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Vestibular disorders in children

Edited by
Jun Yang, Maoli Duan, Klaus Jahn, Toshihisa Murofushi, Lisheng Yu and Qing Zhang

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Vestibular disorders in children

Topic editors

Jun Yang — Shanghai Jiaotong University School of Medicine, China
Maoli Duan — Department of Clinical Science, Intervention and Technology, Karolinska Institutet (KI), Sweden
Klaus Jahn — Schoen Clinic Bad Aibling - Dept. of Neurology, Germany
Toshihisa Murofushi — Teikyo University Mizonokuchi Hospital, Japan
Lisheng Yu — Peking University People's Hospital, China
Qing Zhang — Shanghai Jiaotong University School of Medicine, China

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EDITED AND REVIEWED BY
Michael Strupp,
Ludwig Maximilian University of Munich, Germany

*CORRESPONDENCE
Jun Yang
✉ yangjun@xinhuamed.com.cn
Maoli Duan
✉ maoli.duan@ki.se

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Editorial: Vestibular disorders in children

Jun Yang[1,2,3]*, Yupeng Liu[1,2,3], Qing Zhang[1,2,3], Lisheng Yu[4], Toshihisa Murofushi[5], Klaus Jahn[6,7] and Maoli Duan[8,9]*

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China, [4]Department of Otorhinolaryngology-Head and Neck Surgery, People's Hospital of Peking University, Beijing, China, [5]Department of Otolaryngology, Teikyo University School of Medicine, Mizonokuchi Hospital, Kawasaki, Japan, [6]German Center for Vertigo and Balance Disorders, Ludwig-Maximilians-University, Munich, Germany, [7]Department of Neurology, Schön Klinik, Bad Aibling, Germany, [8]Ear Nose and Throat Patient Area, Trauma and Reparative Medicine Theme, Karolinska University Hospital, Stockholm, Sweden, [9]Division of Ear, Nose and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

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Editorial on the Research Topic
Vestibular disorders in children

Introduction

Due to the limitation of children's expression ability and the lack of diagnostic experience in pediatricians, vestibular disorders in children are often overlooked, and the prevalence of vestibular disorders in children have been underestimated. An epidemiologic study on the American children revealed that prevalence of dizziness and balance problems was 5.3%, and only 29.9% of them received treatment (1). Vestibular disorders in children have left a lot of confusion for clinicians in many years. Causes of vertigo in children include recurrent vertigo of childhood (RVC), vestibular migraine (VM), Meniere's disease, vestibular neuritis, concussion, inflammation and tumors in the central nervous system, hereditary ataxia, and epileptic vertigo, etc. Peripheral vertigo was more common than central vertigo and other causes of vertigo in children. RVC and VM were the most common diagnosis in peripheral vertigo and central vertigo, respectively. However, persistence of RVC attacks during adolescence could lead to a high prevalence of VM (2, 3). There are three major differences between adult and pediatric patients. Firstly, parents often ignore the manifestations of children's vertigo, and think that they are unwilling to cooperate or mischievous. Secondly, due to the limitation of expression ability and, the complexity of vertigo and accompanying symptoms, it is usually difficult for children to correctly express the characteristics of vertigo. Thirdly, the frequency of occurrence is very different between adults and children for a specific etiology. On the other hand, children with sensorineural hearing loss (SNHL) often suffer from vestibular dysfunction (VD) simultaneously. Around 20–85% of children with SNHL are accompanied by either unilateral or bilateral VD, which is usually an independent factor leading to motor retardation or dysplasia. The incidence of vertigo is increasing, which has become a hot topic in clinical research. Therefore, it is necessary to discuss the diagnosis and treatment of vestibular disorders in children separately. This Research Topic "Vestibular Disorders in Children" consists of nine original articles, one systematic review and one review. We summarized these articles within the following categories: Diagnostic Tools,

Common Diseases, and Cochlear implantation and Vestibular Function. Further understanding of the prevalence of various types of vestibular disorders in children, their characteristics, and their management through this Research Topic will benefit pediatric patients and their families, thus decreasing the economic load for the society.

Diagnostic tools

Vestibular function tests have a great diagnostic value in children with vestibular impairment or vertigo. Vestibular evoked myogenic potential (VEMP) is a myogenic potential recorded on the surface of sternocleidomastoid muscle, eye muscle and other muscles under the condition of strong short sound and vibration stimulation. It is generally believed that the neck muscles of 6-month-old infants have sufficient muscle tension to control head movement, and the results of cervical VEMP (cVEMP) tests at this stage are reliable. Ocular VEMP (oVEMP) can be completed in children over 3 years old (4). Shen et al. concluded that the air conduction and bone conduction cVEMP eliciting rates of 3-month-old infants with normal hearing were 88.89% and 100%, respectively, indicating that stable cVEMP waveforms could be obtained at 3-month-old. They also compared the cVEMP characteristics of 3-month-old sensorineural hearing loss (SNHL) infants and normal hearing infants of the same age. The results showed that the elicited rate of air conduction cVEMP in the SNHL group was lower than that in the normal hearing group. Thereby, they raised the feasibility that cVEMP might be a reliable screening tool for vestibular function in infant. Xiao et al. investigated the effects of acoustic stimulation intensity on oVEMP and cVEMP responses elicited by air-conducted sound (ACS) in healthy children. They concluded that 121 dB SPL can be considered a safe stimulus level for children aged 4–10 years for VEMP testing, while reducing noise exposure. The two papers indicated that VEMP is a non-invasive and well-tolerated test and the parameters established in these studies can provide a reference for the promotion of clinical vestibular function tests.

Common diseases

The most common diseases causing dizziness and vertigo in children are recurrent vertigo of childhood (RVC) and vestibular migraine (VM). The pathogenesis of RVC is still unclear. According to the diagnostic criteria of Barany society, the diagnosis of RVC is an exclusion criterion of clinical symptoms, lacking the support of other clinical examinations (5). Therefore, high-quality clinical researches on the pathogenesis, clinical features, treatment, and prognosis of RVC are critical for better understanding of such disease entity. Dunker et al. summarized the clinical features and prognosis of RVC in a study of 42 cases. They concluded that age of onset is later and the frequency of attacks is higher in female patients. 45.8% of patients had spontaneous remission of symptoms after 3.5 years of follow-up. The frequency of RVC can be significantly reduced with the correct preventive measures. The study also indicated that few RVC patients showed pathologic findings in ocular motor examinations, head impulse test and VEMP. However, Sun et al. first applied galvanic vestibular stimulation (GVS) VEMP in the research of RVC. They founded that the latencies of ACS-cVEMP and GVS-cVEMP in RVC patients were prolonged compared with normal children. This result suggested that there may be potential damage to the inferior vestibular nerve and its subsequent nerve conduction pathways in RVC patients. They speculated that the retro-labyrinthine portion and lower brainstem along the sacculo-collic reflex pathway were impaired in RVC patients. Rehabilitation is important in RVC patients with vestibular function impairment. Li et al. evaluate the effectiveness of Vestibulo-Ocular Reflex (VOR) adaptation training in RVC patients. They proposed that VOR adaptation training can relieve vertigo symptoms effectively, and it is more acceptable for children when compared with Cawthorne-Cooksey training.

VM is the second most common vestibular disorder in children. Although VM is considered to be a central vestibular disorder, peripheral vestibular organs may also be damaged. Zhang et al. investigated the damage of peripheral vestibular organs in 22 VM children. The results revealed that the superior vestibular nerve and its nerve conduction pathway are possibly damaged in some of the patients. Li et al. concluded that when compared with RVC patients, children with VM younger than 12 years old are more dependent on visual signals when maintaining body balance, and their central nervous system have poorer ability to integrate surrounding information. Episodic ataxias (EA) is a less frequent vestibular disorder in children than RVC and VM. Overlap syndromes among EA, RVC and VM sometimes make it difficult for the clinicians to get an accurate diagnosis. Filippopulos et al. proposed a diagnostic criterion which can help clinicians identify EA patients in children and adolescents. However, the sensitivity and specificity of the criterion need to be further investigated. Concussion may also lead to vestibular syndromes including dizziness and balance impairments. Alkathiry et al. confirmed that The Gait Disorientation Test (GDT) can help clinicians to distinguish between children with concussion and healthy children.

Cochlear implantation and vestibular function

Due to the close anatomical relationship between the cochlea and vestibule, cochlear implantation (CI) may affect the vestibular function of patients. In the past years, most clinicians paid more attention to the outcome of speech rehabilitation, however, although not many, some studies have noted the vestibular function of patients. The vestibular function of children is inevitably affected after CI (6). Wu et al. conducted a systemic review with 20 clinical studies on the vestibular function changes in children after CI. The results showed a significant increase in abnormal cVEMP, oVEMP and caloric response. A poor Bruininks-Oseretsky Test 2 score was also observed in children after CI, which indicated that static and dynamic balance were also impaired in these children. Deng et al. made a review on the impact and evaluation of vestibular function in children with CI. They summarized the factors which may be associated with postoperative vestibular function change including gender, age, surgical side selection and electrical stimulation, etc. They also proposed valuable strategies

from preoperative evaluation to postoperative intervention for children with CI.

Conclusion

Vestibular disorder in children has its own characteristic, such as difficulty in taking medical history and difficulty in cooperating with some vestibular function tests, etc., and the history of the disease is very important for clinical diagnosis and treatment. Clinicians should be familiar with the common causes of vertigo in children to make the differential diagnosis and reduce unnecessary supplementary examinations. The basic principle of treatment for children with vertigo is to eliminate the cause, relieve vertigo and other accompanying symptoms, and vestibular rehabilitation.

Author contributions

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

Conflict of interest

KJ was employed by Schön Klinik.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Klaus Jahn,
Schoen Clinic Bad Aibling, Germany

REVIEWED BY
Alessandro Capuano,
Azienda Sanitaria Locale di Viterbo, Italy
Francesca Felicia Operto,
University of Salerno, Italy

*CORRESPONDENCE
Abdulaziz A. Alkathiry
a.alkathiry@mu.edu.sa

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Validation of the Gait Disorientation Test in children with concussion

Abdulaziz A. Alkathiry[1]*, Saud F. Alsubaie[2], Bara A. Alsalaheen [3] and Susan L. Whitney[4]

[1]Department of Physical Therapy and Health Rehabilitation, Majmaah University, Majmaah, Saudi Arabia, [2]Department of Physical Therapy and Health Rehabilitation, College of Applied Medical Sciences in Al-Kharj, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia, [3]Department of Physical Therapy, College of Health Sciences, University of Michigan-Flint, Flint, MI, United States, [4]Department of Physical Therapy, School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, PA, United States

Background: Mild traumatic brain injury (mTBI) or concussion is a complex injury that is difficult to diagnose and assess. There are negative impacts on cognition, balance, and mobility after a concussion. The Gait Disorientation Test (GDT) is an objective measure that assesses a person's balance ability by comparing the walking time with eyes open and the walking time with eyes closed in a standardized walking task. The purpose of this study was to assess the validity and the diagnostic properties of the GDT in children with concussions.

Methods: Thirty-six children with concussions, and 91 controls aged between 9 and 18 years old participated in the study. Participants completed demographics, the GDT, the Functional Gait Assessment (FGA), the Pediatric Vestibular Symptom Questionnaire (PVSQ), and the Pediatric Visually Induced Dizziness Questionnaire (PVID).

Results: Children with concussions showed higher (worse) GDT scores ($M = 2.18 \pm 1.93$ s) than healthy controls ($M = 1.13 \pm 0.95$ s), which was statistically significant ($P = 0.014$).

Conclusion: The GDT was able to distinguish between children with concussions and healthy controls. Given the simplicity of the GDT, it can be used to assist in discriminating between children with and without concussion.

KEYWORDS

Gait Disorientation Test, concussion, children, gait speed, balance, mild TBI (mTBI)

Introduction

A concussion is a common brain injury, which may lead to multiple health impairments including physical and cognitive symptoms, such as headache, dizziness, balance impairments, and visual problems (1, 2). In the last decade, concussion awareness has increased in the medical community and has largely focused on adult injuries (3). Several studies indicated that adolescents are more likely to develop concussions compared to adults (4, 5). Previous studies have found that concussion injuries have a negative impact on cognition, balance, and mobility, which recover at

different rates post-concussion (6, 7). Utilizing a functional performance test, as a part of a comprehensive examination of a concussion, may enable health clinicians to better determine the trajectory of recovery following a concussion (8–11). A recent study suggested a new measure, the Gait Disorientation Test (GDT), which is the difference in the time needed to finish a 20-feet walking task between performing the task with eyes open and eyes closed (12). The GDT has been shown to possess excellent discriminative ability to distinguish between adults with vestibular impairments and normal adults.

The purpose of this study was to assess the validity and the diagnostic properties of the GDT in children with and without concussions.

Methodology

Thirty-six children with concussion/mTBI and 91 controls between 9 and 18 years of age participated in the study. Participants with concussions who were seeking medical attention for their concussion were recruited after a neurologic and neuro-otologic examination from a tertiary balance center at the University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, USA. Controls were recruited from middle and high schools in Pittsburgh, PA, USA. Informed consent was obtained from all participants and their guardians. The study was approved by the institutional review board from the University of Pittsburgh and was conducted in accordance with the Declaration of Helsinki.

Participants from both groups completed demographics and the Functional Gait Assessment (FGA), which is a performance-based test that include 10 walking and stair-climbing tasks (13). The performance of each task is rated by the test administrator from 0 to 3 using specific criteria for each score. The FGA total score is calculated by adding the scores of all the tasks and ranged from 0 to 30, with higher scores indicating better performance. The children with concussions completed the Pediatric Vestibular Symptom Questionnaire (PVSQ), which is a self-reported questionnaire comprising 11 questions about the frequency of vestibular symptoms during the past month using a 4-point Likert scale that ranged from "never" to "most of the time"(14). The total score of PVSQ ranged from 0 to 3 with a higher score indicating worse symptoms. The PVSQ score is a normalized score that is calculated by adding all scores from the answered questions divided by the number of questions answered. The cut-off score of the PVSQ to discriminate between healthy children and children with vestibular impairments was found to be $\geq$0.68 (14).

The Pediatric Visually Induced Dizziness Questionnaire (PVID) is a self-reported questionnaire comprising 11 questions about the frequency of feeling dizzy and unsteady in different places and situations during the past month using a 4-point Likert scale that ranged from "never" to "most of the time"(15). The total score of the PVID ranged from 0 to 33 with higher scores indicating worse symptoms. The PVID score is normalized by dividing the total score by the number of questions answered. The cut-off score of the PVID to discriminate between healthy children and children with vestibular impairments was found to be $\geq$0.45 (15).

The GDT is measured in seconds and was calculated by subtracting the time needed to complete the 10-m gait speed test with eyes closed (GS-EC) and the time needed to complete the normal 10-m gait speed test with eyes open (GS). Both GS and GS-EC were timed during the FGA tasks similar to Grove et al. (12, 13). All investigators participated in the data collection of healthy participants. The main investigator performed all the testing and recruitment for the participants with concussions.

Statistical analysis

Outcomes were tested using the Shapiro–Wilk test of normality of the distribution to determine the appropriate statistical methods. Descriptive data were reported with the appropriate statistical methods using means and standard deviations, median and interquartile ranges, or frequency and percentages. Comparisons between children with and without concussion were performed using independent sample *t*-tests or the Man–Whitney *U*-test. Group comparisons were further examined using a one-way ANCOVA to adjust for age, gender, and height differences. The GDT, GS, and GS-EC were tested, as appropriate, using Person or Spearman correlation coefficients against the FGA, PVSQ, and PVID to assess their concurrent validity. The receiver operator characteristic (ROC) analysis was used to assess the diagnostic ability of GDT, GS, and GS-EC to discriminate between the concussed and control children. The optimal cut-off values were calculated using Youden's Index (16). The cut-off values were used to produce the contingency tables for the GDT, GS, and GS-EC. The contingency tables were used to calculate the specificity, the sensitivity, the Positive Likelihood Ratio (LR+) and Negative Likelihood Ratio (LR–), and the Diagnostic Odds Ratio (DOR). Statistical analysis was performed using SPSS. Youden's Index, specificity, sensitivity, LR+, LR–, and DOR were calculated using Microsoft Excel.

Results

Thirty-six children with concussion/mTBI aged between 9 and 17 years old (m = 14.2, SD = 2.4 years) and 91 healthy children aged between 14 and 18 years old (m = 15.6, SD = 1.1 years) completed the study. Significant differences between groups were found in age, weight, and height (P <0.01; Table 1).

Children with concussion were recruited 4–434 days after injury [interquartile range (IQR) = 115 days; m = 130.1; SD = 144.5 days]. Twenty-four (67%) children with concussions

TABLE 1 Characteristics of healthy and concussed children.

	Concussion $n = 36$ M (SD)	Healthy $n = 91$ M (SD)	P-value
Age^	14.22 (2.42)	15.62 (1.05)	0.009**
Gender (Male, %)#	12 (33%)	47 (52%)	0.062
Weight (Kg)^	55.66 (17.95)	63.41 (14.66)	0.002**
Height (cm)	159.81 (13.76)	169.26 (8.43)	<0.001**
BMI^	21.29 (4.00)	22.06 (4.49)	0.409

^Mann-Whitney U-test.
#Chi square.
**$P < 0.01$.
BMI, Body Mass Index.

reported having symptoms of dizziness, 17 children reported spinning sensation (47%), and 17 children reported migraine (47%). Thirty-four (94%) children with concussion tested positive on the PVSQ [$m = 1.21$, SD = 0.44] or the PVID [$m = 1.38$, SD = 0.81] tests using the cut-off scores reported for children with concussion (14, 15). Children with concussions reporting dizziness demonstrated significantly worst performance on GS, GS-EC, GDT, and FGA than those without dizziness (Table 2).

Significant differences in the GDT score were found between children with concussion ($M = 2.18 \pm 1.93$ s) and healthy controls ($M = 1.13 \pm 0.95$ s; $P = 0.014$), indicating that children with concussion demonstrated larger changes compared to healthy controls in walking speed when walking with eye closed compared to eyes open. Gait speed did not differ between the groups ($P = 0.108$), while gait speed with eyes closed was significantly slower in children with concussions than healthy controls ($P < 0.001$). The FGA demonstrated a statistically significant difference between groups demonstrating better performance by the healthy controls ($P = 0.003$). Results from One-way ANCOVA showed that the GDT, the GS-EC, and the FGA were significantly different between the groups with better performance in the control group compared to the concussion group (Table 3).

One-way ANCOVA was conducted to determine a statistically significant difference between children with and without concussion on GDT, GS, GS-EC, and FGA controlling for age, height, and gender. There was a significant effect of the group after controlling for age, height, and gender on GDT, $F_{(1,122)} = 8.305$, $P = 0.005$; GS-EC, $F_{(1,122)} = 11.201$, $P = 0.001$; and FGA, $F_{(1,122)} = 5.600$, $P = 0.020$. There was no significant effect of group on GS after controlling for age, height, and gender, $F_{(1,122)} = 3.164$, $P = 0.078$ (Table 3).

The GDT, gait speed with eyes closed, and the FGA demonstrated significant differences between the groups and were further analyzed for their discriminant validity using ROC analyses. The optimal cut-off scores for the GDT, gait speed with eyes closed, and FGA were determined using the Youden's Index and were 1.5 s,0.9 m/s, and 28 points, respectively (Table 4). For a GDT threshold of 1.5 s, we found that the sensitivity and specificity were.58 and.77, respectively. The diagnostic odds ratio (DOR) = 4.67, LR+ = 2.53, and LR– = 0.54. Sensitivity, specificity, DOR, and positive and negative LRs are reported for gait speed with eyes closed and the FGA in Table 5.

