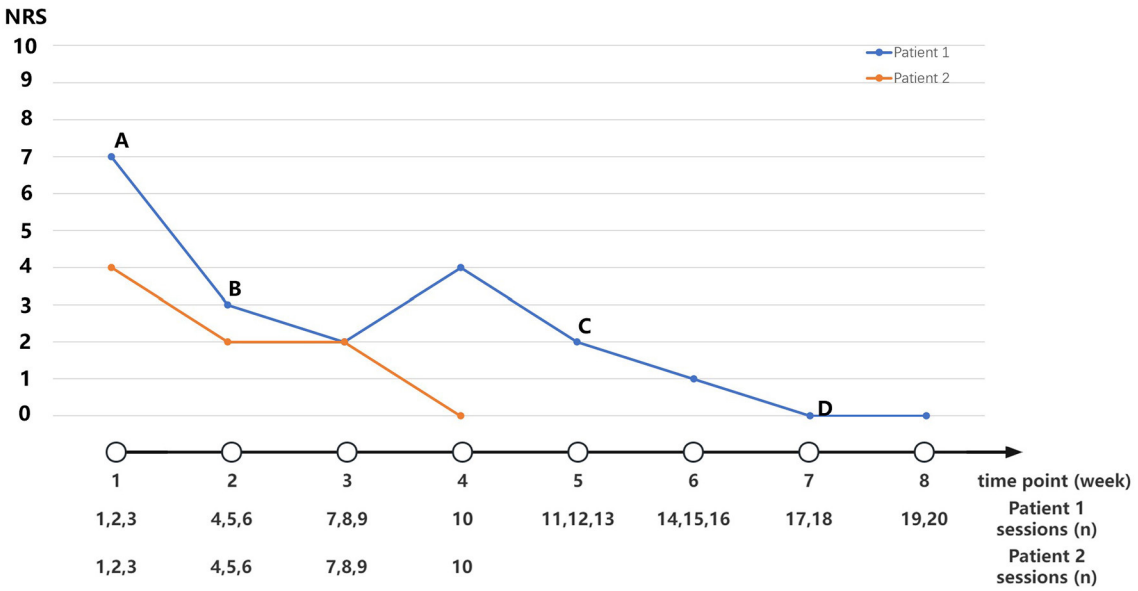

FIGURE 4
Medication adjustment and NRS scores along the timeline of disease. **(A)** Pregabalin 225 mg/day (75 mg 8 am, 150 mg 8 pm). **(B)** Pregabalin 150 mg/day (75 mg Q12 h). **(C)** Pregabalin 75 mg/day (75 mg 8 pm). **(D)** Stop medication intervention.

3. Discussion

Radiotherapy-related neuropathic pain is a common treatment-related adverse effect in the field of radiotherapy with a high prevalence (31%) among cancer survivors (16). It is often manifested as gradual, persisting, or recurrent episodes and shows distinct clinical characteristics in terms of hypersensitivity symptoms (burning, tingling, and electric

shock-like sensation) and hyposensitivity symptoms (numbness and muscle weakness) (17). The symptomatology of RRNP is reliant on the anatomic areas of radiotherapy targeted. The three most commonly involved neural tissues include brachial plexopathy resulting from irradiation for lung or breast cancer, lumbosacral plexopathy after pelvic radiotherapy, and axial neuropathy of the spinal cord following cervical radiotherapy (6).

The pathophysiological mechanisms of RRNP are not yet fully understood. Radiation-induced direct axonal damage and demyelination, nerve compression by indirect extensive radiation-induced fibrosis, and nerve ischemia from microvascular damage are the three key factors involved (18). Pharmaceutical approaches including gabapentin, pregabalin, duloxetine, and tricyclic antidepressive agents are strongly recommended as single agents for first-line treatment in the European Society for Medical Oncology guidance (7). The combination of opioids and adjuvants needs to be carefully dosed because it remains uncertain regarding the risk–benefit trade-off (19, 20). However, the results of most approaches on average could only provide pain relief to less than half of the patients treated (21). In addition, the direct evidence focused on the management of RRNP is limited. There are only a limited number of studies conducted on RRNP (17, 22, 23) that results in the recommendation above which is extrapolated from studies in non-cancer related neuropathic pain. Hence, managing pain adequately for this population remains challenging.

We presented the two cases with RRNP that obtained complete relief after acupuncture. This is the first report to show that acupuncture might release neuropathic pain in patients with cancer after radiotherapy. In patient 1, with a combination of acupuncture and anticonvulsant drugs strategy, the burning and electric shock-like pain in the limb was alleviated in 8 weeks. Patient 2 achieved complete remission of pain through acupuncture in the absence of medication because of the inability to tolerate the adverse events of drugs. Both of them showed no recurrence of pain after stopping interventions and during the follow-up visit. In this study, we applied an enhanced acupuncture strategy that chose the local acupoints at limbs, combining acupoints located at the abdomen and the lumbar. First, the mechanism of the lesion in two cases involves the obstruction of Qi and the blood in the liver, kidney, and spleen meridian. Performing acupuncture at the local acupoints on the above three meridians could regulate the Qi and blood in the meridian and release the pain. Second, according to the theory of meridian, the govern vessel and ren vessel could control all the Yang and Yin meridian. Hence, we applied acupoints at the govern vessel and ren vessel to strengthen the dredging of Qi and blood. Some studies support the effectiveness of this strategy in improving peripheral neural function (26).

An overview of systematic reviews showed that acupuncture is beneficial to cancer survivors with fatigue, insomnia, improved quality of life, nausea and vomiting, bone marrow suppression, menopausal, and CINP (11). In general, many similarities exist between CINP and RRNP in aspects of syndrome and mechanism. Some pilot studies highlighted that the use of local acupoints on toes and fingers is the key factor to the effectiveness of decreasing the intensity of CINP (24). However, we considered that the treatment for RRNP might emphasize the use of proximal segmental acupoints more than local acupoints compared to that for CINP. Although the mechanism by which acupuncture manages RRNP has still not been illustrated, we suggest a possible mechanism based on the mechanism of acupuncture for CINP. First, acupuncture might enhance the perfusion of the vasa nervorum and dependent capillary beds supplying local neurons, which improve the removal of inflammatory factors and reduction of tissue toxicity (13, 25). Second, acupuncture appears to provide a microenvironment conducive to neuroregeneration by stimulating the release of neurotrophin (26).

However, this study is limited because it is a case study. Accordingly, a further study that involves an adequate sample size and appropriate control group is warranted to verify the effect of acupuncture in treating RRNP. Moreover, exploratory research on the mechanisms of acupuncture alleviating RRNP is necessary. In addition, to achieve the optimal outcomes of acupuncture, it is needed to investigate the optimum treatment procedure including stimulation mode, acupoints, and duration.

4. Conclusion

We reported two patients with RRNP who showed a good reaction to acupuncture. The results of this study showed that acupuncture might be promising for controlling neuropathic pain after radiotherapy in patients with cancer, especially who were intolerant or unresponsive to medications.

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 authors.

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 was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

YH-z provided the case. ZD-f and YL-s performed the acupuncture. ZD-f and RJ-c wrote the draft. ZS-z and ZK collected the clinical data. YL-s and TC-z reviewed and edited the draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1163990/full#supplementary-material

SUPPLEMENTARY MATERIAL 1
The procedure of acupuncture in this study.

References

1. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. *Pain.* (2011) 152:2204–5. doi: 10.1016/j.pain.2011.06.017

2. Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain.* (2012) 153:359–65. doi: 10.1016/j.pain.2011.10.028

3. van den Beuken-van Everdingen MHJ, van Kuijk SMJ, Janssen DJA, Joosten EAJ. Treatment of pain in cancer: towards personalized medicine. *Cancers.* (2018) 10:502. doi: 10.3390/cancers10120502

4. Rayment C, Hjermstad MJ, Aass N, Kaasa S, Caraceni A, Strasser F, et al. Neuropathic cancer pain: prevalence, severity, analgesics and impact from the European palliative care research collaborative-computerized symptom assessment study. *Palliat Med.* (2013) 27:714–21. doi: 10.1177/0269216312464408

5. Yoon S Y, Oh J. Neuropathic cancer pain: prevalence, pathophysiology, and management. *Korean J Intern Med.* (2018) 33:1058–69. doi: 10.3904/kjim.2018.162

6. Karri J, Lachman L, Hanania A, et al. Radiotherapy-specific chronic pain syndromes in the cancer population: an evidence-based narrative review. *Adv Ther.* (2021) 38:1425–46. doi: 10.1007/s12325-021-01640-x

7. Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, et al. Management of cancer pain in adult patients: ESMO clinical practice guidelines. *Ann Oncol.* (2018) 29(Suppl 4):v166–91. doi: 10.1093/annonc/mdy152

8. Greco MT, Roberto A, Corli O, Deandrea S, Bandieri E, Cavuto S, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol.* (2014) 32:4149–54. doi: 10.1200/JCO.2014.56.0383

9. Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. *CA Cancer J Clin.* (2018) 68:182–96. doi: 10.3322/caac.21453

10. Ben-Arye E, Hausner D, Samuels N, Gamus D, Lavie O, Tadmor T, et al. Impact of acupuncture and integrative therapies on chemotherapy-induced peripheral neuropathy: a multicentered, randomized controlled trial. *Cancer.* (2022) 128:3641–52. doi: 10.1002/cncr.34422

11. Zhang XW, Hou WB, Pu FL, Wang XF, Wang YR, Yang M, et al. Acupuncture for cancer-related conditions: an overview of systematic reviews. *Phytomedicine.* (2022) 106:154430. doi: 10.1016/j.phymed.2022.154430

12. Xu Z, Wang X, Wu Y, Wang C, Fang X. The effectiveness and safety of acupuncture for chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Front Neurol.* (2022) 13:963358. doi: 10.3389/fneur.2022.963358

13. Friedemann T, Kark E, Cao N, Klaßen M, Meyer-Hamme G, Greten JH, et al. Acupuncture improves chemotherapy-induced neuropathy explored by neurophysiological and clinical outcomes—the randomized, controlled, cross-over ACUCIN trial. *Phytomedicine.* (2022) 104:154294. doi: 10.1016/j.phymed.2022.154294

14. Chan K, Lui L, Lam Y, Yu K, Lau K, Lai M, et al. Efficacy and safety of electroacupuncture for oxaliplatin-induced peripheral neuropathy in colorectal cancer patients: a single-blinded, randomized, sham-controlled trial. *Acupunct Med.* (2022) 2022:1144913107. doi: 10.1177/09645284221125421

15. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, et al. The CARE guidelines: consensus-based clinical case report guideline development. *J Clin Epidemiol.* (2014) 67:46–51. doi: 10.1016/j.jclinepi.2013.08.003

16. Mañas A, Monroy JL, Ramos AA, Cano C, López-Gómez V, Masramón X, et al. Prevalence of neuropathic pain in radiotherapy oncology units. *Int J Radiat Oncol Biol Phys.* (2011) 81:511–20. doi: 10.1016/j.ijrobp.2010.05.047

17. Edwards H, Mulvey M, Bennett M. Cancer-related neuropathic pain. *Cancers.* (2019) 11:373. doi: 10.3390/cancers11030373

18. Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. *Radiother Oncol.* (2012) 105:273–82. doi: 10.1016/j.radonc.2012.10.012

19. Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. *Palliat Med.* (2011) 25:553–9. doi: 10.1177/0269216310378546

20. Kane CM, Mulvey MR, Wright S, Craigs C, Wright JM, Bennett MI. Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis. *Palliat Med.* (2018) 32:276–86. doi: 10.1177/0269216317711826

21. Dupoiron D, Jubier-Hamon S, Seegers V, Bienfait F, Pluchon YM, Lebrec N, et al. Peripheral neuropathic pain following breast cancer: effectiveness and tolerability of high-concentration capsaicin patch. *J Pain Res.* (2022) 15:241–55. doi: 10.2147/JPR.S341378

22. Jiang J, Li Y, Shen Q, Rong X, Huang X, Li H, et al. Effect of pregabalin on radiotherapy-related neuropathic pain in patients with head and neck cancer: a randomized controlled trial. *J Clin Oncol.* (2019) 37:135–43. doi: 10.1200/JCO.18.00896

23. Kouri M, Rekatsina M, Vadalouca A, Siafaka I, Vardas E, Papadopoulou E, et al. Pharmacological management of neuropathic pain after radiotherapy in head and neck cancer patients: a systematic review. *J Clin Med.* (2022) 11:4877. doi: 10.3390/jcm11164877

24. Lee S, Lee CS, Moon JY, Song HG, Yoo Y, Kim J, et al. Electroacupuncture may improve burning and electric shock-like neuropathic pain: a prospective exploratory pilot study. *J Altern Complement Med.* (2020) 26:1136–43. doi: 10.1089/acm.2020.0307

25. Schroeder S, Meyer-Hamme G, Epplee S. Acupuncture for chemotherapy-induced peripheral neuropathy (CIPN): a pilot study using neurography. *Acupunct Med.* (2012) 30:4–7. doi: 10.1136/acupmed-2011-010034

26. He GH, Ruan JW, Zeng YS, Zhou X, Ding Y, Zhou GH. Improvement in acupoint selection for acupuncture of nerves surrounding the injury site: electro-acupuncture with Governor vessel with local meridian acupoints. *Neural Regen Res.* (2015) 10:128. doi: 10.4103/1673-5374.150720

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Headache attributed to giant cell arteritis complicated with rheumatic polymyalgia diagnosed with F18-fluorodeoxyglucose positron emission tomography and computed tomography: a case report

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Giant cell arteritis (GCA) is a kind of systemic vasculitis affecting individuals over 50 years old and is often the cause of new-onset headaches in older adults. Patients with GCA sometimes have rheumatic polymyalgia (PMR). The diagnosis of GCA generally depends on clinical manifestation, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein, and positive imaging findings commonly obtained by ultrasound or temporal artery biopsy. In this study, we report a case of an 83-year-old woman with a new-onset headache and an elevated ESR. The result of the temporal artery ultrasound did not distinguish between vasculitis and atherosclerosis. The F18-fluorodeoxyglucose positron emission tomography and computed tomography (18F FDG PET-CT) were performed and suggested large vessel vasculitis with temporal artery involvement. In addition, polyarticular synovitis and bursitis were also revealed. Finally, the diagnosis of secondary headache attributed to CGA complicated with PMR was established. The patient experienced remission of symptoms after glucocorticoid therapy. PET can become a powerful tool for diagnosis and differential diagnosis when the ultrasound result is ambiguous and a biopsy is not obtained.

KEYWORDS

headache, giant cell arteritis, rheumatic polymyalgia, PET, case report

Introduction

Giant cell arteritis (GCA) is a kind of systemic vasculitis involving the large and middle arteries, also known as temporal arteritis (1). The age of the population with GCA is generally over 50 years, and the annual incidence among individuals over 50 years old is ~10–20 per 100,000, which is highest in Nordic countries and rare in Asia; the average age at diagnosis is over 70 years (2). The prevalence rate of female patients is higher than that of male patients, and the ratio of male to female is 1:2.5–3 (3). GCA is closely related to rheumatic polymyalgia (PMR); 46–60% of GCA patients have comorbid PMR, and 16–21% of PMR patients have comorbid GCA (4). As the temporal artery and other cranial arteries are commonly involved, GCA is one of the causes of new-onset headache in

middle-aged and elderly people (5). Although biopsy is still the golden standard of GCA, its low acceptance of invasive examination limits its uses. If the positive ultrasound result and other supportive evidence are absent, there would be a dilemma for differential diagnosis and optimal treatment. Here, we report a case of GCA complicated with PMR diagnosed by F18-fluorodeoxyglucose positron emission tomography and computed tomography (18F FDG PET-CT). Written informed consent for the personal medical information and images to be published was provided by a legally authorized representative.

Case description

The patient, an 83-year-old woman, went to the Neurologic Clinic, at Peking University People's Hospital on May 9, 2022 because of a paroxysmal headache for 10 days. The pain was located in the right temporal region and waxed and waned, sometimes accompanied by congestion and tears in the right eye. She had no fever, no dizziness, no nausea or vomiting, no blurred vision, no jaw and tongue claudication, and no general malaise. Blood pressure was 100/70 mmHg in the left upper limb but undetectable in the right upper limb by electronic sphygmomanometer. There was no obvious tenderness in the region of the right temporal artery. The routine blood examination showed moderate anemia (hemoglobin content of 85 g/L) and an erythrocyte sedimentation rate (ESR) of 101 mm/h. Considering the possibility of a secondary headache, she was admitted to the neurology ward on May 11, 2022. The patient had a history of neurological deafness, diabetes, and hypertension, but no family history of headache or cerebrovascular disease. Two months ago, an ultrasound examination showed that sclerotic plaque was formed at bilateral subclavian arteries with the intima thickened; the distal end of the right subclavian artery was severely stenosed (about 85%), and the distal part of the left subclavian artery was moderately stenosed (60–65%). A neurological physical examination suggested a positive right Babinski and Chaddock sign, no meningeal irritation sign, and other positive signs of the nervous system.