In children with concussion, the GDT significantly correlated with the FGA demonstrating better outcomes with a decreased or smaller GDT ($P < 0.01$). Gait speed significantly correlated with the FGA, PVSQ, and PVID demonstrating better outcomes with increased gait speed ($P < 0.05$). Gait speed with eyes closed significantly correlated with the FGA and the PVID demonstrating better outcomes with faster gait speed while walking with eyes closed ($P < 0.01$). Time since injury did not show a significant correlation with the functional tests GS, GS-EC, GDT, and FGA or the questionnaires PVSQ and PVID (Table 6).

Discussion

The main findings were that children with concussion walked slower with eyes closed than controls, that gait speed with eyes open was not different between children with and without concussion, and that the GDT and GS-EC were equally able to discriminate between children with and without concussion. The GDT is an objective measure that assesses a person's balance ability by comparing walking time with eyes open and the walking time with eyes closed in a standardized walking task (12), providing a simple objective measure of the effect of eliminating visual input on a simple walking task. Maintaining balance is a complex task that involves the integration of three separate sensory systems: somatosensory, visual, and vestibular system. Normally, one can maintain balance with the removal of one sensory system, such as walking in a dark room. When there is damage or alteration in functioning of more than one postural control system, the effect on balance may be more evident. During the GDT, removing visual input forces the child to rely on vestibular and somatosensory inputs.

The GDT was able to distinguish between healthy subjects and participants with concussions, representing the accepted criterion-validity. This ability to distinguish those with a concussion is a cumulative addition to the measure's ability to differentiate between healthy people and those with vestibular hypofunction (12).

In this study, the average difference in GDT score between participants with a concussion and healthy controls was 2 s, which is less than the 6 s difference reported by 12 in persons with vestibular hypofunction. Howell et al. suggested that adding a cognitive component during walking tasks can demonstrate differences in the performance of the walking task between healthy and concussed adolescents. However, the GDT is

TABLE 2 A comparison of the GDT, GS, GS-EC, and FGA in children with concussion.

	Dizziness			Spinning			Migraine		
	Yes ($n = 24$)	No ($n = 12$)	*T*-test	Yes ($n = 17$)	No ($n = 19$)	*T*-test	Yes ($n = 17$)	No ($n = 19$)	*T*-test
GDT (s)	2.55 (2.22)	1.45 (0.88)	0.044*	2.32 (1.62)	2.06 (2.22)	0.686	2.15 (2.24)	2.21 (1.68)	0.931
GS (m/s)	1.09 (0.14)	1.27 (0.12)	<0.001**	1.12 (0.15)	1.18 (0.17)	0.316	1.12 (0.14)	1.18 (0.17)	0.234
GS-EC (m/s)	0.79 (0.21)	0.98 (0.12)	0.007**	0.82 (0.20)	0.89 (0.21)	0.324	0.83 (0.18)	0.87 (0.22)	0.582
FGA	26.83 (2.09)	28.58 (0.90)	0.002**	27.06 (2.56)	27.74 (1.56)	0.338	27.41 (1.78)	27.42 (2.39)	0.990

*$P < 0.05$. **$P < 0.01$. GDT, Gait Disorientation Test; GS, Gait Speed; GS-EC, Gait Speed with Eyes Closed; FGA, Functional Gait Assessment (optimal score is 30).

TABLE 3 A comparison of the GDT, GS, GS-EC and FGA in children with concussion and healthy controls.

	Concussion $n = 36$	Healthy $n = 91$	*T*-test	ANCOVA#
GDT (s)	2.18 (1.93)	1.13 (0.95)	0.014*^	0.005**
GS (m/s)	1.15 (0.16)	1.20 (0.16)	0.108	0.078
GS-EC (m/s)	0.85 (0.20)	1.00 (0.17)	<0.001**	0.001**
FGA	27.42 (2.09)	28.52 (1.39)	0.003**^	0.020*

#Adjusted for age, height, and gender.
^Mann-Whitney U-test.
*$P < 0.05$.
**$P < 0.01$.
GDT, Gait Disorientation Test; GS, Gait Speed; GS-EC, Gait Speed with Eyes Closed; FGA, Functional Gait Assessment (optimal score is 30).

utilizing a single-task testing approach (the elimination of vision), which may explain the small difference between the groups seen in this study (10, 12).

In addition to the GDT, walking with eyes closed and the FGA score were able to differentiate between healthy participants and participants with a concussion, whereas normal walking speed was not different between children with and without concussion. The GDT, walking with closed eyes, and the FGA include tasks that require the participant to close their eyes during walking, which forces a participant to rely more on the somatosensory and vestibular system, which may be affected because of the concussion injury (17). In contrast, normal walking was not able to differentiate between children with and without concussions. This may be due to the redundancy of sensory inputs that allow participants to rely on the visual and somatosensory systems when there is any reduction in vestibular inputs. Consistent with this finding, Brenker et al. found no differences in normal gait speed between adolescent athletes with and without concussion (8). Previous studies have reported that the vestibular system may be affected because of the concussive injury (18, 19).

Previous studies have compared differences in walking speed during various dual-task conditions with concussed and healthy adolescents (20, 21). Howell et al. (21) compared tandem walking speed with and without divided attention between youth athletes with and without and found that differences between groups were significant during the divided-attention-tandem walking but not during the undivided-attention-walking task. The findings of Howell et al. (21) were consistent with our findings, where there were differences in walking speed between groups walking with eyes closed. Previous studies showed that increasing the complexity of a functional task, such as normal gait speed, by adding a concurrent cognitive task or restricting the base of support (i.e., tandem walking), affects the performance of the task and enhances the tasks ability to discriminate between adolescents with and without concussion (20, 21).

Children with concussions who reported having dizziness demonstrated worse performance in all the functional tests in this study (i.e., GS, GS-EC, GDT, and FGA), while the presence of spinning sensation or migraine did not show differences in those functional tests. Consistent with this finding, Lue et al., in their study about the signs and symptoms that predict a protracted concussion recovery, found that between 12 different post-concussion signs and symptoms, only dizziness indicated a protracted recovery of concussion (22).

TABLE 4 Summary of ROC analyses.

Test	Threshold#	AUC (95% CI)	SE	*P*-value
GDT (s)	1.5	0.682 (0.574–0.790)	0.055	0.001**
GS (m/s)	1.3	0.594 (0.486–0.703)	0.056	0.089
GS-EC (m/s)	0.9	0.698 (0.592–0.804)	0.054	<0.001**
FGA	28	0.668 (0.563–0.772)	0.053	0.002**

#Youden's Index. *$P < 0.05$. **$P < 0.01$.
AUC, area under the curve; SE, standard error; GDT, Gait Disorientation Test; GS, Gait Speed; GS-EC, Gait Speed with Eyes Closed; FGA, Functional Gait Assessment.

TABLE 5 Diagnostic performance.

	TP	FP	FN	TN	Sn (95% CI)	Sp (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
GDT	21	21	15	70	0.58 (0.42–0.74)	0.77 (0.68–0.86)	2.53 (1.59–4.03)	0.54 (0.36–0.81)	4.67 (2.05–10.63)
GS	30	59	6	32	0.83 (0.71–0.96)	0.35 (0.25–0.45)	1.29 (1.05–1.59)	0.47 (0.22–1.03)	2.71 (1.02–7.20)
GS-EC	23	24	13	67	0.64 (0.48–0.80)	0.74 (0.65–0.83)	2.42 (1.59–3.69)	0.49 (0.31–0.77)	4.94 (2.17–11.27)
FGA	24	37	12	54	0.67 (0.51–0.82)	0.59 (0.49–0.69)	1.64 (1.17–2.30)	0.56 (0.34–0.92)	2.92 (1.30–6.56)

TP, true positive; FP, false positive; FN, false negative; TN, true negative; Sn, sensitivity; Sp, specificity; LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratio; CI, confidence interval; GDT, Gait Disorientation Test; GS, gait speed; GS-EC, gait speed with eyes closed; FGA, functional gait assessment.

TABLE 6 Correlation between the dependent variables for children with concussion/mTBI.

	Onset	GDT	GS-EC	GS
Onset		−0.281	0.187	0.148
FGA	0.215	−0.434**	0.686**	0.729**
PVSQ	−0.186	0.247	−0.319	−0.345*
PVID	0.072	0.354*	−0.459**	−0.345*

*$P < 0.05$.
**$P < 0.01$.
GDT, Gait Disorientation Test; GS, gait speed; GS-EC, gait speed with eyes closed; FGA, functional gait assessment; PVSQ, pediatric vestibular symptom questionnaire; PVID, pediatric visually induced dizziness questionnaire.

Limitations

Although GDT was able to distinguish between children with and without concussion, a more useful validation of the GDT is to assess the ability of the GDT to distinguish between children with different diagnoses. Time since the concussion is an important factor in managing individuals with a concussion. Although concussed participants in this study were from a wide range of injury onset, they were recruited while they were seeking medical intervention for their concussion symptoms (23–25).

Another limitation was the difference in gender between the children with a concussion and the healthy children. Although we managed to have an equal number of male and female children in the control group, we recruited all available children with concussions, which resulted in imbalanced gender distribution. However, the one-way ANCOVA analysis was used to adjust for demographic differences between the groups, and neither gender, height, nor age affected the differences in the GDT scores.

Conclusion

The GDT is a feasible, valid, and objective test to discriminate between children with and without concussions. It is a simple test that requires a stopwatch and a marked 20-ft hallway and can be performed within 1–2 min.

Data availability statement

IRB approval must be obtained from the University of Pittsburgh to share patients' information. Requests to access the datasets should be directed at: Abdulaziz Alkathiry, a.alkathiry@mu.edu.sa.

Ethics statement

The studies involving human participants were reviewed and approved by the institutional review board at the University of Pittsburgh, PA, USA. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Conceptualization and visualization: SW and AA. Data curation, methodology, validation, and writing: AA, SW, SA, and BA. Formal analysis: AA and SA. Project administration, software: AA. Resources and supervision: SW. 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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EDITED BY
Jun Yang,
Shanghai Jiaotong University School of Medicine, China

REVIEWED BY
Mario Sanna,
Gruppo otologico, Italy
Abdulrahman Hagr,
King Saud University Medical City, Saudi Arabia
Haibo Wang,
Shandong Provincial ENT Hospital, China

*CORRESPONDENCE
Weijing Wu
Weijwu@163.com

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Vestibular function in children with cochlear implant: Impact and evaluation

Jianhang Deng, Qianchen Zhu, Kangjia Zhang, Dinghua Xie and Weijing Wu*

Second Xiangya Hospital, Central South University, Changsha, China

Over the last 30 years, cochlear implant (CI) has been dedicated to improving the rehabilitation of hearing impairments. However, CI has shown potential detrimental effects on vestibular function. For children, due to atypical symptoms and difficulty in cooperating with vestibular function tests, systematic and objective assessments of vestibular function with CI have been conducted sparsely. This review focuses on the impact of vestibular function in children with CI and summarized the evaluation of vestibular function in children. In addition, some recommended strategies are summarized and proposed.

KEYWORDS

cochlear implant, vestibular function, children, malformation, recommended strategies

Introduction

In the last decades, children with bilateral severe to profound sensorineural hearing loss (SNHL) have benefited greatly from cochlear implants (CI). While the effects of CI surgery on residual cochlear function have been studied more frequently, its effects on vestibular function have received less attention.

Clinical studies have shown a 2–35% incidence of vertigo and a 20–80% incidence of vestibular abnormalities in postoperative CI patients (1). Some scholars believe that patients with CI will develop symptomatic or asymptomatic vestibular impairment sooner or later (2).

CI can cause vestibular impairment by direct damage to vestibular sensory structures, disruption of fluid balance in the inner ear, inflammatory response, or direct electrical stimulation, according to Handzel et al. (3). The normal motor development of newborns and children, as well as optimal motor skill in preschool and school-age children, is dependent on the activity of the inner ear balance organ (vestibular organ). When compared to children without vestibular dysfunction, children with vestibular dysfunction have delayed development of gross motor milestones such as standing and walking (4). We firmly believe that vestibular examination is critical for patients because of its impact on their early development. Vestibular function testing in children can be challenging for a variety of reasons. Children have limited communication skills, atypical symptoms, difficulty recognizing their symptoms are abnormal, short attention span, and sometimes nausea and vomiting reactions (5). Various clinical strategies for adapting vestibular testing to children have been proposed since the 1980s. The most commonly

reported approaches to date are minimized caloric irrigations, adapted rotational tests, video-assisted head impulse test techniques (vHIT), and vestibular evoked myogenic potentials (VEMP) (6).

In this paper, we analyze the factors that cause changes in vestibular function after CI surgery and summarize the assessment methods of vestibular function and vestibular rehabilitation patterns in children with CI. Meanwhile, we explore the outcomes of CI on vestibular function and the selection of corresponding diagnosis and treatment strategies.

Impact of vestibular function in children with cochlear implant

Mechanisms of vestibular function changes due to cochlear implant surgery

Several mechanisms that cause vestibular impairment have been reported, damage to the vestibular end organs may occur as a result of direct trauma caused by possible misalignment of the electrode insertion into the vestibular steps, electrical stimulation of the vestibular organs by the implant, intraoperative perilymphatic deficit, endolymphatic flow disturbance generating endolymphatic edema, and foreign body reaction with labyrinthitis or vestibular fibrosis (7–10). Histopathological studies of the temporal bone after cochlear implantation show cochlear effusion with collapsed vesicles in more than half of the cases (3). Another common finding is the incorrect insertion of electrode arrays in the vestibule (11).

Because of its proximity to the electrode insertion path, the saccule is thought to be more vulnerable to damage than the utricule or semicircular canal, and this proximity may make the saccule more susceptible to surgical injury in the presence of electrode insertion, drilling, or changes in the fluid environment of the inner ear (12, 13).

Different surgical accesses have also been reported to have different effects on vestibular function. Yoon et al. (14) divided the patients into two groups according to surgical access: the cochleostomy group and the round window implant group. Patients in the round window implant group had a lower risk of postoperative vertigo (5.5%) than those in the cochleostomy group (8.8%). Several other studies have shown the round window approach was more beneficial to the protection of vestibular function (15). However, the results of different studies on the surgical approach are currently mixed, and more relevant studies are still needed.

Symptoms of vestibular hypofunction in children

Visual abnormalities, torticollis, clumsiness, recurrent vomiting, episodic spontaneous bouts of dizziness, vegetative lethargy, otalgia, headache, ataxia, lack of postural control, delay in gross motor skills, or learning or reading impairments all common symptoms of vertigo in children (16). In the pediatric population, vertigo and imbalance are frequently underestimated or ignored. Firstly, Children have difficulty expressing abnormal sensations of vertigo, dizziness, or imbalance, adding a layer of complexity to the diagnosis. Secondly, the differential is complicated and distinct from adult vertigo, making it difficult to diagnose. Thirdly, children can usually adapt very quickly and compensate for the lack of vestibular loss, probably as a result of their neuroplasticity and the stability of other sensory input systems, resulting in a short and insignificant duration of symptoms (17).

Besides, in the majority of studies, self-perceived symptoms of vertigo often differ from objective test results. One reason is that most studies have used only one or a few methods of vestibular function detection, making it difficult to analyze the full complexity of the vestibular apparatus as no single vestibular function examination can provide a complete assessment of vestibular function. Another explanation is that while objective testing shows vestibular impairment, central compensation may reduce vertigo symptoms, or that vestibular organ damage is too mild to be detected. In addition, it has also been suggested that psychological factors such as anxiety and depression may be responsible for the disagreement (18).

Consequently, children's vertiginous complaints are often overlooked, erroneously diagnosed as clumsiness, or attributed to behavioral disorders (16). A complete history, standardized questionnaires, routine physical examination, imaging, and even more advanced tests are all required for the diagnosis of pediatric vestibular disorders (19).

Factors influencing postoperative changes in vestibular function

The following factors may be associated with the development of postoperative vertigo: (1) gender; (2) age; (3) surgical side selection; (4) electrical stimulation; (5) inner ear malformation; (6) structural factors

Gender

Data on the relationship between gender and auditory vestibular disorders remain inconclusive. Clinical data suggest that gender may be a potential causative factor in auditory vestibular disorders. Anatomical differences in the inner ear exist between males and females, and physiological and/or hormonal influences between the sexes can produce different clinical findings on audiological and vestibular tests. Besides, Meniere's disease, BPPV, and other vestibular disorders are considered to be related to estrogen levels (20).

Age

Age diversity may cause differences in the results of various vestibular tests.

A meta-analysis showed that only 1.7% of children with CI had postoperative vertigo, compared with 31.3% of patients in the adult CI population (1). The reason for this may be that the child's vestibular function is more compensatory, or the child may not be able to represent their symptoms. The immaturity of central inhibitory vestibulo-ocular reflex regulation, cerebellar control, central vestibular adaptation, and visual-vestibular interactions may explain the much greater levels of rotational gain in children compared to adult normative data (21, 22).

For cVEMP, when pediatric data were compared to adult standards, it was discovered that children had significantly shorter P1 and N1 latencies and larger interpeak amplitudes (23) which could be explained by structural differences (24, 25). Besides, it was reported that N1 latency was significantly positively correlated with age, whereas the threshold parameter was significantly negatively correlated (5). While according to Picciotti et al. (26), no age trends were observed for latency parameters. Kelsch et al. (23) also covered a significant N1 latency extension. These differences may be partly related to differences in test protocols and the equipment used.

Toward the rotatory test, different studies have reached opposite conclusions. Charpiot et al. (27) reported decreasing gain values with increasing age. However, Maes et al. (5) showed no discernible age trends were remarkable for the rotatory test.

There are conflicting findings regarding whether the increase in vHIT in children varies with age. Lower gain values have been observed in children under the age of three, with a quick increase in vHIT gain up to the age of six, and then a slower increase up to the age of sixteen. In addition, with age, the variability of vHIT gain decreases (28). From the age of sixteen, vHIT increase appears to remain stable until the eighth or ninth decade, when it begins to fall (29–31).

The effect of age on vestibular function is inconclusive and still needs further study.

Bilateral and contralateral cochlear implant

As the use of bilateral implants grows, it will be critical to understanding the effects of bilateral CI surgery on the vestibular system, which will be beneficial to both the CI team and the patient. Guan et al. (32) believes no remarkable differences in the abnormality rate between children with first- and second-sided CI implantation 1 month after CI, demonstrating that the effects of unilateral and bilateral sequential CI on vestibular function are similar. The VEMP, on the other hand, revealed that children implanted with a second-side CI had a higher rate of anomalies than children implanted with a first-side CI. This might be explained by the ceiling effect, as these children's vestibular functions had already been harmed by the initial CI. In the case of vHIT, no statistically significant difference in abnormality rates existed before and after implantation, which was in line with earlier findings (33). According to Abouzayd et al. (34) no significant differences in aberrant rates after CI were found between first-side CI-implanted adults and children, or between first- and second-side CI-implanted children, implying that vestibular function abnormalities caused by CI surgery may be independent of age at CI and CI access (unilateral or sequential bilateral).

There were no significant variations in DHI and PVSQ ratings between adults and children pre-and post-implantation for unilateral CI, according to the vertigo questionnaire (32). PVSQ scores in children with bilateral CI were significantly higher on day 3 after implantation but significantly lower on day 30, indicating that these changes could be due to initial postoperative response to anesthesia or a middle/inner ear injury (32).

Das et al. (35) reported that bilateral cochlear implantation may offer extra benefits for vestibular function and is safe, with little risk when compared to unilateral implantation. Meanwhile, Dhondt et al. (36) suggested that CI had modest effects on vestibular function in children. As a result, the various benefits of bilateral implantation at the same time may outweigh the risk of postoperative vestibular impairment. In some situations, sequential bilateral implantation may be required since the impact on vestibular function can be influenced by a range of circumstances, including surgical manipulation, inner ear deformity, and so on. When deciding whether to conduct simultaneous or sequential bilateral CI, consider factors such as vestibular function.

To completely assess the hazards of bilateral cochlear implantation on the vestibular system, more research with long-term follow-up is needed.

Electrical stimulation

Parkes et al. (37) found that cochlear current stimulation can produce vestibular potentials in patients, suggesting that cochlear currents can spread from the cochlea to the vestibule (37). Gnanasegaram et al. (38) reported that about half of the children with CI who had vestibular deficits had spatial disorientation, but that this perceptual deficit was corrected by the current from the cochlear switch-on, possibly because (1) the current stimulation increased vestibular nerve activity and (2) the center could use the electrical stimulation from the cochlea as a supplement to vestibular stimulation. Electrical stimulation of the CI device has been demonstrated to affect VEMP responses in several studies (39).

Furthermore, Xu et al. (40) hypothesized that electrical stimulation of the CI could influence both ipsilateral and contralateral responses. When the device is turned on, electrode stimulation may alter the central vestibule to account for changes in contralateral cVEMP amplitude. Others speculated

on the possibility of hyperexcitability as a result of electrical stimulation (41).

Research on the effects of electrical stimulation on vestibular function is insufficient and needs more attention.

Inner ear malformation

Congenital inner ear malformation (IEM) is a group of diseases that cause structural abnormalities in the inner ear due to developmental disorders at different stages of embryonic life. It is one of the common causes of congenital sensorineural deafness, with a group incidence rate of 1/2,000 to 1/6,000 (42). According to Jensen (43), 20% of children with congenital sensorineural hearing loss (SNHL) will have an inner ear defect. Among the malformation of bone labyrinth in the inner ear, the large vestibular aqueduct syndrome (LVAS), common cavity deformity (CCD), and Mondini malformation are more common (42). IEM was initially considered a contraindication to CI, but now CI has helped many IEM patients improve their hearing.

Large vestibular aqueduct syndrome

Sensorineural deafness is a symptom of large vestibular aqueduct syndrome, a congenital abnormality of the inner ear. Wang et al. (44) looked at vestibular function in kids with LVAS and kids with normal CT performance. They discovered that in children with normal CT, the overall VEMP abnormality rate increased significantly from pre to post ci, however in children with LVAS, there was no significant change in the overall VEMP abnormality rate. The findings imply that the effects of CI on otolith function differ between children with LVAS and those with normal CT. The pressure created during electrode insertion in children with LVAS can be discharged or released into the endolymph fluid *via* the larger vestibular aqueduct with less injury. Zhou et al. (45) evaluated vestibular function in LVAS patients, and the results of VEMPs suggested hyperactive vestibular function while the Caloric Irrigation suggested hypoactive vestibular function, the inconsistency needs to be evaluated comprehensively.

Common cavity deformity

Common cavity deformity (CCD) accounts for 25% of IEM cases (46). "A cystic cavity resembling the cochlea and vestibule, but without demonstrating any differentiation into cochlea and vestibule," is how the CCD is defined (47). With this pathology, the patient may have normal, narrow, or wide internal auditory canals (IAC). According to McElveen et al. (48), patients with CCD rely on their visual and somatosensory systems rather than much vestibular input. Therefore, despite the fact that the entrance site corresponds to the lateral semicircular canal, it is unlikely that patients will have vertigo or dizziness after CI. Due to deformed inner ear architecture, the facial nerve typically follows an abnormal path in CCD, and the round window may not be apparent (49). The most likely cause of postoperative nystagmus is direct stimulation of the vestibular branch and after 3 months, this phenomenon exhibited adaptability. Three-dimensional TSE MRI is essential in the demonstration of cochlear and vestibular divisions of cochleovestibular nerve (49).

Mondini malformation

Mondini's dysplasis (MD), is brought on by a developmental stop in the seventh week of pregnancy. Currently, it is categorized as incomplete partition type 2 (IP-2) and is distinguished by 1.5 turns of cochlea with a normal basal turn, cystic apex caused by merged middle and apical turns, enlarged vestibular aqueduct, and dilated vestibule (50–52).

Patients with MD have been found to experience degenerative alterations in their vestibular system and have underdeveloped vestibular sensory organs and an enlarged vestibular aqueduct is one of the inner ear anomalies connected to Mondini dysplasia that is most typical (53). In Kaya's study (54), 44% of patients with MD had aplastic semicircular canals and the loss of spiral ganglion cells was either severe or mild in the temporal bone samples with semicircular canal anomalies. The loss of vestibular type I and type II hair cells they observed in the MD group was statistically significant in all semicircular canals. This fact should be taken into account when evaluating cochlear implants.

Structural factors

Vestibular dysfunction is often present in children with deafness, and the literature reports a prevalence of 20–70% (55, 56). Alexandra (57) believes that the degree of vestibular function impairment is related to the degree of hearing loss. Wolter et al. (58) found that children with unilateral deafness also develop balance deficits, hypothesizing that the "auditory preference syndrome" caused by unilateral deafness and the lack of symmetrical auditory stimulation in the brain may be responsible for the balance deficits.

Evaluation of vestibular function in children

There are fewer studies on the assessment of vestibular function in children, mainly because children have difficulty describing vertigo symptoms and cooperating with vestibular function tests. It is necessary and important to have an appropriate assessment of vestibular function in children.

Pediatric vestibular function questionnaire

Vertigo and vestibular dysfunction in children can cause several symptoms. Furthermore, youngsters may not be able to

fully express their symptoms. As a result, clinicians can use an appropriate questionnaire to measure the degree and impact of dizziness or vestibular loss (59). There are limited studies using questionnaires for pediatric populations, even though there are many questionnaires used to assess vestibular symptoms in adults.

Pavlou et al. (59) designed the PVSQ to accurately assess the severity of vestibular symptoms in children with vestibular symptoms. The test has "excellent accuracy" in distinguishing the presence or absence of abnormal levels of dizziness and/or instability. In 95% of children, the optimal cut-off score correctly identified abnormal levels of vestibular symptoms and accurately reported them in 85% of healthy children. The PVSQ provides the physician with a preliminary understanding of whether the child has symptoms related to vestibular hypofunction, and is also essential for screening children for vestibular function.

Motor development and balance

Initial understanding of motor development can be obtained by knowing when the child lifts his head, sits crawls, and walks, as well as some motor development schedules. The balance test portion of the Bruininks-Oseretsky Test of Motor Proficiency Second Edition (BOT-2) is a generally used balance assessment method.

Adequate attention should be given to the child's motor development and balance.

Vestibular function test

Assessment of vestibular function includes otolithic and semicircular canal function.

Otolithic function

Otolith organs include the saccule and utricle. VEMPs can reflect the functional status of the saccule and utricle. The evaluation of the results includes threshold, wave amplitude, latency, etc. VEMPs are muscle responses elicited by sound, electric current, or bone-conducted vibration stimulation of the vestibular end organs.

The cVEMP recorded from the sternocleidomastoid muscles and the oVEMP recorded from extraocular muscles have both been characterized. To put it another way, cVEMP is a test for saccular (inferior vestibular nerve) otolith functions, while oVEMP is for utricular (superior vestibular nerve) otolith functions (60). The vestibular nerve assessment approach cVEMP is now the most widely utilized to examine the effects of CI on vestibular function in children. This could be related to cVEMP's simpler fit and the fact that, because of its proximity to the CI insertion site, the balloon is thought to be the most vulnerable to surgical effects. Furthermore, VEMPs are straightforward to assess and work with for younger children.

When assessing extremely young children, particularly newborns under the age of 6 months, cVEMP is especially significant because the VOR is naturally faulty in these youngsters. The cVEMP can be examined in a child's supine posture (<15 months) or in a child's sitting upright position to generate cervical muscle activation through head suspension or continuous rotation. Owing to the many procedural biases that can arise in VEMP recordings, there is a danger of erroneous pathological findings (not due to a lack of response due to vestibular insufficiency). Therefore, Verrecchia et al. (6) consider the absence of VEMP responses as true vestibular insufficiency in at least three consecutive trials.

When peripheral vestibular nerve involvement is suspected, VEMP testing of the vestibule in children is advised. In newborns, cVEMP testing is possible. However, oVEMP pathway does not mature until 3 years of age and reaches amplitudes and latencies similar to those of adults. Janky et al. (61) recommend that all children at age 3 should complete oVEMP testing.

Semicircular canal function

Video head impulse test

The vestibulo-ocular reflex (VOR) arising from the three semicircular canals is measured using the video Head Impulse Test (vHIT). As a result, vHIT also evaluates both branches of the vestibular nerve; posterior canal vHIT is an assessment of the inferior portion of the vestibular nerve and anterior and horizontal canal vHITs are assessments of the superior portion of the vestibular nerve (61). The vHIT (together with VEMPs) is a relatively recent assessment approach that provides a quick, objective vestibular exam ideal for youngsters. As a result, it's ideal for a follow-up evaluation in the pediatric population (6). The vHIT is the optimum approach for testing canal function, according to Verrecchia et al. (6).

Lower gain values have been observed in children under the age of three, with a quick increase in vHIT gain up to the age of six, and then a slower increase up to the age of sixteen. When defining standard values for children, age-related changes in vHIT gain should be taken into account, as should the possibility of corrective sweep when vHIT is regarded abnormal.

VHIT has several advantages. Firstly, it can independently assess the functional status of the six semicircular canals. Secondly, it is the only test that can assess the function of the anterior and posterior semicircular canals. Thirdly, during high-frequency stimulation, it can respond to the function of the semicircular canals. Furthermore, regardless of the condition of the middle ear, including the existence of pressure equalization tubes, perforations, or a mastoid cavity, vHIT can be performed (61).

However, due to visual fixation and VOR development in children under 6 months of age, false-positive results may be obtained during evaluation (6). This factor should be taken into account when performing vHIT on children.

Caloric irrigation

Caloric irrigation uses a temperature gradient to test the horizontal semicircular canal and the inferior branch of the vestibular nerve. The mini ice-water caloric test (mIWC) is an altered version of an ice-water caloric method that was previously proposed.

The time spent in cold water was reduced by 10 s, yet there was enough of a temperature gradient (water temperature $\leq 10^{\circ}$C) to guarantee optimal vestibular activation. In comparison to other ways previously tested, this method significantly increased the child's cooperation (62, 63). Only when caloric nystagmus was absent on two test repetitions was it thought to be indicative of vestibular insufficiency.

Caloric irrigation offers low-frequency information about the superior branch of the vestibular nerve and the horizontal semicircular canals that are particular to the ear.

By 6 to 12 months, the caloric response in newborns is assumed to be mature, and the likelihood of having a normal response improves as children gain weight. The magnitude of slow-phase velocities in response to caloric stimulation declines with age in children aged 2–10 (64).

However, this test can cause dizziness and nausea, so it is often difficult for children to tolerate. Due to a certain fear of the child during the examination and discomfort, the degree of cooperation is poor.

Rotary chair

Rotary chair is a midfrequency (0.01–0.64 Hz) assessment of the horizontal canal and superior branch of the vestibular nerve. Cushing et al. (56) concluded that the swivel chair test is the test of choice for suspecting vestibular damage in children because that can be used at any age and is easy to match. Reduction in VOR gain is the best predictor of kinesthetic imbalance. Rotary chair testing is commonly used to assess overall vestibular reactivity and is particularly useful in detecting bilateral vestibular loss and determining the severity of bilateral vestibular loss. It should be noted that middle ear effusion can affect the swivel chair reaction, therefore, it is recommended to use the swivel chair test for tympanometry (65).

Noteworthy, because these tests examine diverse structures of the vestibular system, there may be some disagreement between otolaryngologic and otolithic testing. This divergence may be because the test partially damaged inner ear organs with different levels of function at different test sites. Therefore, the otolith/ear canal inconsistency is interpreted as a reduced vestibular function rather than full vestibular dysfunction (6). Besides, the divergence between vHIT and mIWC also occurs when subjects have inner ear malformations.

In conclusion, caloric testing is frequently not an option for examining vestibular function in youngsters due to tolerance or time constraints. The swivel chair test is considered the gold standard for diagnosis in patients with bilateral vestibular injuries (66). The chair test and vHIT results, on the other hand, may not be consistent.

In patients with severe bilateral vestibular loss, Judge et al. (66) discovered higher agreement between rotary chair and vHIT. While vHIT showed a pattern consistent with unilateral vestibular loss in 25% of individuals with bilateral vestibular loss, rotary chair showed a pattern consistent with bilateral vestibular loss. The degree of vestibular loss might vary in youngsters, where vHIT and rotary chair are the key measures. It is suggested that vHIT is a sufficient first-level evaluation. Rotary chair test is not required if the vHIT findings are abnormal. If rotary chair test is normal, it can aid in the detection of additional signs of vestibular loss.

Mild vestibular loss has no effect on vHIT or rotary chair. vHIT and rotary chair abnormalities are often not present until caloric weakness surpasses 40–45% in the case of unilateral weakness. Caloric testing can be used to rule out moderate, unilateral vestibular loss when vestibular involvement is indicated and the swivel chair and/or vHIT are normal (67).

Recommended strategies

Pre-operative

Surgeons need to take a detailed history and complete imaging studies. The feasibility of performing bilateral and contralateral CI is fully evaluated preoperatively, and vestibular function must be taken into account as an important consideration.

Vestibular screen

A large-scale, safe and affordable vestibular test for newborns and infants is worth consideration as well as an early vestibular assessment in terms of cochlear implantation (CI). Documented vestibular failure may lead to the diagnosis of SNHL with vestibular failure in the clinical setting, where up to 35% of patients with congenital SNHL (sensorineural hearing loss) do not have a precise diagnosis. This is especially common in disorders such as inner ear abnormalities (61).

For all children experiencing dizziness, a vestibular evaluation is suggested. Furthermore, because of the high prevalence of vestibular loss in children with SNHL, the vestibular loss should be considered when hearing loss is suspected. Clinicians can utilize a vestibular screen to see if a kid has vestibular impairment and if more testing is needed.

The modified clinical test of sensory integration on balance, the bedside head thrust test, the Emory clinical vestibular chair test, the dynamic visual acuity test, single-leg stance, tandem

standing, age of gross motor attainment, and severity of hearing loss have all been recommended as screening measures for children with hearing loss (61). Besides, the excellent feasibility of VEMP coupled with the newborn hearing screen program was proven by Verrecchia et al. (68). VEMP measurements could be completed in the majority of examined ears (86%) and in up to 97% of recordings with pre-stimulus EMG within the reference in the second step of hearing screening or after the clinical ABR. Furthermore, more than three-quarters of the trials yielded a clearly visible VEMP response, with the percentage rising to 91.5 percent when the test was performed under optimum clinical conditions.

Screen tests should be economical, simple to administer, benign, and cover populations with a high prevalence of the target condition, in addition to being diagnostic in nature (69). VEMP was recently included as a secondary vestibular nerve examination for all neonates with SNHL found in a hearing screen program in a large multicenter nationwide study (70). For all children who are evaluated following the first phase of the hearing test, it is advised that VEMP be incorporated into the hearing screen program (68).

In addition, parental worries about the degree of gross motor delay, sitting and walking delays, and hearing loss in children with hearing loss are markers of vestibular loss. These characteristics can be very useful in determining whether a child has bilateral vestibular loss. As a result, these indicators should be incorporated into screening tools for children with hearing loss (71).

To establish the diagnostic accuracy of VEMP as a sort of vestibular screen in children, more research is needed.

Vestibular prediction

The high prevalence of vestibular damage is linked to specific etiologies of hearing loss; for example, in some etiologies, such as meningitis, vestibular damage occurs in practically all patients, whereas other etiologies have varied effects on vestibular function (56).

Because of the enormous impact of vestibular loss on big muscle motor development and other outcomes, as well as the benefits of early management, it is critical to detect children with vestibular loss as soon as possible.

In early childhood, vestibular nerve injury is linked to the severity of hearing loss and motor impairments. Vestibular loss is thought to affect 30–74% of infants with severe hearing loss (72). According to reports, 50% of youngsters who are candidates for cochlear implants (CI) suffer from vestibular loss (56, 73).

In children with CI, vestibular damage is associated with an increased risk of falls and CI device failure (74). Hearing loss is more severe in children with bilateral vestibular impairment compared to children with normal or unilateral vestibular impairment (75).

Janky et al. (71) show that in a younger group, particular characteristics can predict vestibular loss. Vestibular loss was predicted by age to sit, age to walk, bilateral PTA, and parental worries about gross motor developmental delay. These four indicators may assist evaluate whether or not a kid with hearing loss need vestibular testing. According to ROC analysis, employing a threshold of 7.25 months for age-to-sit and 14.5 months for age-to-walk for detecting vestibular loss provides reasonable sensitivity and specificity (71). According to ROC analysis, employing a bilateral PTA cutoff of 40 dB has excellent sensitivity (80%) and a bilateral PTA cutoff of 66 dB has excellent specificity (91%). These indicators are more sensitive in detecting children who have suffered bilateral vestibular damage.

A vestibular test should be undertaken for children who have a hearing loss of more than 66 dB, particularly those who sit later than 7.25 months or walk later than 14.5 months, or whose parents have concerns about gross motor development (71).

Vestibular function test

Patients with severe dizziness disorder are at risk for social isolation, anxiety, depression, falls, and injury, hence identifying these patients with vestibular hypofunction before surgery is crucial (18). By knowing the side of vestibular insufficiency, preoperative vestibular assessment can play a role in minimizing the risk indications for CI, considering the potential vestibular impairment effect of CI (76), CI can be reconsidered when only the functional vestibular side is suggested. If unavoidable, parents can be informed about the possible risk of motor proficiency sequelae and reminded them the possibility of early adaptive intervention.

Intra-operative

Appropriate surgical manipulation can reduce vestibular damage. The optimal surgical route for cochleostomy has been explored to minimize damage to the inner ear structures and the round window approach is recommended. Studies have shown that the anterior inferior/inferior way to cochleostomy, where the hole is drilled from below toward the round window annulus and gradually advanced toward the lower surface of the cavity, causes the least damage to the cochlea (77–79).

Inner ear damage induced by electrode insertion is linked to the size and shape of the CI electrodes utilized, in addition to the surgeon's surgical approach. Inner ear injury is more common with large-diameter and straight electrodes than with thin and curved electrodes. The use of "soft surgery" techniques in cochlear implantation is also considered to be beneficial in preserving residual hearing and balance function. Coordes et al. (80) proposes that ensuring that the electrode is fixed in the tympanic step reduces the incidence of postoperative vertigo. Slow insertion of electrodes and intraoperative topical

application of corticosteroids may have a protective effect on vestibular function (81). While the depth of electrode insertion does not affect the postoperative vestibular function test (82). Undeniably, the insertion of CI electrodes requires even more attention in the case of anomalous or abnormal anatomy (7).

Exolymphatic fluid leakage can cause vertigo symptoms, and conical electrodes may prevent fistula-related symptoms, while Dania (83) believes that restabilization of electrodes may alleviate postoperative vertigo.

Post-operative

Many factors affect vestibular function after CI surgery. With increasing attention to changes in vestibular function after CI surgery, more and more treatments have been proposed.

Vestibular rehabilitation

Postoperative vestibular function rehabilitation is plastic and can be improved through training or corresponding treatment. Vestibular function can be improved through training or treatment, but it is difficult to fully recover. Saki et al. (84) studied 21 patients with vertigo and balance disorders after CI surgery, who underwent vestibular rehabilitation. The DHI and VAS were performed at weeks 1, 2, and 4, with the results that the DHI and VAS scores at weeks 2 and 4 were significantly better than those of the control group, indicating that vestibular rehabilitation had a positive effect on the vestibular symptoms of the patients receiving CI. Magdalena et al. (85) performed preoperative and postoperative vestibular function examinations in 55 CI patients with low-frequency residual hearing, and all of them underwent postoperative electroacoustic stimulation (EAS). The results showed an injury rate of 15.79% for the saccule, 19.04% for the utricle, and a decrease of 15.79% for the horizontal semicircular canals response, which is an average decrease of about 20% compared to the injury rate of the previous study. Compared to the previous study, concluded that EAS treatment was effective in improving vestibular function in patients with residual hearing.