The C-reactive protein (CRP) was elevated (39.1 mg/L). Cytokeratin 19 fragment was slightly elevated (3.32 ng/ml, reference $<$ 3.30 ng/ml) among the tumor marker measurements. The urine and stool routine, blood biochemical analysis, antinuclear antibody, anti-ENA antibody, ANCA, Coomb's test, rheumatoid factor, immunoglobulin, galactomannan test (1,3)-β-D-glucan and galactomannan test, T-cell spot test for tuberculosis infection, PPD test, anti-double-stranded DNA antibody, serum and urine immunofixation electrophoresis, IL-2/4/6/10, IFN-γ, TNF-α, cytomegalovirus, EB virus, and adenovirus nucleic acid detection showed no markedly abnormal findings.

The brain MR (Figures 1A–F) showed several lacunar foci in bilateral basal ganglia and thalamus (especially on the left), leukoencephalopathy, and atrophy. An MRI angiogram (Figure 1G) suggested intracranial arteriosclerosis and mild to moderate stenosis of the M1 segment of the left middle cerebral artery. Temporal artery ultrasound (TAU) showed hypoechogenic non-smooth thickening of the bilateral superficial temporal artery wall with the presence of a few punctate strong echo plaques (Figure 2), which could not tell vasculitis from atherosclerosis clearly. After a consultation with a rheumatologist, the patient underwent an 18F FDG PET-CT examination. The results showed that FDG uptake increased unevenly in the temporal arteries, ascending aorta, aortic arch, brachiocephalic trunk, descending aorta, abdominal aorta, bilateral subclavian arteries, axillary arteries, carotid arteries, femoral arteries, popliteal arteries, and

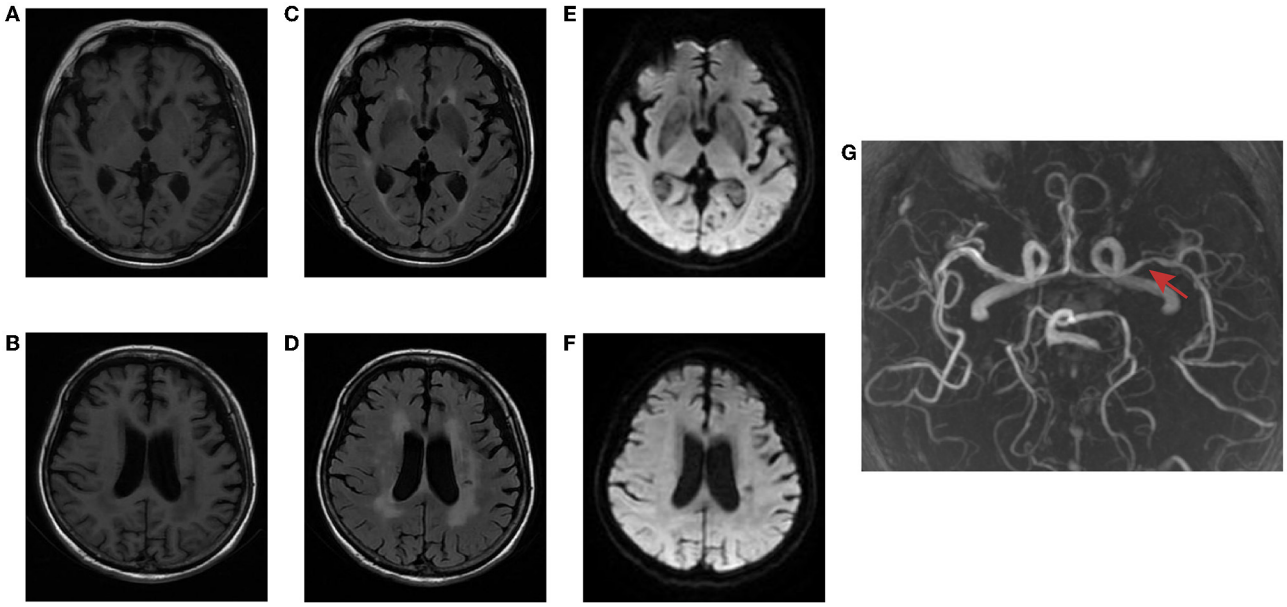

FIGURE 1
Brain MR of the patient. T1-weighted imaging **(A, B)** and FLAIR **(C, D)** showed several lacunar foci in bilateral basal ganglia and thalamus, leukoencephalopathy, and atrophy. No hyperintense on DWI **(E, F)**. MRI angiogram suggested stenosis of the left middle cerebral artery (red arrow) **(G)**.

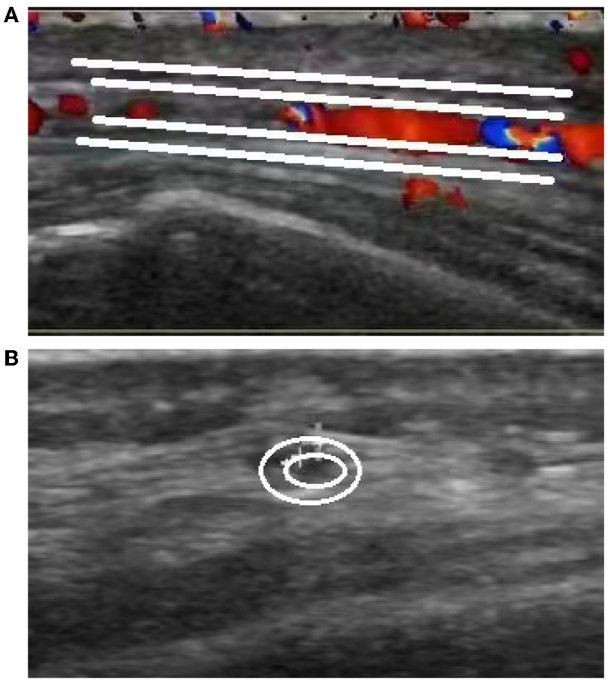

FIGURE 2
Ultrasound images of the temporal artery. Long-axis section of the temporal artery **(A)** exhibits irregular wall morphology characterized by thickening and the presence of a few punctate strong echo plaques. Short-axis section of the temporal artery **(B)** demonstrates non-uniform thickening with a non-smooth appearance.