Vestibular implant

The vestibular implant (VI) is comparable to a cochlear implant in that it captures motion rather than sound using a gyroscope (86). After that, the motion data is sent to a processor, which turns it into an electrical signal. Electrodes are then inserted near the ampullar branches of the vestibular nerve to transmit these electrical signals and stimulate the vestibular nerves (86). Motion information is transmitted to the brain in this way (87).

The Geneva-Maastricht group was the first to implant a completely working VI into a human, indicating that VI is feasible in humans (87). First, an electrically evoked vestibulo-ocular reflex could be elicited in the plane of the stimulated canal, and vestibular function could be partially restored in both low and high frequencies of movement (88, 89). Second, the brain can adjust to baseline inputs while continuing to respond to the implant's motor-induced conditioning (87). Third, the electrically evoked VOR had properties that were similar to those of natural VOR (90). Fourth, vestibulo-ocular and vestibulospinal reflexes can be elicited and recorded using vestibular evoked myogenic potentials and postural alterations, respectively (91).

Fifth, the VI's input perception varies: it's not always the sense of vertigo or spinning, but it can also be other sensations like sound or pressure (87). Sixth, residual natural vestibular information can be overcome by VI information when the brain performs non-linearly. In the case of fluctuating vestibular function, this could open the way for the VI to be used as a "vestibular pacemaker" (92, 93).

VI is a new treatment that uses direct cerebral nerve stimulation to treat bilateral vestibular lesions and other underlying vestibular illnesses.

Even though numerous hurdles remain in the development of the device and its implantation technology, the study reveals the feasibility and value of VI in improving clinical outcomes for individuals with certain vestibular illnesses who have failed to respond to standard treatments (86).

Future trials should validate this approach in a larger patient population.

Testing time

Different research on the impact of cochlear implant surgery on vestibular function varies widely from study to study and may depend on the lack of a standardized postoperative testing time.

Currently, there is no definite conclusion on the time of vestibular function evaluation after cochlear implantation. In some studies on vestibular function changes after cochlear implantation, the time of vestibular function evaluation varies from 1 month to 12 months after surgery (18, 94–96). Long-term follow-up is available to observe the long-term effects of cochlear implantation on vestibular function in children. It is generally believed that the results of vestibular function assessment can be attributed to the surgical procedure at 6–8 weeks after surgery, before the initial CI device activation, and therefore before the child has experienced electrical stimulation. Other studies have shown that vestibular function of patients deteriorates 3–6 months after cochlear implantation and tends to be stable about 14 months after implantation (18). Therefore, vestibular function evaluation can be conducted at different postoperative time points. At our center, vestibular

function was studied at 1 day preoperatively and 1,6,12 months postoperatively.

Conclusion

Although clinical researchers are now becoming aware of the importance of preserving vestibular function, vestibular function testing on children is still a relatively new area. Even though most children exhibit large and rapidly compensating sensory deficits, vestibular dysfunction cannot be ignored. When possible, screening of all patients requiring vestibular neurological examination is necessary, as is postoperative evaluation. Intraoperative thin and curved electrodes, "soft surgery" technique and round window placement may reduce vestibular dysfunction, but this remains to be proven.

In addition, vestibulo-cochlear implantation with artificial electrical stimulation of the vestibule through external electrodes similar to CI is a new technique to be explored for the treatment of patients with severe and very severe sensorineural deafness with persistent vestibular function. More research is needed to better guide the clinical application of CI and to provide optimal outcomes for CI implantation patients with optimal implantation and rehabilitation outcomes.

Author contributions

JD and WW contributed to conception of the study and wrote the first draft of the manuscript. QZ and KZ wrote sections of the manuscript. DX supervised the manuscript. All authors contributed to manuscript revision, read, 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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EDITED BY
Jun Yang,
Shanghai Jiao Tong University School of Medicine, China

REVIEWED BY
Hong Ju Park,
University of Ulsan, South Korea
Saba Battelino,
University Medical Centre Ljubljana, Slovenia

*CORRESPONDENCE
Konstanze Dunker
Konstanze.Dunker@med.uni-muenchen.de

†These authors have contributed equally to this work

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Recurrent Vertigo of Childhood: Clinical features and prognosis

Konstanze Dunker[1]*, Lutz Schnabel[2], Eva Grill[1,3], Filipp Maximilian Filippopulos[1,2†] and Doreen Huppert[1,2†]

[1]German Center for Vertigo and Balance Disorders (DSGZ), Ludwig-Maximilians-Universität München, Munich, Germany, [2]Department of Neurology, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany, [3]Institute for Medical Information Processing, Biometrics and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany

Introduction: "Recurrent Vertigo of Childhood" (RVC) has recently replaced the term "Benign Paroxysmal Vertigo of Childhood" and was defined as recurrent spells of vertigo without evidence of a vestibular migraine of childhood (VMC). RVC and VMC are considered the most frequent causes of vertigo and dizziness in children below 18 years of age. Diagnosis might be challenging since clinical features of RVC and VMC may overlap.

Objective: This study aims to characterize clinical and instrument-based findings in patients with RVC and to evaluate the course of the disorder.

Methods: We prospectively collected clinical and instrument-based data of children/adolescents younger than 18 years, who presented at the German Center for Vertigo and Balance Disorders (DSGZ) at the LMU University Hospital in Munich. All patients underwent a comprehensive neurological, ocular motor, vestibular and cochlear examination. Furthermore, findings from follow-up examinations were analyzed.

Results: Overall 42 children (24 male and 18 female) with RVC were included in the study. The mean age at diagnosis was 7 ± 3.6 years with a mean onset of symptoms at the age of 5.6 ± 3.4 years. Attack duration ranged between 1 min and 4 h. The most common accompanying symptoms included nausea, vomiting, expression of fear, and falls. Non-migrainous headaches were reported by 11 patients during initial presentation, 7 of whom were later diagnosed with migraine. Female patients showed a higher age at symptom onset, a higher attack frequency, and attack duration. Eleven of the 24 patients seen at a 3.5 year follow-up reported a complete cessation of attacks. Patients still experiencing vertigo attacks had a significantly reduced attack frequency, especially those who implemented at least one prophylactic measure.

Conclusion: A precise characterization of symptoms is essential for diagnosing children with RVC. Age at symptom onset does not exceed the age of 12. Gender-specific differences should be considered and may further support the evidence of an association with migraine. The disease course of RVC is benign, nevertheless implementing prophylactic measures such as regular exercise, increased fluid intake, sleep hygiene, and relaxation exercises, can improve attack frequency.

KEYWORDS

Recurrent Vertigo of Childhood, children, adolescents, vertigo, dizziness, vestibular migraine of childhood

Introduction

Approximately 5% of children and adolescents complain of vertigo/dizziness and balance problems (1). Symptoms can occur with varying frequencies, from only once over a certain time period (monophasic), with recurrent attacks (episodic), or persistently (2). Children commonly suffer from episodic vertigo attacks with the most frequent diagnoses being "Recurrent Vertigo of Childhood" (RVC) and "Vestibular Migraine of Childhood" (VMC) (2–5).

RVC, as recently defined by the Bárány Society, is characterized by at least three episodes with vestibular symptoms of moderate or severe intensity, lasting between 1 min and 72 h without a current or past history of migraine with or without aura and associated migraine features in over 50% of episodes in children and adolescents below 18 years of age (6). The syndrome was first described in 1964 by Basser (7) with an onset at the age of four. It was labeled "Benign Paroxysmal Vertigo of Childhood" due to the spontaneous cessation of attacks between ages 8–10 without persistent vestibular or neurological deficits. Among "dizzy" children and adolescents, RCV is diagnosed in about 18–23% of cases and constitutes the second most frequent diagnosis in patients under the age of 18 (2, 3, 8, 9). Notably, the proportion of children with RCV has been shown to be especially high in children under the age of seven (71–87.5%) and between seven and 12 years (30%) (8, 10, 11). Symptom remission typically occurs between 3 months to 8 years after onset (12, 13), but may persist longer in some children/adolescents or may be followed by the diagnosis of migraine (13, 14). The underlying pathophysiology of RVC is still unknown, but a possible link with migraine has been suggested due to a high reported prevalence of migraine in children suffering from RVC (12, 13, 15, 16).

Diagnosing RVC can be challenging, particularly in its distinction from VMC. Due to the lack of prospective clinical studies on children/adolescents with RVC, the diagnostic criteria of the Bárány Society (6) define RVC as episodes with vestibular symptoms that do not fulfill the criteria of VMC, or any other medical condition. In other words, RVC is a diagnosis by exclusion; inclusion criteria based on clinical or instrument-based findings have not been included. However, a number of studies have described distinct findings in patients with RVC, for example evidence of vestibulo-cochlear dysfunction (15) or elevated serum levels of creatine kinase-MB (CK-MB) (17).

In the present study, in order to characterize children/adolescents with RVC in detail, we prospectively collected clinical and instrument-based findings including ocular motor testing, a broad vestibular and cochlear assessment as well as imaging results. Furthermore, follow-up examinations up to 4 years were conducted in a proportion of patients to better characterize the course and prognosis of the disease.

Materials and methods

Subjects

All children and adolescents diagnosed with RVC at the German Center for Vertigo and Balance Disorders (DSGZ) at the LMU University Hospital in Munich between January 2016 and May 2022 were prospectively included in the study. All patients fulfilled the current diagnostic criteria for RVC of the Bárány Society (6). Written informed consent was obtained from all participants included in the study and their parents/legal guardians.

Clinical and instrument-based examination

All included patients underwent structured history-taking and standardized neurological, ocular motor and neuro-otological examinations. Data collected included age of onset, frequency and duration of attacks, trigger factors, underlying medical conditions, and family history. Furthermore, the following instrument-based examinations were conducted if possible (depending on age):

- Caloric irrigation and video Head-Impulse-Test (vHIT) were used to quantify peripheral vestibular function of the horizontal semicircular canal. Caloric irrigation values above 30% side asymmetry and/or a vHIT gain of less than 0.7 were considered pathological.
- Ocular and cervical Vestibular-Evoked Myogenic Potentials (o- and c-VEMP's) were utilized to evaluate function of the utricle and saccule.
- Posturography was used to quantify body sway patterns.
- Audiometry and Auditory Evoked Potentials (AEP's) were used to evaluate cochlear function.

Follow-up visits were conducted when medically indicated. In addition, each patient was contacted to assess the course of the disease using a standardized questionnaire. The questionnaire included questions about current attack characteristics, accompanying symptoms, trigger factors, implemented prophylactic measures and, if applicable, age of attack cessation. To evaluate a possible link to migraine disorders, we ascertained information about occurrence and characteristics of headaches as well as accompanying symptoms during headache attacks.

Statistics

After data collection, all data were irreversibly anonymized for data analyses. For data description, we used mean values

TABLE 1 Characteristics of vertigo/imbalance attacks in 42 children with Recurrent Vertigo of Childhood.

Attack characteristics		
Vertigo type	Torsional	34 (81%)
	Swaying	15 (36%)
	Dizziness	5 (12%)
	Duration in minutes [*mean±sd; (min.; max)*]	25.5 ± 36.4; [1; 240]
	Attack frequency per month [*mean±sd; (min.; max)*]	15.9 ± 23; [0.08; 90]
	Number of patients with clustered attacks	14 (33%)

Attack duration varied between one and 240 minutes, attack frequency between 0.08 and 90 attacks/month. Attacks reoccurring up to seven days in a "cluster of attacks" were described in 33% of patients.

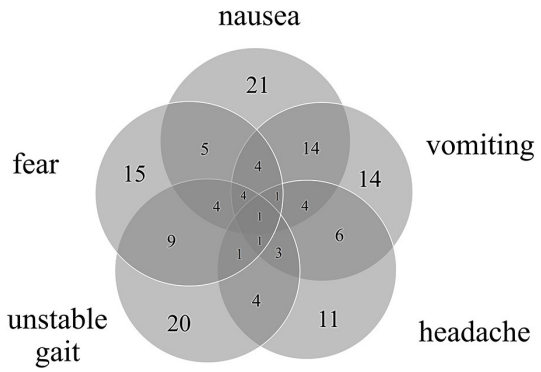

FIGURE 1
Number of accompanying symptoms and their overlap in 42 patients with RVC. All patients had at least one accompanying symptom, most commonly nausea, unstable gait, and expression of fear.

and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. Statistical differences were calculated between male and female patients, between attack-free patients and patients with ongoing attacks as well as differences between characteristics at first presentation and follow-up. We performed a *t*-test to test for differences in continuous variables and a Pearson's chi-squared test for categorical variables.

Results

Patient and attack characteristics

Of 453 patients who presented at the DSGZ during the recruitment phase, 42 patients between 2 and 15 years were diagnosed with RVC. The mean age at first clinical evaluation was 7.0 ± 3.6 years. The mean age when symptoms first were noted by patients, or their parents was 5.6 ± 3.4 years. Female patients had a significantly higher age of symptom onset than male patients (male: 4.7±3.7 years; female: 6.9 ± 3.3 years; $p = 0.029$). Attack frequency varied between one attack per year and three attacks per day with a mean of 13.7 ± 18.9 attacks per month. Attack duration ranged between 1 min and 4 h; female patients experienced significantly longer (mean: male = 13.3 min; female = 41.2 min; $p = 0.008$) and more frequent attacks than male patients (mean: male = 8.8 ± 10.2; female = 20.3 ± 25.3; $p = 0.042$). A clustering of attacks up to seven days, followed by a longer period without attacks was reported in 33% of the patients (Table 1).

The most common accompanying symptoms during vertigo attacks were nausea (50%), unstable gait (47%) and expression of fear (Figure 1). Male patients had a significantly higher incidence of vomiting (male = 54%; female = 17%; $p = 0.047$) while non-migrainous headaches tended to be more common in females (male = 16%; female = 39%; $p = 0.105$). The most frequent trigger factors were psychosocial stress (36%) and a systemic or respiratory infection (15%).

Clinical and instrument-based findings

All patients showed no pathologic findings in the neurological and neuro-otological examinations. In the broad ocular motor examination 12% of patients showed a vertical saccadic smooth pursuit, and 5% an impaired vertical fixation suppression. One child showed an isolated head-shaking nystagmus, two had a slight deviation of the subjective visual vertical, all without any additional evidence of a central or vestibular disorder. The cranial magnetic resonance imaging (MRI) performed in 64% of patients did not reveal any structural pathological findings. Furthermore, all cochlear examinations including AEP's and VEMP's were normal (Table 2).

Follow-up

Twenty-four patients (57%) presented for follow-up examinations and/or completed the follow-up questionnaire. The mean follow-up interval was 3.5 ± 2.6 years. Of the 24 children/adolescents, 13 (54%) still reported suffering from vertigo/dizziness attacks, while in 11 children/adolescents (46%) the attacks had ceased. The mean age of attack cessation was 4.7 ± 2.8 years. In patients still experiencing vertigo attacks the mean attack duration was 41 ± 2.8 min with a frequency of 3.6 ± 5.0 attacks per month. Attack frequency was significantly reduced compared to the initial patient evaluation (initial attack frequency of follow-up patients: 11.9 attacks/month; $p = 0.038$).

TABLE 2 Detailed ocular motor and instrument-based findings in the attack-free interval in children with RVC.

Ocular motor examination	% occurrence
Strabismus	2/42 (5%)
Spontaneous nystagmus in primary position	0/42 (0%)
Gaze-induced nystagmus	0/42 (0%)
Head-shaking nystagmus	1/42 (2%)
Upbeat-/Downbeatnystagmus	0/42 (0%)
Saccadic smooth pursuit movements (horizontal)	0/42 (0%)
Saccadic smooth pursuit movements (vertical)	5/42 (12%)
Impairment of fixation supression (vertical)	2/42 (5%)
Impairment of optokinetic nystagmus (OKN)	0/42 (0%)
Subjective Visual Vertical	2/42 (5%)
Ocular Torsion (under Scanning Laser Ophthalmoscope)	1/42 (2%)
Instrument-based findings	
Video-head-impulse-test	0/33 (0%)
Caloric irrigation	1/20 (5%)
Ocular- and cervical evoked potentials	0/21 (0%)
Auditory evoked potentials	0/24 (0%)
Audiometry	0/14 (0%)
Functional sway in posturography	13/25 (52%)
Cranial MRI	0/27 (0%)
EEG	0/24 (0%)
Cardiological examination	0/20 (0%)

The ocular motor examination showed a vertical saccadic smooth pursuit in 12%, an impaired vertical fixation suppression in 5% and a slight deviation of the subjective visual vertical in 5%. The most common finding in the instrument-based diagnostics was a functional sway pattern on posturography. MRI, magnetic resonancy imaging; EEG, Electroencephalography.

At follow-up 70% of patients had implemented at least one recommended prophylactic measure, most commonly increased fluid intake and improved sleep hygiene (in 58% of patients). The implementation of measures led to a significantly reduced attack frequency compared to patients that did not conduct any prophylactic measures (0.9 vs. 3.8 per month, $p = 0.03$; see Figure 2), regardless of the implemented measure.

Migraine association

At initial presentation 11 patients (26%) reported headaches without any migrainous features as an accompanying symptom during vertigo attacks. Five patients (12%) reported only photo-/phonophobia (without headache) during the vertigo attacks. Non-migrainous headaches irrespective of the vertigo attacks were described in 10 patients (23%).

Although initially, none of our patients reported migrainous headaches with photo-/phonophobia or other migraine features during or outside vertigo attacks, at follow-up seven children/adolescents fulfilled the diagnostic criteria for migraine (three with aura, four without aura), of which five still experienced vertigo attacks. In all five cases vertigo attacks were associated to the migraine attacks, fulfilling the diagnostic criteria for VMC. Further details are presented in Figure 3.

Motion sickness as a commonly associated symptom of migraine was only reported in a low number (16%) of all 42 patients. A family history of migraine was positive in 24 patients (57%).

Discussion

Clinical characteristics of RVC

In the present cohort of children with RVC, the mean age at first presentation was of 7.1 ± 3.6 years, which is in line with previous findings (15, 18). In most cases, the vertigo/dizziness attacks were described as a torsional or spinning sensation, that lasted 25 min on average and occurred every other day (see Table 1). In the literature, the mean attack duration is similar to the present findings (13, 14), but the reported range varies between very brief attacks (few seconds) (14) and very long attacks (up to 7 days) (13). In our cohort, the shortest attack lasted 1 min and the longest 4 h; the latter considerably differing from previous reports and the diagnostic criteria of the Bárány Society. This disparity is likely due to the fact that 33% of children originally reporting longer attacks (several hours to days), upon more detailed questioning, clearly described brief recurrent vertigo attacks (e.g. few minutes) followed by a vertigo free interval (over several minutes to hours). Such episodes were considered "clustered attacks" (see Table 1) with a high attack frequency and relatively short duration (minutes). We therefore argue that previously described very long RVC attacks may in fact represent a clustering of attacks instead of one attack with the duration of several hours (more than 4–6) or days.

All children reported accompanying symptoms during RVC attacks, most frequently nausea, unstable gait or imbalance, emotional symptoms such as spontaneous crying or expression of fear, vomiting and headache (see Figure 1), consistent with previous findings (13, 14). Notably, 19% of the children included in this study reported falls during the attacks, which has not been previously described. Most of these children also experienced an unstable gait, which might lead to an increased occurrence of falls.

Symptom onset was 2 years later in female patients, attack duration was 30 min longer, and attack frequency more than twice that of male patients. Female patients also had more than twice the incidence of accompanying non-migrainous headaches without phono-/photophobia (male = 16%; female = 39%) at initial presentation. These are to our knowledge

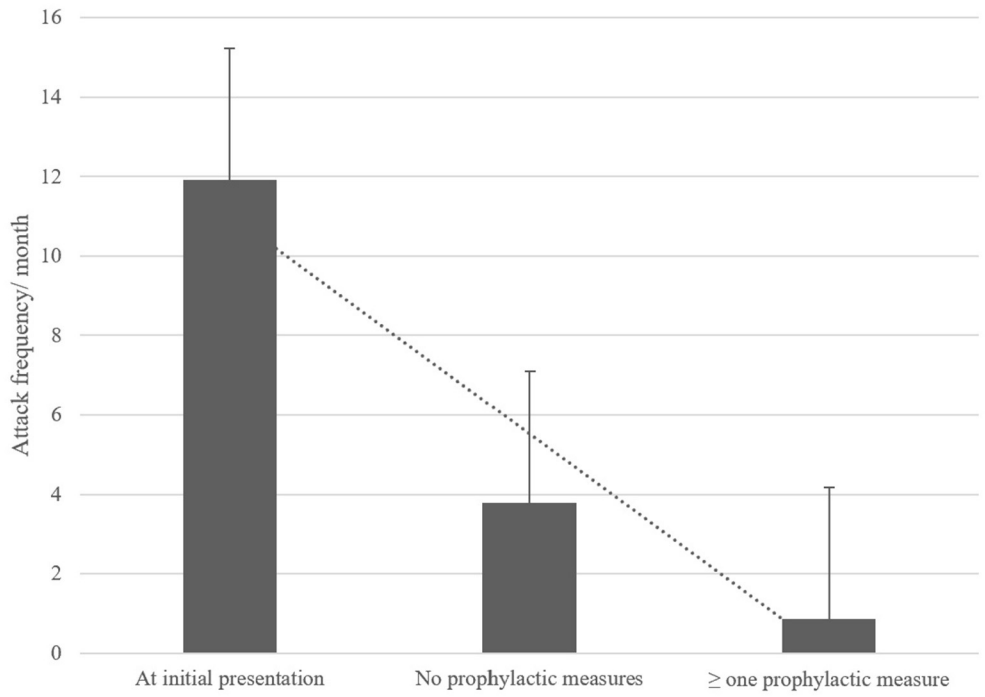

FIGURE 2
Comparison of attack frequency per month at initial presentation and at follow-up with and without the implementation of prophylactic measures. These measures included regular exercise, increased fluid intake, sleep hygiene, relaxation exercises, daily intake of weight-adapted magnesium. Attacks significantly reduced over time, especially with prophylactic measures.

the first reports of gender specific differences in RVC. Few gender specific differences in children and adolescents have been reported in headache disorders (19, 20), and vertigo/dizziness complaints (21). Particularly it seems, that the gender specific findings in the present cohort resemble the findings in a pediatric migraine population, that has shown a female predominance in the occurrence of headaches as well as a higher attack frequency with increasing age (20). Whether this finding supports the suggested link of RVC to migraine remains hypothetical.

Ocular motor and instrument-based findings

In the attack-free interval ocular motor abnormalities were found in a total of 19% of the children with RVC, most frequently a vertical saccadic smooth pursuit and disturbed vertical fixation suppression (see Table 2). We are not aware of any other studies on children with RVC that describe ocular motor findings. Positional nystagmus has previously been found in 20% of children with RVC (15, 22), which we did not find in any examined child; albeit one child had a head-shaking nystagmus with no evidence of any other central or peripheral vestibular imbalance. The observed rate of strabismus is the normal range for children/adolescents (23).

Further instrument-based findings (e.g., MRI, VEMP's, AEP's, etc.) were all normal, except one child showing a pathological side difference in the caloric irrigation. Vestibulo-cochlear symptoms have been described in RVC by Marcelli et al. (15), but caloric irrigation was not conducted. The recently described increased N1-latency and interval of cVEMP's in children with RVC (24) was not observed in the present cohort, although we used standardized VEMP-parameters for the evaluation and did not conduct a further comparison with a healthy, age-matched control group. Overall, slight vestibulo-cochlear deficits such as a pathological caloric irrigation or pathological VEMP findings might be present in a small number of children with RVC and should therefore not lead to the exclusion from the diagnosis of RVC. Furthermore, the examination of balance and postural sway revealed a functional sway pattern (increased postural sway at base-line with "paradoxical" improvement in more demanding conditions) in 52% of patients. This may be indicative of a higher risk of secondary psychosomatic development, as has been described in VMC and migraine-related disorders (25, 26). However, none of the children examined developed a persistent functional disorder over time.

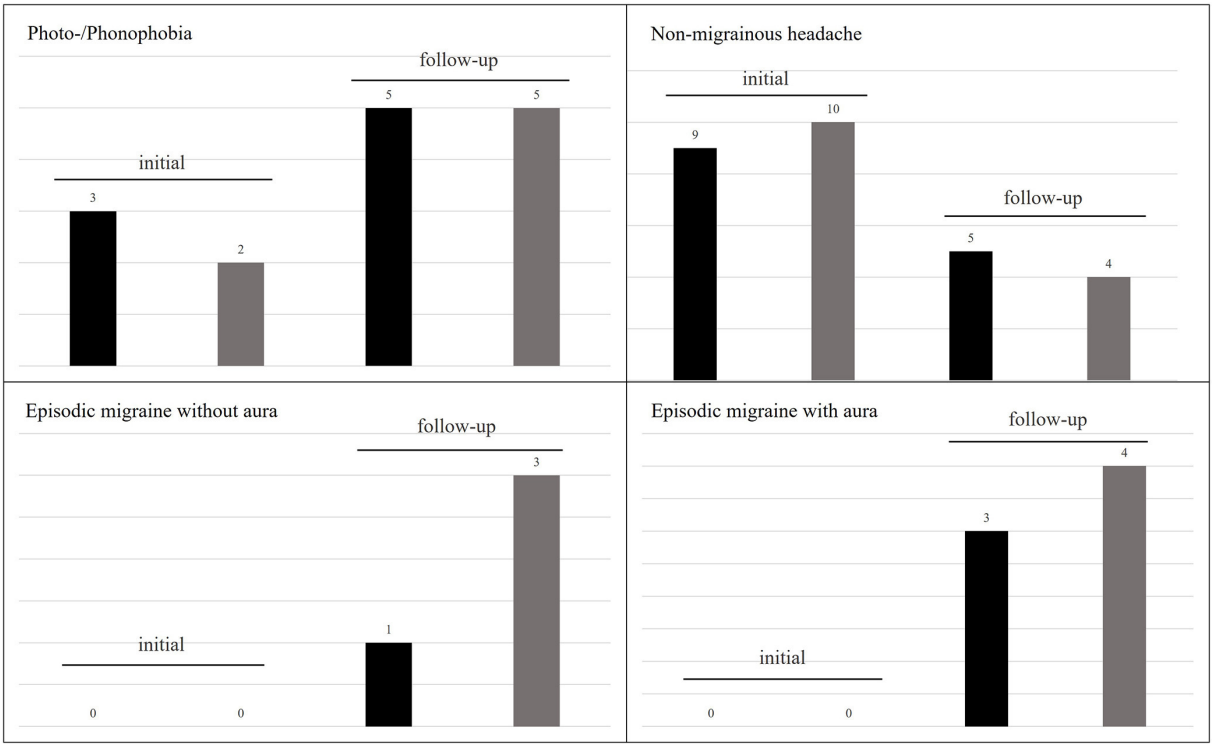

FIGURE 3
Frequency of headaches and associated symptoms in RVC at initial and follow-up examination. Photo-/phonophobia increased over the course of the disease, while non-migrainous headaches decreased. However, seven patients developed an episodic migraine. The black columns represent patients reporting this symptom during and the gray columns outside of vertigo attacks.

Long-term follow up and therapeutic approach

Children with RVC commonly show a benign disease course (7, 27–29). Similarly, in the present cohort a cessation of attacks was observed in 44% of patients after a mean follow-up interval of 3.5 years. Furthermore, a significant reduction of attack frequency from an initial mean of 15.9 attacks per month to 3.8 attacks per month was observed at follow-up, suggesting a benign course and spontaneous remission. As a novel finding, the implementation of one or more prophylactic measures (regular exercise, increased fluid intake, sleep hygiene, relaxation exercises, daily intake of weight-adapted magnesium) (see Figure 2), led to a further decrease in attack frequency to 0.9 attacks per month on follow-up, regardless of type and number of implemented measures. These prophylactic measures strongly resemble those applied in children with migraine (30), further underlying the potential causative link between migraine and RVC.

Headache and migraine

It has been broadly suggested that RVC may be a precursor of migraine (10, 12, 13, 15, 22, 31, 32), although evidence to the contrary also exists (27). While none of our patients reported headaches suggestive of migraine during or in-between vertigo attacks at initial presentation, 40% of patients fulfilled the diagnostic criteria for migraine (38% with, 62% without aura) according to the International Classification of Headache Disorders - ICHD-3 (33) at follow up. Of these, 62% were still experiencing vertigo attacks now accompanied by migrainous headaches, fulfilling the Bárány diagnostic criteria for VMC (6). Overall, our RVC cohort showed a higher prevalence of migraine at the follow-up (after 3.5 ± 2.6 years) than the general population at that age (in children <14 years: female = 7%; male = 5%) (19). This finding further supports a link of RVC to migraine, although the reason or underlying cause remains unknown.

Conclusion

In accordance with the present findings from a large cohort of children with RVC, we suggest a more precise characterization of RVC for diagnostic evaluation than suggested by the Bárány-Society. In particular, the age of symptom onset in RVC does not exceed 12 years of age in the present and in any previously published cohort (12, 13, 15, 27, 28). Nevertheless,

due to a considerable interval between symptom onset and first evaluation by a physician, the diagnosis of RVC should still be considered in children/adolescents up to 18 years. When evaluating attack duration, a clustering of attacks should be considered, since very long RVC attacks (above 12 h) are rarely mentioned in literature (13) or may be interpreted in the scope of clustered attacks. The presence of slight ocular motor deficits or vestibulo-cochlear dysfunction should not lead to an exclusion of RVC. Furthermore, even though RVC has a benign course, prophylactic measures such as regular exercise, increased fluid intake, sleep hygiene, and relaxation exercises, should be recommended to affected children and their parents.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of the LMU (414-15). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

KD: data collection, statistical analysis, interpretation of data, conception of tables and figures, and drafting the manuscript. LS: data collection and statistical analysis. EG: data collection, interpretation of data, and revising the manuscript. FF: statistical analysis, interpretation of data, and writing and revising the manuscript. DH: study concept and design, interpretation of data, and revising the manuscript. 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.

Publisher's note

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EDITED BY
Erin Gillikin Piker,
James Madison University,
United States

REVIEWED BY
Daniel Romero,
Vanderbilt University Medical Center,
United States
Kristen Leigh Janky,
Boys Town, United States

*CORRESPONDENCE
Yulian Jin
jinyulian8548@xinhuamed.com.cn
Jun Yang
yangjun@xinhuamed.com.cn
Maoli Duan
maoli.duan@ki.se

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Cervical vestibular evoked myogenic potentials in 3-month-old infants: Comparative characteristics and feasibility for infant vestibular screening

Jiali Shen[1,2,3], Lu Wang[1,2,3], Xiaobao Ma[1,2,3], Zichen Chen[4], Jianyong Chen[1,2,3], Xueyan Wang[5], Kuan He[1,2,3], Wei Wang[1,2,3], Jin Sun[1,2,3], Qin Zhang[1,2,3], Min Shen[1,2,3], Xiangping Chen[1,2,3], Qing Zhang[1,2,3], Kimitaka Kaga[6], Maoli Duan[7,8]*, Jun Yang[1,2,3]* and Yulian Jin[1,2,3]*

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China, [4]Department of Otorhinolaryngology-Head and Neck Surgery, Second Affiliated Hospital of Xi'an Jiaotong University School of Medicine, Xi'an, China, [5]Department of Otolaryngology-Head and Neck Surgery, Yanbian University Hospital, Yanji, China, [6]National Institute of Sensory Organs, National Hospital Organization Tokyo Medical Center, Tokyo, Japan, [7]Ear Nose and Throat Patient Area, Trauma and Reparative Medicine Theme, Karolinska University Hospital, Stockholm, Sweden, [8]Division of Ear, Nose, and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

Objective: We compared the characteristics of air-conducted sound cervical vestibular evoked myogenic potential (ACS-cVEMP) and bone-conducted vibration cVEMP (BCV-cVEMP) among 3-month-old infants with normal hearing and sensorineural hearing loss (SNHL), and healthy adults to explore the feasibility and optimal strategies for infant vestibular screening.

Methods: 29 infants (58 ears) were divided into two groups according to hearing (group I: normal hearing ears; group II: SNHL ears), 20 healthy adults were defined as group III. The results of response rate, P13 and N23 latency, P13-N23 interval, amplitudes, and corrected interaural asymmetry ratio (IAR) were recorded and compared among three groups.

Results: The response rates of ACS-cVEMP in three groups were 88.89, 62.00, 100%, respectively. The P13 and N23 latencies, and P13-N23 interval did not differ significantly between group I and II ($p = 0.866$, $p = 0.190$, $p = 0.252$). A significant difference was found between group I and III ($p = 0.016$, $p < 0.001$, $p < 0.001$). No significant difference was observed in raw or corrected amplitude between group I and II ($p = 0.741$, $p = 0.525$), while raw and corrected amplitudes in group III were significantly larger than group I ($p < 0.001$, $p < 0.001$). For BCV-cVEMP, the response rates in three groups were 100, 86.36, 100%, respectively, No significant difference existed in the P13 and

N23 latency, or P13-N23 interval between group I and II ($p = 0.665$, $p = 0.925$, $p = 0.806$), however, P13 and N23 latencies were significantly longer in group III than group I ($p < 0.001$, $p = 0.018$), but not in P13-N23 interval ($p = 0.110$). There was no significant difference in raw or corrected amplitude between group I and II ($p = 0.771$, $p = 0.155$) or in raw amplitude between group I and III ($p = 0.093$), however, a significant difference existed in corrected amplitude between group I and III ($p < 0.001$).

Conclusions: Compared with adults, 3-month-old infants with normal hearing presented with equivalent response rates, shorter P13 and N23 latencies, smaller corrected amplitudes, and a wider IAR range for both ACS and BCV-cVEMP. SNHL infants had equivalent response rates of BCV-cVEMP, lower response rates of ACS-cVEMP than normal hearing infants. When responses were present, characteristics of ACS and BCV-cVEMP in SNHL infants were similar with normal hearing infants. ACS combined with BCV-cVEMP are recommended to improve the accuracy of vestibular screening.

KEYWORDS

cervical vestibular evoked myogenic potentials, infant, vestibular screening, hearing, hearing loss, hearing screening

Introduction

The vestibular sensory organ plays a non-substitutable role in the balance control. The vestibular system begins to develop *in utero* earlier than cochlea, and its morphology is well differentiated on the 49th day of gestation (1–3). At birth, the vestibular nerves are completely myelinated, and the vestibular end organs are well-structured (2, 3).

Vestibular dysfunction leads to poor balance and delayed gross motor development (2–5). Furthermore, it causes detrimental influence on learning skills, mental health, and social emotional development as well (4–6). Therefore, early diagnosis and timely intervention are crucial to reduce adverse effects on all aspects (2–6).

The incidence of vestibular dysfunction in infants and young children ranges from 0.7 to 25% (7, 8). Several studies have shown that children with hearing loss are at a high risk of vestibular impairment, nearly 20–85% of children with sensorineural hearing loss (SNHL) having unilateral or bilateral vestibular dysfunction (9, 10). This wide range might be related to the different pathologies, the degree of hearing loss, the selection of the vestibular test and the diagnostic criteria (7–10). Angeli (11) reported that there were 20–70% infants who referred Universal Newborn Hearing Screening (UNHS) have vestibular disorders. The comorbidity of cochlear and vestibular impairment is likely related to the two organ's similar embryonic origin, approximate genetic basis of sensory epithelium, close anatomical structures, and same blood supply source. Therefore, they could be affected by the same genetic embryonic factors, drugs, pathogenic microbial infection, and environment (10, 12–16).

However, vestibular dysfunction in children is often underestimated or ignored due to their limited expressiveness for precisely described symptoms, and feasibility of vestibular tests (17–19). Vestibular assessment in pediatric is quite challenging, but it has gained increasing attention and interests in recent years. Given the importance and high incidence of vestibular dysfunction, the necessity and feasibility of vestibular screening naturally emerge.

At present, vestibular screening has not been widely performed due to several reasons: firstly, it is difficult for infants and younger children to actively cooperate with the vestibular assessments, resulting in extremely challenging evaluation process; Secondly, specific screening tools, target population for screening, and the screening time point are not unified yet; Thirdly, the maturity of the vestibular system varies at different developmental stages, and test results from infants and younger children cannot be directly compared with reference data from adults. Normal reference values matching with children remain scanty.

UNHS has been conducted worldwide, contributing to early detection/diagnosis, and subsequent rehabilitation for infants with hearing loss. The international consensus (ICON) (20) and Joint Committee on Infant Hearing (JCIH) (21) recommended that those who failed hearing screening should accept diagnostic audiological assessment before 3 months of age. Whether the vestibular screening could be performed combining with diagnostic hearing test at 3rd month after birth

to save travel time and reduce unnecessary troubles such as repeated appointments is worth attention and discussion.

Cervical vestibular evoked myogenic potential (cVEMP) recorded from the contracted sternocleidomastoid muscle (SCMM) is an objective, non-invasive, timesaving, reproducible and well-tolerated evaluation method, which can be selected as a screening test to evaluate the otolith function in young children (22, 23). In terms of its evoked stimuli, air conducted sound (ACS), the most commonly used stimulus, is frequently used to elicit cVEMP. Chen et al. (24) performed ACS-cVEMP in 24 healthy newborns aged 2–5 days, and the response rate was 75%, indicating that the sacculocollic reflex pathway is well responsive at birth. Sheykholesami et al. (25) reported the morphology of ACS-cVEMP in infants aged 1–12 months was similar to adults. Erbek et al. (3) observed presented ACS-cVEMP from all 20 full-term healthy infants aged 5–24 weeks. All these studies imply that cVEMP can be elicited at an early age. However, ACS-cVEMP is not suitable for subjects with conductive hearing loss. In contrast, bone conducted vibration cVEMP (BCV-cVEMP) can bypass the middle ear, allowing to evaluate the saccule and inferior vestibular nerve pathway for subjects with middle ear pathology (10, 23, 26). Verrecchia et al. (15) implemented BCV-cVEMP in infants aged 1–6 months who referred for the 2nd hearing screening due to the failure of the 1st hearing screening or had high risk factors of hearing loss, and those who came for diagnostic hearing assessment. Their subjects included both normal hearing and SNHL infants, however, they were not grouped by hearing. Marten et al. (16) conducted BCV-cVEMP as a vestibular screening tool in 6-month-old infants with hearing loss from 2018 to 2020. The study was quite instructive and reemphasizes the importance of vestibular screening, however, lack of age-matched normal controls and specific normal reference values were not displayed in their study.

The purpose of this study is to investigate the characteristics of ACS-cVEMP and BCV-cVEMP in 3-month-old infants with normal hearing, same age infants with SNHL and healthy adults, and explore the feasibility and optimal strategies for infant vestibular screening at 3rd month after birth.

Materials and methods

Subjects

Twenty-nine full-term 3-month-old infants who failed the 2nd hearing screening and referred to the Diagnosis and Treatment Center of Hearing Impairment and Vertigo in Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine from May 2021 to March 2022 were enrolled in this study, including 14 males and 15 females. All of them accepted ACS-cVEMP without sedation and 23 of them completed BCV-cVEMP as well. Then all of them completed tympanogram, Distortion Product Otoacoustic Emission (DPOAE), click-evoked Auditory Brainstem Response (c-ABR) and Tone-Burst ABR (TB-ABR) at 500 and 1,000 Hz under sedation. Some infants also completed 2,000 and 4,000 Hz TB-ABR, Auditory Steady-State Response (ASSR), depending on the degree of hearing loss.