tibial arteries (SUVmax: 1.4–5.3). Vessel walls were slightly thickened, and strip calcification was seen in part of them (Figure 3). In addition, increased FDG uptake (SUVmax: 4.2) could be seen in atlantoaxial, shoulder, wrist, hip, knee, sternoclavicular joints, and lumbar spinous processes, with synovium thickened or synovial capsule enlarged (Figure 4). In the meantime, the patient presented another clinical clue that she had bilateral shoulder joint, knee joint, hip, and waist pain in the past 2 years. Finally, the diagnosis of GCA complicated with PMR was established.

She received 40 mg of intravenous methylprednisolone daily for 7 days and then 50 mg of oral prednisone daily. The headache and limb pain were significantly relieved. ESR decreased from 101 to 25 mm/h, and CRP decreased from 39.1 to 2.7 mg/L. The disease was kept under good control at follow-up.

Discussion

This case involved an elderly woman with new-onset headache, accompanied by an elevation of ESR and CRP. Except for the positive right Babinski and Chaddock sign, which could be explained by old lesions of the brain revealed by the MRI, no other positive sign was found. The secondary headache attributed to GCA was suspected. On the basis of the GCA diagnostic criteria put forward by the American College of Rheumatology (ACR) in 1990 (6), ACR and the European League Against Rheumatism (EULAR) introduced the "halo sign" of TAU and high FDG uptake of large arteries in FDG-PET into the diagnostic criteria in 2022. After the introduction of TAU and PET, the new criteria have a sensitivity of 87% and a specificity of 95% (7). A halo sign is defined as a hypo- or iso-echogenic dark aspect of the vessel walls (8). The TAU in this case showed hypoechogenic uneven thickening of the artery wall with punctate plaques, which did not fit the typical halo sign and failed to distinguish between vasculitis and atherosclerosis (9, 10). According to EULAR's recommendations on the application of imaging in the clinical practice of large vessel vasculitis, a temporal artery biopsy (TAB) or further imaging examination was needed to confirm the diagnosis (11).

TAU is convenient and easy to perform, and it is the preferred imaging method when GCA is clinically suspected (11). According to the literature, the halo sign of TAU has a sensitivity of 77% and a specificity of 96% for the diagnosis of GCA (12). TAB is still the gold standard for diagnosing GCA (13), but biopsy is invasive, and its acceptance by patients is low. Pooled data showed that the sensitivity of TAB was similar to TAU findings, but the positive rate of biopsy showed a decreasing trend year by year (14). The patient refused an invasive examination. In recent years, studies have found that FDG-PET had high sensitivity and specificity for the diagnosis of GCA, which were 80–90% and 73–98%, respectively (15). In this case, there was no typical halo sign, which made the involvement of the temporal artery doubtful. In pathological process, functional changes often precede structural changes, and FDG-PET theoretically has a higher sensitivity to early vascular inflammation with only functional involvement. In addition, although ESR was elevated in this elderly woman, other rheumatic and immune-related indicators and pathogenic agent tests were negative. Therefore, the possibility of tumors could not be ruled out, and PET is more helpful for the differential diagnosis. Therefore, PET-CT was finally chosen.

The results of PET-CT showed that the aorta, its main branches, and even the distal arteries showed high uptake of linear FDG. Combined with other clinical features, according to the classification criteria of ACR/EULAR in 2022, the diagnosis of GCA was established (7). Meanwhile, PET-CT revealed no signs of a tumor. Although the result of TAU was ambiguous, abnormal FDG uptake of the temporal artery in PET-CT confirmed that PET could detect vessel wall inflammation before significant changes in anatomical morphology. Therefore, PET can also show the extent of disease involvement earlier and more systematically. In addition, PET can also quantitatively display the inflammation level of the blood vessel wall, and different stages of the disease can be displayed as standard uptake values (SUV) of different degrees on PET, so as to better reflect the activity of the disease (16).

Notably, polyarticular synovitis and bursitis were also detected, suggesting PMR, which was overlooked in the initial clinical inquiry related to headache. PMR lacks specific diagnostic methods, and its diagnosis depends on clinical criteria and exclusion diagnoses. PET can not only detect the presence of GCA but also reveal the abnormal FDG uptake characteristic of PMR (17). The study by Yamashita et al. suggested that when PET showed that two or more parts of the ischial tubercle, greater trochanter, and lumbar spinous process were involved, the sensitivity and specificity of diagnosing PMR were 85.7 and 88.2%, respectively. The sensitivity and specificity of the

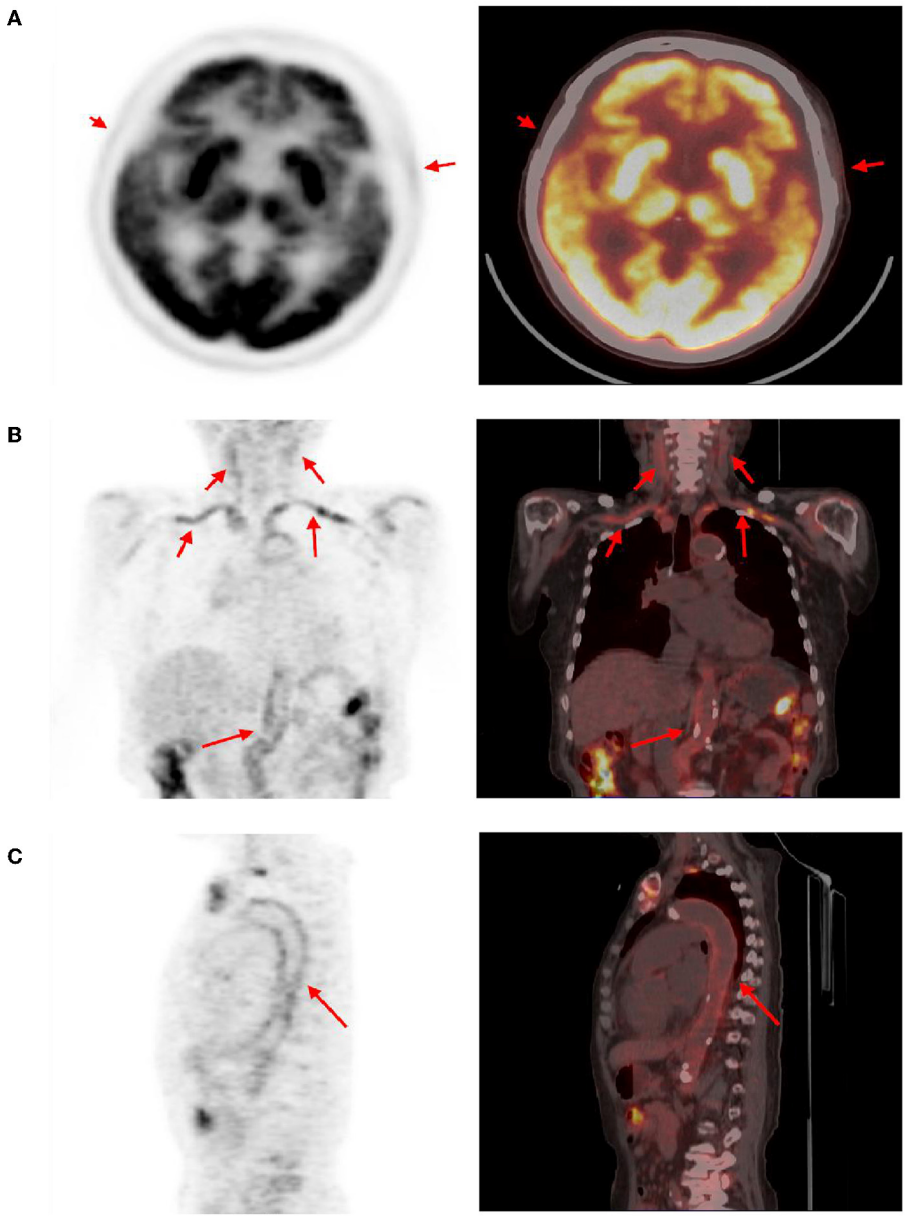

FIGURE 3
Abnormal findings of arteries in PET-CT. The temporal arteries **(A)**, subclavicular arteries, brachial trunk, axillary arteries, carotid arteries **(B)**, aortic arch, descending aorta, abdominal aorta **(C)**, and several other arteries showed an uneven increase in FDG uptake (red arrow, SUVmax distribution in 1.4–5.3), and corresponding CT showed slightly thicken vascular wall. Calcification can be seen in some artery walls.

lumbar spinous process alone can also reach 78.6 and 82.4%, respectively. Other parts, such as sternoclavicular joints, shoulder joints, elbow joints, wrist joints, hip joints, knee joints, and others, also have abnormal manifestations but lack specificity (18). Other studies have also summarized the PET imaging characteristics of PMR (19, 20). Compared to ultrasound, PET imaging results are more specific (21). In this case, several regions including the spinous process of the lumbar spine were involved. Based on the patient's clinical manifestations and hematological indicators, the diagnosis of GCA complicated with PMR was established (22). The patient's response to treatment also supports the diagnosis.

The diagnosis and the treatment process, in this case, were not perfect. It can be seen from the figure that the subject's brain tissue showed high uptake of 18F-FDG, while the walls of the cerebral arteries were too thin to be detectable against the background. The patient's MRA showed stenosis of the left middle cerebral artery, and there were many old lesions in the left cerebral hemisphere. Therefore, it was not clear whether the intracranial artery was involved. Kinoshita et al. reported a case of cerebral infarction caused by GCA with middle cerebral artery involvement. After 3 months of prednisolone therapy, the patient's middle cerebral artery stenosis improved (23). Perhaps follow-up observation or other imaging