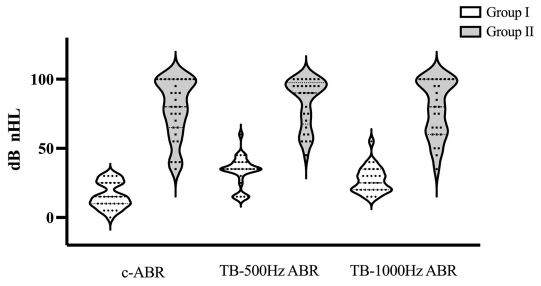

FIGURE 1
Hearing distributions in Group I and Group II. If there was no response at 95 dB nHL, a threshold of 100 dB nHLwas assumed. c-ABR, click-evoked Auditory Brainstem Response; TB-ABR, Tone-burst Auditory Brainstem Response.

Twenty-nine infants (58 ears) were divided into two groups according to their hearing. Group I included 27 normal hearing ears. Criteria for normal hearing as followings: no family genetic history, hypoxia, jaundice, viral infection, and other risk factors for hearing loss. Normal tympanogram with single or twin peaks at 1,000 Hz, passed DPOAE (four points passed at least in the six selected frequencies), air conducted c-ABR threshold $\leq$30 dB nHL. Group II included 29 SNHL ears. Criteria for SNHL: normal tympanogram, referred DPOAE ($<$4 points passed in the six selected frequencies), elevated air c-ABR threshold ($>$30 dB nHL), air and bone-conducted c-ABR threshold gap within 10 dB nHL.

For comparison, 20 healthy young adults (8 males and 12 females) were recruited as Group III, aged from 21 to 33 years old, with an average age of 25.10 $\pm$ 4.53 years old. All of them had normal tympanogram, 250–8,000 Hz pure-tone threshold $\leq$20 dB HL, no history of middle ear pathology, vestibular or neurological disease.

All the infants' parents and healthy adults signed the informed consent.

Methods

Instruments and recording parameters of cVEMP

ACS-cVEMP was recorded by the electrophysiological device (Neuropack MEB-9400, NIHON KOHDEN, Japan). Sound stimulus of TB-500 Hz (the rise/fall time = 1 ms, the plateau time = 2 ms) at 132 dB peSPL (105 dBnHL) was presented monaurally through a calibrated headphone TDH-39

TABLE 1 Subjects characteristics in three groups.

	ACS-cVEMP			BCV-cVEMP		
	Group I ($n = 27$)	**Group II ($n = 29$)**	**Group III ($n = 40$)**	**Group I ($n = 22$)**	**Group II ($n = 22$)**	**Group III ($n = 40$)**
Gender						
Male	11	16	20	10	14	20
Female	16	13	20	10	8	20
p		0.550			0.548	
χ^2		1.195			1.204	

Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.
n = number of ears.
Two ears (1 male and 1 female) with conductive hearing loss were not grouped.
The chi-square test showed there was no significant difference in gender among three groups of ACS-cVEMP or BCV-cVEMP (p = 0.550, 0.548, respectively).

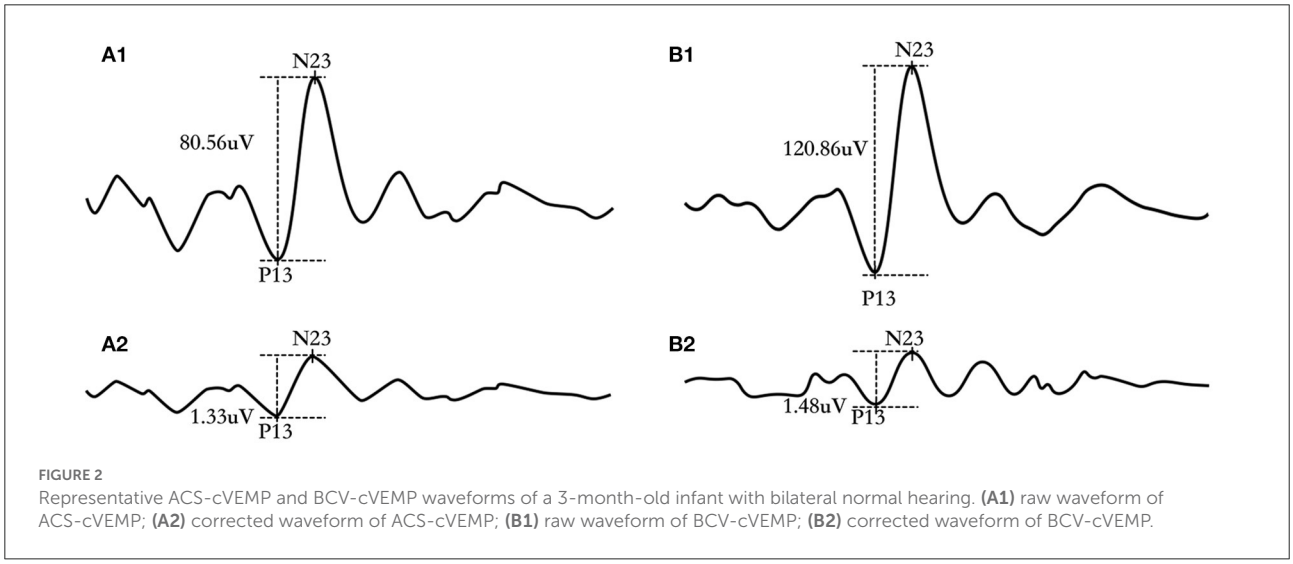

FIGURE 2
Representative ACS-cVEMP and BCV-cVEMP waveforms of a 3-month-old infant with bilateral normal hearing. **(A1)** raw waveform of ACS-cVEMP; **(A2)** corrected waveform of ACS-cVEMP; **(B1)** raw waveform of BCV-cVEMP; **(B2)** corrected waveform of BCV-cVEMP.

at a rate of 5 Hz. BCV-cVEMP was performed using the Eclipse device (Interacoustics, Denmark). Bone-conducted stimulus of TB-500 Hz was delivered using a B81 bone vibrator on the mastoid at 129.5 dB FL (60 dBnHL), and the stimulus rate was 5.1 Hz.

For both ACS-cVEMP and BCV-cVEMP, a minimum of 50 sweeps were averaged, and at least repeated twice to verify the waveform repeatability. The electromyogram (EMG) signals were amplified and bandpass filtered between 10 and 3,000 Hz. The recording window was −20–80 ms.

cVEMP testing procedure

Infants were entirely awake and placed in a supine position on the bed during testing. The local skin was treated with 75% alcohol and scrubbed lightly before the electrode placement. For ACS-cVEMP, the two reference electrodes were positioned at the upper third of the bilateral SCMM, the active electrodes were placed on the medial end of the clavicle on both sides. For BCV-cVEMP, the reference electrodes were positioned at the upper third of the bilateral SCMM, with an active electrode put on suprasternal notch, and the ground electrode was placed on the forehead in both tests. Electrode impedance was <5 kΩ and interelectrode impedance was roughly equivalent.

One audiologist operated the software, another one turned infant's head to the opposite side and tried to make the chin touched the shoulder to keep SCMM fully contracted. A family member comforted the infant and gently pressed the infant's shoulder to keep it from lifting. Toys and videos were used to distract the infant's attention. At least two trials were recorded on each side to confirm the waveform repeatability.

The cVEMP test parameters and electrode placement on healthy adults were the same as infants, while they were asked to rotate their heads toward the shoulder in the supine

TABLE 2 The response rate of ACS-cVEMP and BCV-cVEMP in three groups.

Group	Response rate	
	ACS-cVEMP	BCV-cVEMP
I	88.89% (24/27)	100% (22/22)
II	62.00% (18/29)[a]	86.36% (19/22)[c]
III	100% (40/40)[b]	100% (40/40)

Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.
[a]The chi-square test was used to compare the response rate of ACS-cVEMP between Group I and II. $p^a = 0.021$, $\chi^2 = 5.364$.
[b]The chi-square correction for continuity test was used to compare the response rate of ACS-cVEMP between Group I and III. $p^b = 0.120$, $\chi^2 = 2.418$.
[c]The chi-square correction for continuity test was used to compare the response rate of BCV-cVEMP between Group I and II. $p^c = 0.232$, $\chi^2 = 1.431$.

position, keeping the SCMM activated and tense until a certain procedure stopped.

Amplitude correction

For ACS-cVEMP, EMG activity was monitored on the screen. The mean rectified EMG of 20 ms pre-stimulation was calculated automatically by the device. The raw amplitude was divided by the mean rectified EMG to obtain the corrected amplitude. For BCV-cVEMP, the recording device has a function of EMG scaling to obtain the corrected amplitude. EMG activity was maintained at least >20 μV (15, 16, 24).

Investigational parameters of cVEMP

Characteristics of P13 and N23 latencies, P13-N23 interval, raw and corrected P13-N23 amplitudes were recorded. Since the cVEMP amplitude is strongly related to the strength of SCMM contraction, the interaural asymmetry ratio (IAR) was calculated using the corrected amplitude to compensate the bilateral amplitude difference caused by uneven EMG activity.

IAR = (AL – AS)/(AL + AS) × 100%, where AL is the larger corrected amplitude, AS is the smaller corrected amplitude (22, 24, 26).

The mean + 2SD of each parameter in normal hearing infants defined as the upper normal limit. Absent response or value exceeding the normal range was considered as abnormal.

Audiological assessment

All infants were sedated with Chloral Hydrate (50 mg/kg) for subsequent audiological assessment. Tympanogram was obtained by Interacoustics AT235H Middle Ear Analyzer (Interacoustics, Denmark). Single or twin peaks at 1,000 Hz probe tone was considered as a normal middle ear function (27, 28).

DPOAE and ABR were recorded by the same instrument as BCV-cVEMP (Interacoustics, Denmark). For DPOAE, primary tone stimulus intensities were set at L1 = 65 dB SPL and L2 = 55 dB SPL, and the primary tone frequency ratio (f2/f1) was 1.22. 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz were selected as test frequencies. Less than four of above frequencies passed with SNR ≥ 6 dB was defined as the refer criterion (29, 30).

For diagnostic ABR test, the active electrode was positioned on the center of the forehead, the ground electrode was put on the nasal root, and the reference electrodes were placed at the mastoid on both sides. Sound stimulus of click/Tone Burst in alternating polarity was delivered using a calibrated ER-3A inserted earphone at a stimulation rate of 37.1 Hz. The B81 bone vibrator was put on the mastoid of the test side and the non-test ear was masked. The bandpass filtered between 100 and 3,000 Hz. The recording window was 0–20 ms. A minimum of 1,024 sweeps were averaged. The maximum output of the stimulus was 95 dB nHL for air-conducted ABR and 45 dB nHL for bone-conducted ABR. The initial c-ABR stimulus intensity was 70 dB nHL. The stimulus intensity was initially reduced in 20 dB steps if wave-V was recognized, and if no wave-V was obtained at 70 dB nHL, the stimulus level delivered at 90 dB nHL directly. The ABR threshold was defined as the lowest stimulus intensity at which wave-V was still identifiable and repeatable. Two waveforms of absent wave-V at 5 dB nHL below the threshold intensity were necessary. The test sequence was air-conducted click, 500 and 1,000 Hz TB-ABR, bone-conducted c-ABR in order. TB-ABR at 2,000 and 4,000 Hz, ASSR were performed if necessary.

Statistical analyses

Data were analyzed using SPSS software 26.0 (IBM, Armonk, NY). Normal distribution was evaluated by the Shapiro-Wilk test. A comparison between groups was performed by independent *t*-test for parametric variables and Mann-Whitney *U*-test for non-parametric variables. The chi-square test or chi-square correction for continuity test was used to compare the response rate of ACS-cVEMP and BCV-cVEMP between Group I and II, and between Group I and III, respectively. Independent *t*-test or Non-parametric Mann-Whitney *U*-test was used to compare the P13 and N23 latencies, P13-N23 interval, and the raw and corrected amplitudes between groups, respectively. $p < 0.05$ was considered to be statistically significant.

Results

Subject characteristics

Twenty-nine infants participated in this study, in which 12 infants had bilateral normal hearing, 14 infants had bilateral

TABLE 3 The P13 and N23 latencies and P13-N23 interval of ACS-cVEMP in three groups.

Group	*n* (ears)	P13 latency (ms)				N23 latency (ms)				P13-N23 interval (ms)			
		Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR
I	24	13.13	1.90	13.08	11.61–13.80	18.40	1.85	17.83	17.43–19.36	5.27	1.20	5.13	4.68–5.79
II	18	13.21[a]	0.97	13.30	12.25–13.68	19.10[b]	1.40	19.48	17.96–20.10	5.73[c]	1.26	5.65	4.81–6.46
III	40	14.26[d]	1.69	14.10	12.83–15.43	21.63[e]	2.31	21.40	20.03–23.60	7.37[f]	1.70	7.55	6.10–8.40

Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.
n = number of ears.
[a,b,c,d]Independent t-test was used to compare the P13 and N23 latencies and P13-N23 interval of ACS-cVEMP between Group I and II, and between Group I and III.
$p^a = 0.866$, t = 0.170; $p^b = 0.190$, t = 1.335; $p^c = 0.252$, t = 1.163.
$p^d = 0.016$, t = 2.474; $p^e < 0.001$, t = 5.816; $p^f < 0.001$, t = 5.283.
SD, Standard deviation; IQR, interquartile range.

SNHL, and 3 infants had unilateral hearing loss. There were 2 ears with abnormal tympanogram in the unilateral hearing loss group which were excluded for ACS-cVEMP. Therefore, there were 27 normal hearing ears and 29 SNHL ears enrolled in ACS-cVEMP. Of these infants, 10 infants with bilateral normal hearing, 11 infants with bilateral SNHL and 2 infants with unilateral conductive hearing loss also completed BCV-cVEMP. On the whole, BCV-cVEMP was performed in 22 ears with normal hearing, 22 ears with SNHL and 2 ears with conducive hearing loss. Hearing distributions in Group I and Group II were depicted in Figure 1. The chi-square test showed there was no significant difference in gender among three groups of ACS-cVEMP or BCV-cVEMP (p = 0.550, 0.548, respectively, Table 1).

The waveform and response rate of ACS-cVEMP and BCV-cVEMP

Figure 2 depicted raw and corrected ACS-cVEMP (Figures 2A1,A2) and BCV-cVEMP (Figures 2B1,B2) waveforms from a 3-month-old infant with normal hearing. P13 and N23 were marked at the initial positive and negative peak.

The response rate of ACS-cVEMP in three groups were 88.89, 62.00, and 100%, respectively (Table 2). A significantly lower response rate was found in group II than that in group I (p = 0.021), while there was no statistically significant difference between group I and group III (p = 0.120). The response rates of BCV-cVEMP in three groups were 100, 86.36, and 100%, respectively, in which there was no statistically significant difference between group I and II (p = 0.232), or between group I and III.

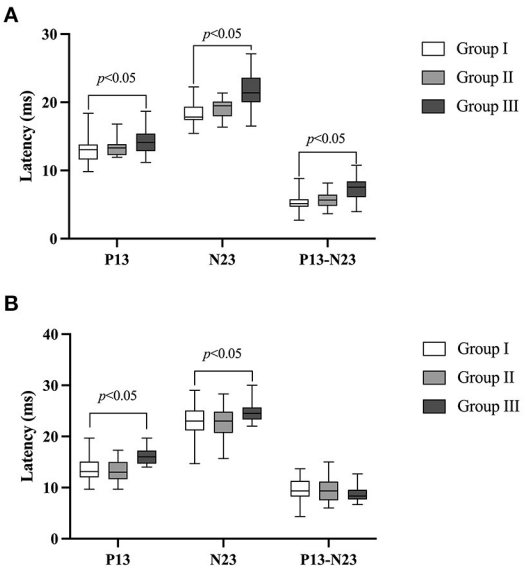

FIGURE 3
Comparison of the P13 and N23 latencies and P13-N23 interval of ACS-cVEMP and BCV-cVEMP. **(A)** Comparison of the P13 and N23 latencies and P13-N23 interval of ACS-cVEMP. The white box plot represented group I (n = 24 ears), light gray box plot represented group II (n = 18 ears), dark gray box plot represented group III (n = 40 ears). **(B)** Comparison of the P13 and N23 latencies and P13-N23 interval of BCV-cVEMP. The white box plot represented group I (n = 22 ears), light gray box plot represented group II (n = 21 ears), dark gray box plot represented group III (n = 40 ears). There was no significant difference of ACS-cVEMP in P13, N23 latency or P13-N23 interval between group I and group II. Significant differences were observed in all those parameters between groups I and group III. There was no significant difference of BCV-cVEMP in terms of P13 latency, N23 latency or P13-N23 interval between group I and group II. P13 and N23 latencies presented in Group III were significantly longer compared with group I, but not in the P13-N23 interval. In this study, no parameter comparison was made between group II and group III. Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.

P13 and N23 latencies and P13-N23 interval of ACS-cVEMP and BCV-cVEMP

The descriptive data including mean, standard deviation (SD), median and interquartile range (IQR) of three groups were displayed in Table 3. The independent t-test revealed that the P13 and N23 latencies and P13-N23 interval of ACS-cVEMP

TABLE 4 The P13 and N23 latencies and P13-N23 interval of BCV-cVEMP in three groups.

Group	*n* (ears)	P13 latency (ms)				N23 latency (ms)				P13-N23 interval (ms)			
		Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR
I	22	13.50	2.19	13.17	12.00–15.08	22.97	3.47	23.00	21.17–25.08	9.47	2.32	9.34	8.24–11.33
II	21	13.22[a]	1.98	13.00	11.67–15.00	22.87[b]	3.18	23.00	20.67–24.84	9.65[c]	2.51	9.34	7.51–11.17
III	40	16.11[d]	1.46	16.00	14.67–17.25	24.86[e]	1.92	24.50	23.33–25.67	8.74[f]	1.46	8.34	7.67–9.59

Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.
n = number of ears.
[a,b,c,d]Independent t-test was used to compare the P13 and N23 latencies and P13-N23 interval of BCV-cVEMP between Group I and II, and P13 latency between Group I and III.
$p^a = 0.665$, t = 0.435; $p^b = 0.925$, t = 0.094; $p^c = 0.806$, t = 0.247; $p^d < 0.001$, t = 5.629.
[e,f]Mann-Whitney U-test was used to compare the N23 latency and P13-N23 interval of BCV-cVEMP between Group I and III. $P^e = 0.018$, z = 2.359; $P^f = 0.110$, z = 1.599.
SD, Standard deviation; IQR, interquartile range.

TABLE 5 The raw and corrected amplitudes of ACS-cVEMP in three groups.

Group	*n* (ears)	Raw amplitude (μV)				Corrected amplitude (μV)			
		Mean	SD	Median	IQR	Mean	SD	Median	IQR
I	24	68.00	41.13	58.96	35.39–84.90	1.14	0.53	1.07	0.77–1.30
II	18	70.74[a]	40.36	57.18	46.73–83.00	1.07[b]	0.54	0.90	0.65–1.34
III	40	205.40[c]	138.97	179.26	74.94–300.63	1.93[d]	0.89	1.91	1.23–2.25

Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.
n = number of ears.
[a,b,c,d]Mann-Whitney U-test was used to compare the raw and corrected amplitudes of ACS-cVEMP between Group I and II, and between Group I and III.
$p^a = 0.741$, z = 0.330; $p^b = 0.525$, z = 0.636; $p^c < 0.001$, z = 4.535; $p^d < 0.001$, z = 3.932.
SD, Standard deviation; IQR, interquartile range.

did not differ significantly between group I and group II ($p = 0.866$, $p = 0.190$, $p = 0.252$, respectively Figure 3A). In contrast, statistically significant differences were found in these values between group I and group III ($p = 0.016$, $p < 0.001$, $p < 0.001$, respectively Figure 3A), indicating that significantly longer P13 and N23 latencies and P13-N23 interval presented in group III compared with group I.