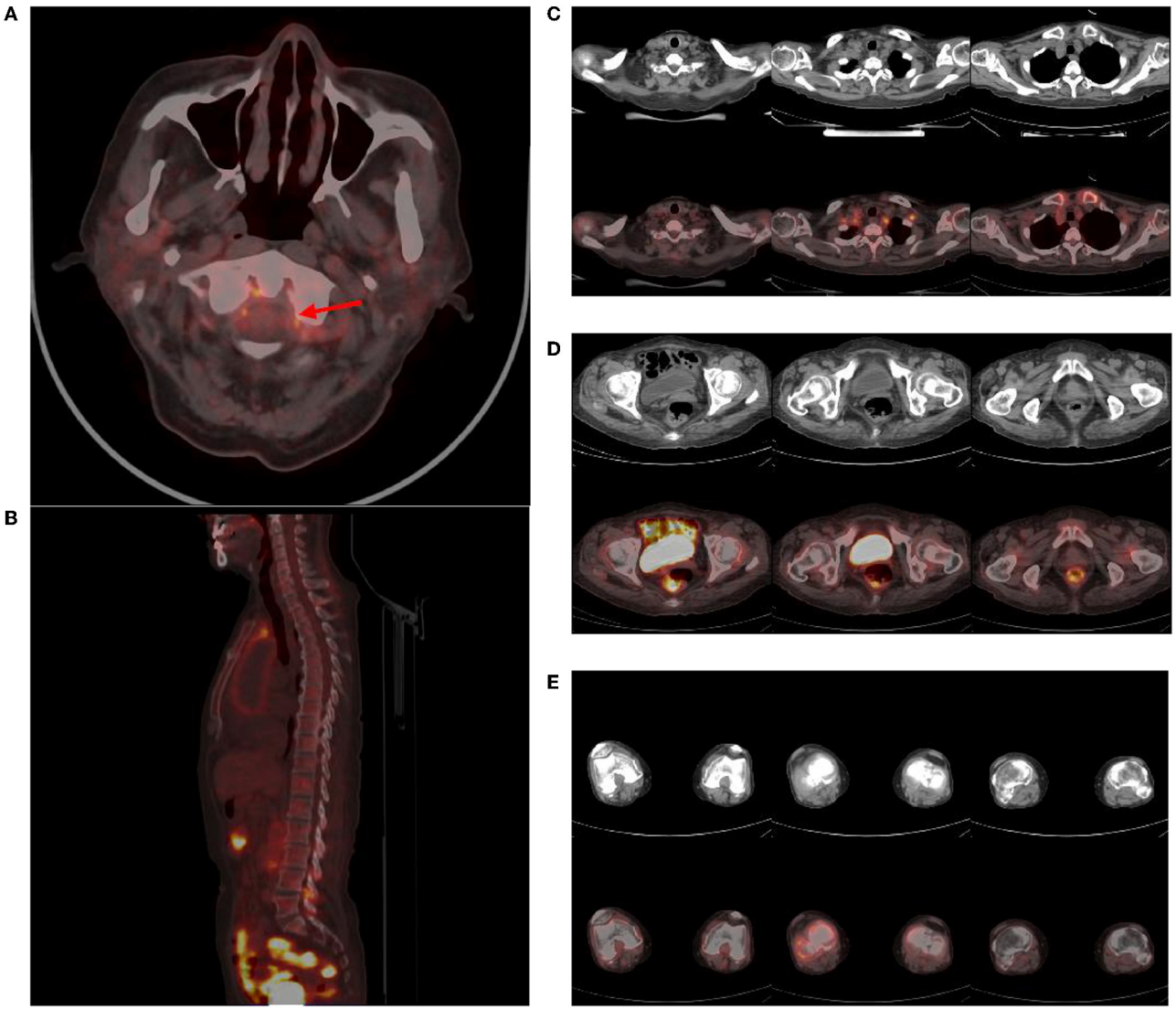

FIGURE 4
Abnormal findings of joints in PET-CT. Atlantoaxial joint (red arrow) **(A)**, lumbar spinous processes **(B)**, sternoclavicular and shoulder joints **(C)**, hip joints **(D)**, knee joints **(E)**, and several other regions showed an increase in FDG uptake (SUVmax: 4.2), and corresponding CT showed synovial thickening or bursae enlargement.

examinations, such as a high-resolution MRI angiogram, can make up for the defect of PET in the evaluation of intracranial blood vessels.

PET has certain advantages in assisting the diagnosis of GCA and PMR, such as higher sensitivity and specificity, quantitative evaluation of the inflammation level, and evaluation of the disease extent involved. Of course, factors such as high costs and radiation exposure also limit its promotion. Although it cannot be used as a routine inspection, PET can become a powerful tool for diagnosis when the TAU result is negative and the TAB is not agreed upon.

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 humans were approved by the Ethics Committee of Peking University People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HJ, ZL, and HG contributed to the conception and design of the study. DW wrote the initial manuscript. XZ, LP, and MC contributed to the clinical analysis. LY contributed to the imaging

analysis. HJ contributed to the manuscript's revision. All authors read and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

References

1. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. *N Engl J Med.* (2003) 349:160–9. doi: 10.1056/NEJMra022694

2. Sharma A, Mohammad AJ, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: a systematic literature review. *Semin Arthritis Rheum.* (2020) 50:1040–8. doi: 10.1016/j.semarthrit.2020.07.005

3. Lacy A, Nelson R, Koyfman A, Long B. High risk and low prevalence diseases: giant cell arteritis. *Am J Emerg Med.* (2022) 58:135–40. doi: 10.1016/j.ajem.2022.05.042

4. Kermani TA, Warrington KJ. Polymyalgia rheumatica. *Lancet.* (2013) 381:63–72. doi: 10.1016/S0140-6736(12)60680-1

5. Ward TN, Levin M. Headache in giant cell arteritis and other arteritides. *Neurol Sci.* (2005) 26(Suppl. 2):s134–7. doi: 10.1007/s10072-005-0426-5

6. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* (1990) 33:1122–8. doi: 10.1002/art.1780330810

7. Ponte C, Grayson PC, Robson JC, Suppiah R, Gribbons KB, Judge A, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. *Ann Rheum Dis.* (2022) 81:1647–53. doi: 10.1136/ard-2022-223480

8. Noumegni SR, Hoffmann C, Cornec D, Gestin S, Bressollette L, Jousse-Joulin S. Temporal artery ultrasound to diagnose giant cell arteritis: a practical guide. *Ultrasound Med Biol.* (2021) 47:201–13. doi: 10.1016/j.ultrasmedbio.2020.10.004

9. Greigert H, Ramon A, Tarris G, Martin L, Bonnotte B, Samson M. Temporal artery vascular diseases. *J Clin Med.* (2022) 11:275. doi: 10.3390/jcm11010275

10. Fernandez-Fernandez E, Monjo-Henry I, Bonilla G, Plasencia C, Miranda-Carus ME, Balsa A, et al. False positives in the ultrasound diagnosis of giant cell arteritis: some diseases can also show the halo sign. *Rheumatology.* (2020) 59:2443–7. doi: 10.1093/rheumatology/kez641

11. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis.* (2018) 77:636–43. doi: 10.1136/annrheumdis-2017-212649

12. Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt WA, Ramiro S. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. *RMD Open.* (2018) 4:e000612. doi: 10.1136/rmdopen-2017-000612

13. Gribbons KB, Ponte C, Craven A, Robson JC, Suppiah R, Luqmani R, et al. Diagnostic assessment strategies and disease subsets in giant cell arteritis: data from an international observational cohort. *Arthritis Rheumatol.* (2020) 72:667–76. doi: 10.1002/art.41165

14. Rubenstein E, Maldini C, Gonzalez-Chiappe S, Chevret S, Mahr A. Sensitivity of temporal artery biopsy in the diagnosis of giant cell arteritis: a systematic literature review and meta-analysis. *Rheumatology.* (2020) 59:1011–20. doi: 10.1093/rheumatology/kez385

15. Slart R, Writing Group, Reviewer Group, Members of EANM Cardiovascular, Members of EANM Infection & Inflammation, Members of Committees, SNMMI Cardiovascular, et al. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. *Eur J Nucl Med Mol Imaging.* (2018) 45:1250–69. doi: 10.1007/s00259-018-3973-8

16. Tezuka D, Haraguchi G, Ishihara T, Ohigashi H, Inagaki H, Suzuki J, et al. Role of FDG PET-CT in Takayasu arteritis: sensitive detection of recurrences. *JACC Cardiovasc Imaging.* (2012) 5:422–9. doi: 10.1016/j.jcmg.2012.01.013

17. Kubota K, Yamashita H, Mimori A. Clinical value of FDG-PET/CT for the evaluation of rheumatic diseases: rheumatoid arthritis, polymyalgia rheumatica, and relapsing polychondritis. *Semin Nucl Med.* (2017) 47:408–24. doi: 10.1053/j.semnuclmed.2017.02.005

18. Yamashita H, Kubota K, Takahashi Y, Minaminoto R, Morooka M, Ito K, et al. Whole-body fluorodeoxyglucose positron emission tomography/computed tomography in patients with active polymyalgia rheumatica: evidence for distinctive bursitis and large-vessel vasculitis. *Mod Rheumatol.* (2012) 22:705–11. doi: 10.3109/s10165-011-0581-x

19. Wakura D, Kotani T, Takeuchi T, Komori T, Yoshida S, Makino S, et al. Differentiation between polymyalgia rheumatica (PMR) and elderly-onset rheumatoid arthritis using 18F-fluorodeoxyglucose positron emission tomography/computed tomography: is enthesitis a new pathological lesion in PMR? *PLoS ONE.* (2016) 11:e0158509. doi: 10.1371/journal.pone.0158509

20. Takahashi H, Yamashita H, Kubota K, Miyata Y, Okasaki M, Morooka M, et al. Differences in fluorodeoxyglucose positron emission tomography/computed tomography findings between elderly onset rheumatoid arthritis and polymyalgia rheumatica. *Mod Rheumatol.* (2015) 25:546–51. doi: 10.3109/14397595.2014.978936

21. Caporali R, Montecucco C, Epis O, Bobbio-Pallavicini F, Maio T, Cimmino MA. Presenting features of polymyalgia rheumatica (PMR) and rheumatoid arthritis with PMR-like onset: a prospective study. *Ann Rheum Dis.* (2001) 60:1021–4. doi: 10.1136/ard.60.11.1021

22. Dasgupta B, Cimmino MA, Kremers HM, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 Provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Arthritis Rheum.* (2012) 64:943–54. doi: 10.1016/j.ymed.2012.09.009

23. Kinoshita A, Otsuka Y, Deguchi K, Wakabayashi H. Giant cell arteritis of the middle cerebral artery. *BMJ Case Rep.* (2022) 15:318. doi: 10.1136/bcr-2022-250318

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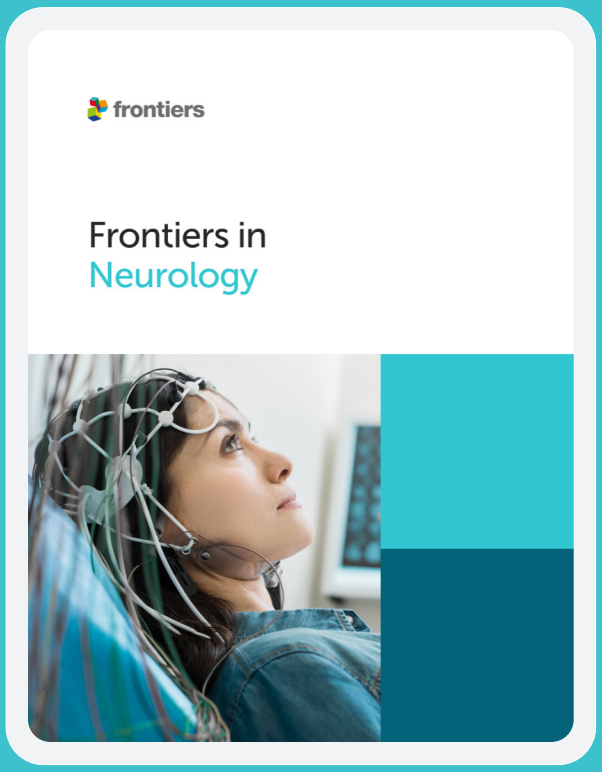

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