The descriptive statistics of BCV-cVEMP in three groups were displayed in Table 4. The results indicated that there was no significant difference in the P13 latency, N23 latency or P13-N23 interval of BCV-cVEMP between group I and group II ($p = 0.665$, $p = 0.925$, $p = 0.806$, respectively Figure 3B). However, P13 and N23 latencies were significantly longer in group III than that in group I ($p < 0.001$, $p = 0.018$, respectively Figure 3B), but not in the P13-N23 interval ($p = 0.110$).

Raw and corrected amplitudes of ACS-cVEMP

The comparison of ACS-cVEMP between group I and group II demonstrated no significant difference in the raw or corrected amplitude ($p = 0.741$, $p = 0.525$, respectively, Table 5; Figure 4), while raw and corrected amplitudes in group III were significantly larger than that in group I ($p < 0.001$, $p < 0.001$, respectively, Table 5; Figure 4).

Raw and corrected amplitudes of BCV-cVEMP

There was no significant difference of BCV-cVEMP in the raw or corrected amplitude between group I and group II ($p = 0.771$, $p = 0.155$, respectively, Table 6; Figure 5). The raw amplitude was larger in group III compared with group I, but the difference did not reach statistical significance ($p = 0.093$). Significant difference existed between group I and group III with respect to the corrected amplitude of BCV-cVEMP ($p < 0.001$, Table 6; Figure 5).

Corrected IAR of ACS-cVEMP and BCV-cVEMP

The corrected IAR distribution in infants and adults were depicted in Figure 6. The corrected IAR of ACS-cVEMP had a median value of 30% in normal hearing infants (range: 4–40%, IQR: 25.50–34.75%), 15.00% in SNHL infants (range: 5–32%, IQR: 8.00–20.00%), and 13.50% in normal hearing adults (range:

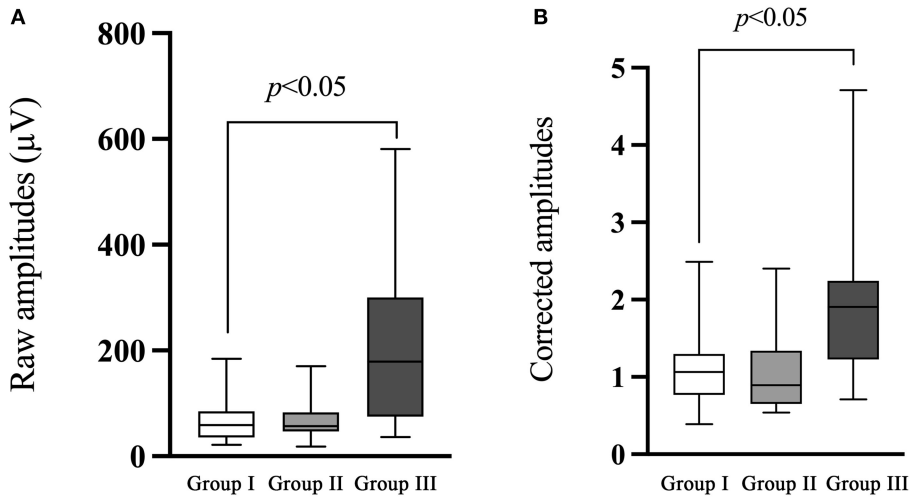

FIGURE 4
Comparison of the raw and corrected amplitudes of ACS-cVEMP. **(A)** The comparison of the raw amplitude of ACS-cVEMP. **(B)** The comparison of the corrected amplitude of ACS-cVEMP. The white box plot represented group I ($n = 24$ ears), light gray box plot represented group II ($n = 18$ ears), dark gray box plot represented group III ($n = 40$ ears). There was no significant difference in the raw or corrected amplitude between group I and group II. Group III had significantly larger raw and corrected amplitudes than that in group I. In this study, no parameter comparison was made between group II and group III. Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.

3–30%, IQR: 10.00–23.75%). For BCV-cVEMP, the median values of corrected IAR were 13.50% in normal hearing infants (range: 2–42%, IQR: 2.75–30.25%), 25.00% in SNHL infants (range: 5–45%, IQR: 15.50–39.50%), and 13.50% in normal hearing adults (range: 0–26%, IQR: 6.25–20.50%).

The mean and SD of corrected IAR of ACS-cVEMP and BCV-cVEMP in normal hearing infants and adults who elicited cVEMP response bilaterally were shown in Table 7. Mean + 2SD was defined as the upper limit of normal values. The upper normal limit of IAR in normal hearing infants was larger than that in adults. The results showed that the corrected IAR ranges of ACS-cVEMP and BCV-cVEMP in infants with SNHL (5–32% in ACS-cVEMP, 5–45% in BCV-cVEMP) were within upper normal limit of infants with normal hearing.

Discussion

Limited by the lack of B81 vibrator, unified test protocol, ACS-cVEMP is more accessible for most institutions compared with BCV-cVEMP at present. However, several studies have indicated BCV-cVEMP has the advantage of delivering sound directly to the inner ear and can be applied in infants and younger children who frequently present with conductive problems such as middle ear effusion, sebaceous glands and cerumen embolism in the external canal (1, 10, 15, 16). We performed both ACS-cVEMP and BCV-cVEMP, in order to provide normal reference values of these two stimuli modalities, and further promote the development of vestibular screening program.

Comparison of cVEMP characteristics in infants and adults

To explore the maturation of sacculocollic reflex pathway and establish normal values for infants at the age of 3 months, we compared cVEMP characteristics between healthy adults and 3-month-old infants. Our results showed that the response rates of ACS-cVEMP and BCV-cVEMP did not differ significantly between ears from normal hearing infants and adults, indicating that the sacculocollic reflex has well developed at the 3rd month after birth, and its function can be evaluated by cVEMP reliably, which were consistent with the previous studies (25, 31, 32).

Shorter latencies in infants and children have been discovered in some previous studies (25, 33, 34). In the present study, we also observed significantly shorter P13 and N23 latencies in ears from infants than those from adults for both ACS-cVEMP and BCV-cVEMP (2, 25, 35–37). Authors reported that P13 and N23 latencies are highly correlated to the degree of myelinization and the length of the sacculocollic reflex pathway (2, 38, 39). Incomplete development and maturation of the vestibular reflex pathway would influence the nerve conduction velocity, resulting in prolonged latencies. Additionally, since the common embryonic origin of the saccule and cochlea, the delayed latency can also appear in the ABR test. It has

TABLE 6 The raw and corrected amplitudes of BCV-cVEMP in three groups.

Group	*n* (ears)	Raw amplitude (μV)				Corrected amplitude (μV)			
		Mean	SD	Median	IQR	Mean	SD	Median	IQR
I	22	124.69	61.59	114.55	73.85–148.73	1.04	0.52	1.00	0.53–1.54
II	21	143.49[a]	97.40	126.00	61.65–193.60	1.44[b]	0.88	1.24	0.77–2.06
III	40	162.69[c]	89.41	141.70	88.41–211.48	2.33[d]	1.05	2.03	1.67–2.98

Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.
n = number of ears.
[a,b,c,d]Mann-Whitney U-test was used to compare the raw and corrected amplitudes of BCV-cVEMP between Group I and II, and between Group I and III.
$p^a = 0.771$, z = 0.292; $p^b = 0.155$, z = 1.422; $p^c = 0.093$, z = 1.677; $p^d < 0.001$, z = 5.017.
SD, Standard deviation; IQR, interquartile range.

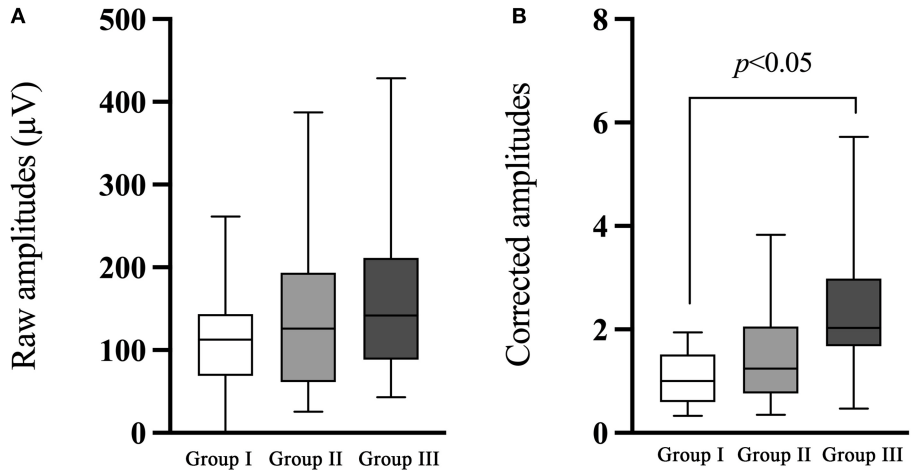

FIGURE 5
Comparison of the raw and corrected amplitudes of BCV-cVEMP. **(A)** The comparison of the raw amplitude of BCV-cVEMP. **(B)** The comparison of the corrected amplitude of BCV-cVEMP. The white box plot represented group I (*n* = 22 ears), light gray box plot represented group II (*n* = 21 ears), dark gray box plot represented group III (*n* = 40 ears). There was no significant difference of BCV-cVEMP in the raw or corrected amplitude between group I and group II, or in raw amplitude between group I and III. A significant difference existed in the corrected amplitude between group I and III. In this study, no parameter comparison was made between group II and group III. Group I: Normal hearing ears from infants; Group II: Sensorineural hearing loss ears from infants; Group III: Normal Hearing ears from adults.

been concluded that the vestibular system is fully developed and responsive at full-term birth, and the sacculocollic reflex pathway grows rapidly after birth (6, 39–42), however, the increased latencies mainly occur in preterm or neonates younger than 3 days as a result of hypomyelination. Our subjects were all 3-month-old full-term infants, and no prolonged latency presented during the ABR test. Therefore, we can safely assume that the maturation has no significant effect on latency in the current study. Moreover, studies reported the neck length can be used as an alternative way to estimate the pathway length, thereby a neck length of 15.3 cm as a cut-off point was proposed. There is a positive correlation between the neck length and cVEMP latency when it is within 15.3 cm. When exceeds this cut-off point, results are similar to that in adults (2, 43). Kelsch et al. (38) presented similar data, they found normal hearing children aged 3–5 years old had shorter latencies in comparison to those older than 5 years old, which is likely attributed to the increased path length with age.

In consideration of cVEMP amplitude, many studies have reported that smaller amplitude present in children compared with adults, which can be explained by the smaller muscle contraction in children (33). In agreement with previous studies, we also found a statistically significant smaller amplitude in ears from infants than that from adults. It has been well documented that EMG level is strongly correlated with cVEMP amplitudes (25). Raw amplitudes are less repeatable and present with wider variations due to the variability in SCMM contraction. Therefore, it is recommended that corrected amplitudes should be used if possible. Lee et al. (44) demonstrated that scaled amplitudes can provide more reliable and accurate information in the diagnosis of vestibular disorders. In this study, we monitored the EMG activity during

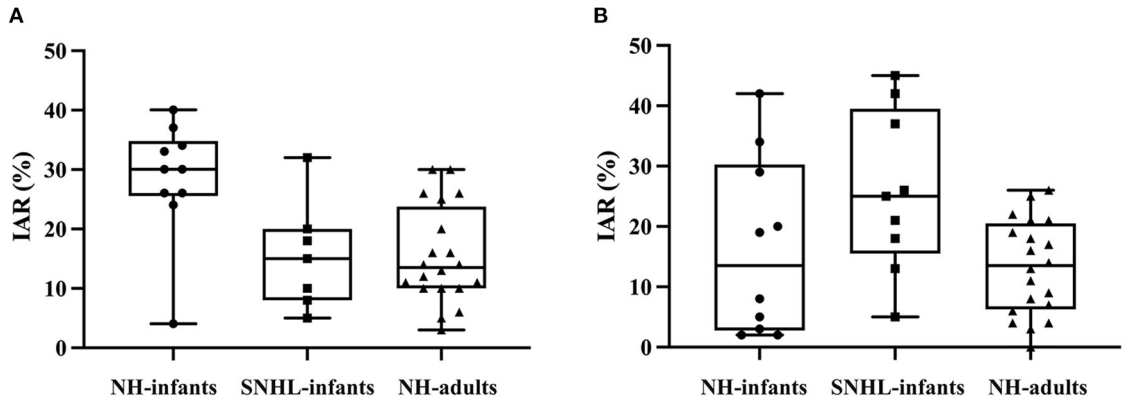

FIGURE 6
The distribution of corrected IAR of ACS-cVEMP and BCV-cVEMP. **(A)** The distribution of corrected IAR of ACS-cVEMP. **(B)** The distribution of corrected IAR of BCV-cVEMP. A wider range occurred in normal hearing infants compared with adults in both ACS-cVEMP and BCV-cVEMP. The corrected IAR of ACS-cVEMP in SNHL infants were fallen into the range of normal hearing infants. However, for BCV-cVEMP, the maximum corrected IAR of SNHL infants exceeded the maximum value of normal hearing infants. IAR: interaural asymmetry ratio. NH-infants: Normal hearing infants. SNHL-infants: Sensorineural hearing loss infants. NH-adults: Normal hearing adults.

TABLE 7 The Corrected IAR of ACS-cVEMP and BCV-cVEMP in group I and group III.

	Corrected IAR of ACS-cVEMP (%)				Corrected IAR of BCV-cVEMP (%)			
	Mean	SD	Mean + 2SD	*n*	Mean	SD	Mean + 2SD	*n*
Normal hearing infants	28.40	9.96	48.32	10	16.40	14.68	45.76	7
Normal hearing adults	15.40	8.15	31.70	20	13.20	7.85	28.90	20

n = number of subjects who elicited cVEMP response bilaterally.
IAR, interaural asymmetry ratio; SD, Standard deviation.
Mean + 2SD was defined as the upper limit of normal values.

the test procedure, and finally obtained the normalized values. As shown in Figures 4B, 5B, significantly larger corrected amplitudes of ACS-cVEMP and BCV-cVEMP were found in ears from adults than those from infants, which is probably due to the test conditions. Unlike adults, 3-month-old infants are unable to elevate or rotate their heads to contract the SCMM. As an alternative, one audiologist lifted infant's head and rotated it to the opposite side, during which infant may resist and cry, and the earphones and bone vibrator held by another audiologist may change position or slide, leading to smaller amplitudes. Consequently, it is of great importance to establish normal values in different age groups before using VEMP results for clinical diagnosis.

Comparison of cVEMP characteristics in infants with normal hearing and SNHL

Many investigators have reported children with SNHL are at high risk of vestibular dysfunction, which could be explained by the close anatomical and embryological relationship between cochlea and vestibular end organs (45–48). Additionally, it has been reported that the etiology and degree of SNHL may be important predictors of vestibular dysfunction (45). Tribukait et al. (34) investigated vestibular function in children with profound hearing loss aged 15–17 years old indicating that the incidence of vestibular dysfunction was correlated with the degree of hearing loss, and it increased significantly when hearing loss worse than 90 dB nHL. Maes et al. (13) found that children with profound hearing loss had significantly higher abnormality rate of vestibular dysfunction than that in children with moderate hearing loss. Therefore, vestibular assessment of SNHL subjects is quite necessary.

While studies have demonstrated that cVEMP is a viable technique to evaluate the vestibular function in the pediatric population. Most of them targeted on children with vertigo symptoms, cochlear implant candidates, and SNHL children at an older age. Few studies included an age-matched normal controls, especially in infants, leading to a lack of normal reference values for comparison.

In the current study, we divided ears from infants into two groups by hearing. Our results showed that the response rate

of ACS-cVEMP in SNHL ears was 62.00%, lower than that in normal hearing ears (88.89%). The results were agreement with previous studies (49, 50). For BCV-cVEMP, the response rate in ears with SNHL was 86.36%, which was in accordance with the recent studies (10, 16). Martens et al. (16) implemented BCV-cVEMP as a vestibular screening tool in 169 infants with hearing loss at the age of 6 months, nearly 88.8% infants passed the 1st screening, and 90.5% passed the 2nd screening at the age of 9 months. On the contrast, Verrecchia et al. (15) reported a higher BCV-cVEMP refer rate of 36.4% in children regardless of hearing. Verbecque et al. (9) demonstrated the refer rate of ACS-cVEMP in SNHL children was 43%. The various percentages of abnormalities may possibly relate to the following factors: Firstly, different characteristics of targeted subjects. Due to the close relationship between cochlea and vestibular organs, the etiology and degree of hearing loss play important role on the abnormal percentage. The study of Verrecchia et al. (15) included infants who had meningitis, fetal virus infections etc., which may result in a higher abnormal rate. Furthermore, the majority of the targeted population of Verbecque et al. (9) consisted of children with severe-profound hearing loss, while our study targeted at infants with different degree of hearing loss ranged from mild to profound. Thus, a higher risk of vestibular dysfunction may exist in their study. Secondly, test conditions are different. The stimulus modality (air conducted or bone vibration), intensity, and test position (supine or sit) are all related to the cVEMP results. Moreover, unequal diagnostic criteria in different institutions also lead to various interpretations (26, 51).

Interestingly, we observed there was no significant difference in terms of the response rate of BCV-cVEMP between normal hearing ears and SNHL ears, which was inconsistent in comparison with ACS-cVEMP. In addition to the individual-related and test-related influence factors which has been mentioned above, the response rate is highly related to the stimulus modality, which may also be used to explain the higher response rate of BCV-cVEMP than ACS-cVEMP in ears with SNHL in this study. Previous studies found lower response rate of ACS-cVEMP compared with BCV-cVEMP in adults (52–54). Taylor et al. (55) and Huang et al. (56) reported the abnormal prevalence of cVEMP elicited by ACS was higher than that of BCV in patients with Ménière's disease. On one hand, this may contribute to the different stimulus modality. Studies have reported that the mechanisms of ACS and BCV to activate otolith organs are different (57). It seems that ACS predominantly activates saccular afferents, while BCV stimulates both saccular and utricular afferent (58). Animal experiments have demonstrated that apart from the ipsilateral saccule pathways, otolith projections to the SCMM also include active potentials from the utricle (53, 58). Additionally, it has been shown that BCV stimulus can generate linear acceleration of the skull, while ACS stimulus only make labyrinth flow by pumping the stapes, so more otolith fibers are activated by BCV (41, 53, 58–60). Another hypothesis is that the hair cell cilia in the otolith deflect differently when stimulated by ACS and BCV. BCV induces more effective shear movement on the otolith membrane, leading to more hair cells activated (60). However, the exact mechanism is still being studied. On the other hand, it possibly caused by the limited number of subjects in our study, which should be further discussed in an enlarged sample size. In addition, the response rate of ACS-cVEMP is related with the middle ear status. The amniotic fluid and mesenchyme in the middle ear are not completely disappeared in newborns and infants. In our study, we performed 1,000 Hz tympanometry to assess the middle ear condition. However, some studies reported that although 1,000 Hz tympanometry is recommended to evaluate the middles ear status in infants under 6 months, it still has some limitations in terms of sensitivity and specificity (61, 62). Wideband tympanometry (WBT) has a wide range of stimulus from 226 to 8,000 Hz, which is more sensitive and could provide more informative data about the middle ear condition than traditional 226 or 1,000 Hz tympanometry. Studies indicated that WBT combined with previous medical history and otoscopy can improve the accuracy of middle ear function assessment (63–65). Therefore, the criterion of normal middle ear function in our study may not comprehensive enough, WBT should applied in further study.

In this study, characteristics of ACS-cVEMP and BCV-cVEMP in SNHL ears were similar with those in normal hearing ears. No significant difference was detected between two groups in P13 latency, N23 latency, P13-N23 interval, raw or corrected amplitude, which was in agreement with other studies. Maes et al. (13) investigated cVEMP in SNHL children aged 4–13 years old, demonstrating no significant difference existed in the above parameters when compared with normal-hearing peers. These findings may imply the response rate plays an important role in interpreting cVEMP results clinically.

Corrected IAR of ACS-cVEMP and BCV-cVEMP

Previous studies recommended that amplitude normalization technique should be used during cVEMP test (66). Consequently, we mainly focused on the corrected IAR rather than raw IAR in different groups. Our results showed that the IAR range in normal hearing infants was broader than that in normal hearing adults in both ACS-cVEMP and BCV-cVEMP. And the IAR ranges of ACS-cVEMP and BCV-cVEMP in infants with SNHL were within the upper normal limit of normal hearing infants, implying that bilateral vestibular function is symmetrical in SNHL infants. Due to the small number of subjects in this study, it may not powerful enough

to establish normal IAR reference values, further large-scale studies of IAR are required.

Recommendations and strategies for vestibular screening in infants

Early detection of vestibular impairment can promote timely rehabilitation and reduce the negative impact on subsequent motor and balance development. In our study, clear and reproducible waveforms can be elicited by both ACS and BCV in normal hearing infants, and response rates were comparable to those of adults, indicating the feasibility of conducting cVEMP in infants at the age of 3 months. Additionally, it is recommended that infants who failed the 2nd hearing screening are expected to accept diagnostic hearing tests at the age of 3 months (20, 21). Based on these findings, our study performed cVEMP integrated with the clinical ABR diagnostic tests at 3 months of age. It was quite convenient as most ABR equipment includes VEMP module. In addition, it can avoid multiple round trips, reduce the number of appointments etc., which can contribute to a higher participate rate. Thus, we conclude that implementing the vestibular screening at 3rd months after birth may be appropriate and vestibular screening is technically feasible.

In terms of stimulus modality, majority of previous studies applied ACS in the vestibular assessment in infants and children. However, it should be noted that the response rate of ACS-cVEMP would be influenced by the conductive hearing loss which is common in pediatrics. BCV can bypass middle ear and suitable for subjects with middle ear pathology. However, limited by technology and cVEMP developmental maturity, not many institutions have access to the appropriate bone vibrator. Thus, it is meaningful to explore both ASC and BCV-cVEMP for extensive vestibular screening in different centers. Those who present with absent cVEMP are suggested to accept the 2nd screening at the age of 6 months to confirm the abnormality, which is also coincides with the 2nd diagnostic hearing loss tests and hearing-aid fitting if necessary. For centers equipped with bone vibrator, ACS-cVEMP combined with BCV-cVEMP are recommended in order to improve the accuracy of vestibular screening.

Limitations

There are some limitations in this study should be noted. Firstly, not all subjects completed both ACS-cVEMP and BCV-cVEMP in this study, so there may be some deviations in subject selection that may affect the results. Secondly, limited by the number of infants in the current study, we did not discuss the effect of the degree or etiology of hearing loss on cVEMP characteristics, which should be further studied in a large sample scale. Thirdly, the devices for ACS-cVEMP and BCV-cVEMP were not unified. Furthermore, the specific passing criterion for vestibular screening needs to be further refined. And it should be noted that cVEMP does not reflect the canal function, a comprehensive evaluation is required in combination with other tests at an older age.

Conclusion

According to this study, we draw a conclusion that ACS-cVEMP is feasible to evaluate vestibular function in infants at 3rd month after birth with a high response rate. ACS-cVEMP combined with BCV-cVEMP are recommended to improve the accuracy of vestibular screening, especially in those who have conductive middle ear problems. Early vestibular screening combined with hearing diagnosis is meaningful and worth of attention, which can minimize the negative effects on all aspects of life. Parameter values established in this study can provide references in clinical vestibular screening.

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 the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine (Approval No. XHEC-D-2022-138). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JSh was responsible for data interpretation and manuscript preparation. LW and XW collected the clinical data. XM contributed to data analysis. ZC helped to optimize the cVEMP test procedure. KH, WW, JSu, and QinZ were responsible for auditory tests and cVEMP test assistance. JC, XC, and MS contributed to statistical consultation. QingZ, KK, and MD reviewed and revised the manuscript and study design. YJ and JY were responsible for the research design and manuscript revision. 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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EDITED BY
Katsumi Doi,
Kindai University, Japan

REVIEWED BY
Takeshi Tsutsumi,
Tokyo Medical and Dental University, Japan
Klaus Jahn,
Schoen Clinic Bad Aibling—Dept. of Neurology, Germany
Munetaka Ushio,
Japan Community Healthcare Organization (JCHO), Japan

*CORRESPONDENCE
Yulian Jin
jinyulian8548@xinhuamed.com.cn
Jianyong Chen
chenjianyong@xinhuamed.com.cn
Jun Yang
yangjun@xinhuamed.com.cn

†These authors have contributed equally to this work

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Potential vestibular pathway impairment in children with recurrent vertigo: An investigation through air-conducted sound and galvanic vestibular stimulation-triggered vestibular evoked myogenic potentials

Xiayu Sun[1,2,3†], Dekun Gao[1,2,3†], Jiali Shen[1,2,3†], Qi Zhu[4], Lu Wang[1,2,3], Xiaobao Ma[1,2,3], Wei Wang[1,2,3], Xiangping Chen[1,2,3], Qing Zhang[1,2,3], Yulian Jin[1,2,3*], Jianyong Chen[1,2,3*] and Jun Yang[1,2,3*]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China, [4]Department of Otorhinolaryngology-Head & Neck Surgery, Yuyao People's Hospital, Yuyao, China

Objective: This study aims to investigate the potential vestibular pathway impairment through vestibular evoked myogenic potentials (VEMPs) and to explore the pathophysiological significance of these instrument-based findings in children with recurrent vertigo.

Materials and methods: The clinical data of 21 children (mean age 4.67 ± 1.39 years) diagnosed as RVC who met the inclusion criteria of the Bárány Society and 29 healthy children (mean age 4.83 ± 1.34 years) enrolled as the control group from February 2021 to December 2021 were collected and analyzed retrospectively. All the subjects underwent both cervical VEMP (cVEMP) and ocular VEMP (oVEMP) triggered by air-conducted sound (ACS) and galvanic vestibular stimulation (GVS), respectively. The elicit rate, latency, and amplitude asymmetry ratio (AAR) of ACS-cVEMP, ACS-oVEMP, GVS-cVEMP, and GVS-oVEMP were analyzed.

Results: (1) The elicit rates of ACS-cVEMP and ACS-oVEMP were similar in the two groups ($P > 0.05$), as well as GVS-cVEMP and GVS-oVEMP ($P > 0.05$). (2) P1 and N1 latencies of ACS-cVEMP and GVS-cVEMP in the RVC group were longer than those in the control group ($P < 0.05$). (3) The N1 latency of ACS-oVEMP in the RVC group was shorter than that in the control group ($P < 0.05$), while there was no significant difference in the P1 latency of ACS-oVEMP ($P > 0.05$). The N1 and P1 latencies of GVS-oVEMP were not significantly different ($P > 0.05$). (4) There was no statistical difference in the AAR of ACS-cVEMP and

GVS-cVEMP. Although there was an increased AAR of ACS-oVEMP in the RVC group ($P < 0.05$), the AAR was within the normal range. However, no statistical difference was found in the AAR of GVS-oVEMP in the two groups ($P > 0.05$).

Conclusion: The latencies of ACS-cVEMP and GVS-cVEMP in children with recurrent vertigo were significantly prolonged compared with those in healthy children, and there was no difference in elicit rates of ACS-cVEMP and GVS-cVEMP, suggesting that there might be potential impairment in the inferior vestibular nerve and the subsequent nerve conduction pathway in RVC.

KEYWORDS

recurrent vertigo of childhood, vestibular evoked myogenic potential, elicit rate, latency, saccule, utricle, vestibular pathway

Introduction

The spectrum of vertigo diseases in children and adults is different. In children, the most common diseases that cause vertigo are vestibular migraine (VM) and benign paroxysmal vertigo of childhood (BPVC) (1, 2). BPVC, first reported by Basser in 1964 (3), is characterized by recurrent spontaneous attacks of vertigo, which may be associated with vomiting, pallor, fearfulness, postural imbalance, ataxia, and/or nystagmus in otherwise healthy children (4). Children with BPVC present with recurrent episodes of dizziness or vertigo, without accompanied by visual aura, photophobia, phonophobia, and ear symptoms such as tinnitus, aural fullness, hearing loss, or neurological symptoms such as change in consciousness.

The Committee of Vestibular Disorders of the Bárány Society and the International Headache Society released the latest diagnostic criteria of vertigo disorders in children in 2021. Since then, the diagnostic nomenclature BPVC has been replaced by "recurrent vertigo of childhood (RVC)". The diagnostic criteria of RVC include (1) at least three episodes with vestibular symptoms of moderate or severe intensity, lasting between 1 min and 72 h; (2) none of the criteria for VM, with no history of migraine with or without aura, photophobia, and phonophobia; (3) age <18 years; and (4) not better accounted for by another headache disorder, vestibular disorder, or other conditions (4).

At present, the pathogenesis of RVC remains unclear. Some studies suggested that children with RVC have abnormal vestibular evoked myogenic potentials (VEMPs) (5–7), mainly reflected as the failure of elicitation and latency delay, indicating that there is a potential impairment in the otolith and vestibular nerve conduction pathway. VEMPs can be induced by air-conducted sound (ACS), bone-conducted vibration (BCV), and galvanic vestibular stimulation (GVS). Both ACS-VEMPs and BCV-VEMPs depend on the intactness of the otolith, while GVS directly stimulates the vestibular verve endings to elicit VEMPs. Therefore, those findings induced by different VEMPs can be compared to locate the lesion of the vestibular pathway in intra-labyrinthine or retro-labyrinthine (8). More often, GVS-VEMPs can be recorded in adults; however, there is no research on GVS-VEMPs in children (9, 10). Our study intends to investigate the potential vestibular pathway impairment through VEMPs and to explore the pathophysiological significance of these instrument-based findings in children with RVC.

Materials and methods

Design of the study

This study was conducted in the Department of Otorhinolaryngology-Head & Neck Surgery of Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine, which was designed and conducted following the ethical standards of the Helsinki Declaration. It was completed from February 2021 to December 2021 after approval from the ethical committee of the institute (No. XHYY-2021-039).

The inclusion criteria for healthy children in the control group were as follows: (1) no history of dizziness, vertigo, or headache; (2) no history of brain disease and trauma; (3) no history of ear diseases; (4) pure tone average (500–2,000 Hz) in the normal range of 0–25dB HL; and (5) no cognitive impairment.

The inclusion criteria for children with RVC were (1) at least three episodes with vestibular symptoms of moderate or severe intensity, lasting between 1 min and 72 h; (2) no history of migraine with or without aura, photophobia, and phonophobia; (3) age <18 years; and (4) not better accounted for by another headache disorder, vestibular disorder, or other condition.

The exclusion criteria for children with RVC were as follows: (1) a history of benign paroxysmal positional vertigo, vestibular neuritis, Meniere's disease, and other peripheral vestibular vertigo diseases; (2) a history of VM and headache; (3) a history of known neurological diseases; (4) a history of ear diseases; and (5) unable to cooperate to complete VEMP tests.

A detailed explanation of the procedures that they may undergo was given to the participants, and a signed informed consent form was obtained from the guardian of each participant. ACS-VEMPs and GVS-VEMPs were applied to both ears of each participant who met the inclusion criteria.

Participants

A total of 29 healthy children aged 3–9 (4.83 ± 1.34) years and 21 children with RVC aged 3–9 (4.67 ± 1.39) years participated. In total, 15 boys and 14 girls were in the control group, while 12 boys and 9 girls were in the RVC group. The distribution of girls and boys in each group was equal. All participants were evaluated with ACS-cVEMP, ACS-oVEMP, GVS-cVEMP, and GVS-oVEMP tests.

ACS-VEMPs

The ACS-VEMP tests were performed using Neuropack MEB-9404 C (NIHON KOHDEN, Japan). A 500-Hz tone burst was given as a stimulus to obtain a VEMP response, and a rate of 5.1/s and an intensity of 105 dB nHL (132 pe SPL) were presented to the ipsilateral ear by air conduction insert earphones. The rise/fall time was 1 ms, and the plateau was 2 ms.

The cVEMP test was performed in the participants in a sitting position. They were required to turn their heads away from the stimulated ear in order to elicit an appropriate and replicable contraction level of the sternocleidomastoid muscle (SCM). Electrode placement: two record electrodes were placed symmetrically at the upper third of bilateral SCMs, the reference electrode was placed on the sternal end of the SCM, and the ground electrode was placed over the forehead. The oVEMP test was performed with participants in a sitting position with their heads kept straight. They were required to gaze at a maximal comfortable up-gaze position to elicit appropriate and replicable contraction level of the inferior oblique muscle (IOM). Electrodes placement: two record electrodes were placed symmetrically below the center of each lower eyelid, two reference electrodes were placed 2–3 cm inferior to the record electrodes and the ground electrode was placed over the forehead.

An electromyography (EMG) recording window also displayed the background muscle activity at the same time, which could reflect whether the muscle strength of SCM or IOM was maintained within the ideal range required for the test, which is usually above 50 mV for the SCM in children older 3 years (11).

The VEMP waveform have a positive and a negative peak, which are named P1 and N1, respectively. VEMP indices include elicit rate, P1 latency, N1 latency, P1-N1 amplitude, and amplitude asymmetry ratio (AAR). The P1 latency, N1 latency, and P1-N1 amplitude value were recorded on both ears of each participant. The AAR was calculated using the formula (AL -AS) / (AL + AS) × 100%, where AL is the larger P1-N1 amplitude value between two ears, while AS is the smaller one. In other words, AAR is the difference of bilateral amplitudes divided by the sum of bilateral amplitudes. The AAR value is between 0 and 1. The closer the value to 0, the better the symmetry of bilateral VEMPs. The closer the value to 1, the worse the symmetry of bilateral VEMPs, considering that there might be dysfunction of the unilateral otolith and vestibular nerve conduction pathway (12).

Our study set the upper limit standard of the normal AAR value of cVEMP to 33%, that is, when the P1-N1 amplitude of one ear is less than half that of the other ear, it is judged to be abnormal (13).

In the review on VEMPs written by Dlugaiczyk (14), it was mentioned that the "AAR value exceeding 40% indicates the asymmetry of bilateral utricle and the superior vestibular nerve conduction pathway". Therefore, our study set the upper limit standard of the normal AAR value of oVEMP to 40%.

GVS-VEMPs

The GVS-VEMP tests were performed using Neuropack MEB-9404 C (NIHON KOHDEN, Japan). The stimulus rate was 5 Hz, the stimulus duration was 1 ms, and the current level was 3 mA. For each trace, the number of stimuli was 100. EMG recordings were amplified for analysis. A 20- to 2,000-Hz bandpass filter and notch filter were applied on collected recordings. The analysis time window was 50 ms.

The GVS-VEMP tests were performed with the participants in a sitting position in two stages. In the first stage, when the SCM/IOM was not contracted, the first trace was obtained by sending the galvanic stimulus over the mastoid of the side being tested. In the second stage, when the SCM/IOM was contracted, the second trace was obtained by sending the galvanic stimulus. There were artifacts from the galvanic stimulus in both traces. Since these waveforms included very high artifacts, the subtraction method was used to eliminate artifacts. The first trace (without contraction of SCM/IOM) was subtracted from the second trace (with contraction of SCM/IOM), and finally, the GVS-VEMP waveforms were obtained (10).

Recording parameters were identical to those of ACS-VEMPs. For GVS-cVEMPs, two record electrodes were placed symmetrically at the middle of bilateral SCMs, a reference electrode was placed on the superior sternal fossa, a ground electrode was placed on the nasion, a negative stimulus electrode was placed on the mastoid, and a positive stimulus electrode was placed over the forehead. For GVS-oVEMPs, two record electrodes were placed symmetrically below the center of each lower eyelid, two reference electrodes were placed 2–3 cm inferior to the record electrodes, a ground electrode was placed

on the nasion, a negative stimulus electrode was placed on the mastoid, and a positive stimulus electrode was placed over the forehead.

Statistical analysis

The data were analyzed by IBM SPSS Statistics 26.0 (Chicago, IL, United States). The mean and standard deviation for latencies and amplitudes of VEMPs and the percentages of elicit rate and AAR were calculated. Parametric tests were used for all statistical analyses. Two independent sample *t*-tests were used for the comparison between the healthy children and children with RVC. The chi square test was used to compare the elicit rates. Statistical significance was set at $P < 0.05$.

Results

General data of participants

This study was carried out with 29 healthy children (58 ears) and 21 children with RVC (42 ears). In the control group, a total of 15 boys and 14 girls participated in the study, while in the RVC group, 12 boys and nine girls were involved. No statistical significance was observed in the comparison of the gender between the two groups ($\chi^2 = 0.144$, $P = 0.704$). All the participants' ages ranged from 3 to 9 years, in which the age of the control group was 4.83 ± 1.34 years and the age of the RVC group was 4.67 ± 1.39 years. There was no significant difference in age between the two groups ($t = 0.413$, $P = 0.682$).

Comparison of cVEMP elicit rates

The cVEMP elicit rates of the two groups are shown in Table 1. The ACS-cVEMP elicit rate was 98% in the RVC group and 97% in the control group, with no statistically significant difference between the two groups ($\chi^2 = 0.095$, $P = 0.758$). The GVS-cVEMP elicit rate was 98% in the RVC group and 93% in the control group, with no statistically significant difference between the two groups ($\chi^2 = 1.046$, $P = 0.306$). Typical results of ACS-cVEMP and GVS-cVEMP are shown in Figure 1.

Comparison of oVEMP elicit rates

The oVEMP elicit rates of the two groups are shown in Table 2. The ACS-oVEMP elicit rate was 90% in the RVC group and 83% in the control group, with no statistically significant difference between the two groups ($\chi^2 = 1.205$, $P = 0.272$). The GVS-cVEMP elicit rate was 95% in the RVC group and 88% in the control group, with no statistically significant difference between the two groups ($\chi^2 = 1.588$, $P = 0.208$). Typical results of ACS-oVEMP and GVS-oVEMP are shown in Figure 2.

Self-comparison of cVEMP and oVEMP elicit rates in the control group

The cVEMP and oVEMP elicit rates of the control group are shown in Table 3. The elicit rate of ACS-cVEMP was 97%, which was higher than the 83% value of ACS-oVEMP, with a statistical significance in the comparison ($\chi^2 = 5.949$, $P = 0.015$). The GVS-cVEMP and GVS-oVEMP elicit rates of the control group were 93 and 88%, respectively, with no statistical significance in the comparison ($\chi^2 = 0.904$, $P = 0.342$).

Self-comparison of cVEMP and oVEMP elicit rates in the RVC group

The cVEMP and oVEMP elicit rates of the RVC group are shown in Table 4. The elicit rate of ACS-cVEMP was 98%, which was similar to the 90% value of ACS-oVEMP, with no statistical significance in the comparison ($\chi^2 = 1.914$, $P = 0.167$). The GVS-cVEMP and GVS-oVEMP elicit rates of the RVC group were 98 and 95%, respectively, with no statistical significance in the comparison ($\chi^2 = 0.346$, $P = 0.556$).

Comparison of latencies and intervals of cVEMP

The cVEMP P1 latencies, N1 latencies, and intervals of the two groups are shown in Figure 3. The P1 and N1 latencies of ACS-cVEMP and GVS-cVEMP in the RVC group were longer than those in the control group, with statistical significance in the comparison ($P < 0.05$). The interval of GVS-cVEMP in the

TABLE 1 Comparison of cVEMP elicit rates between the RVC group and the control group.

Group	ACS-cVEMP				GVS-cVEMP			
	Elicite (ears)	Not elicite (ears)	χ^2	P	Elicite (ears)	Not elicite (ears)	χ^2	P
RVC	41	1	0.095	0.758	41	1	1.046	0.306
Control	56	2			54	4		

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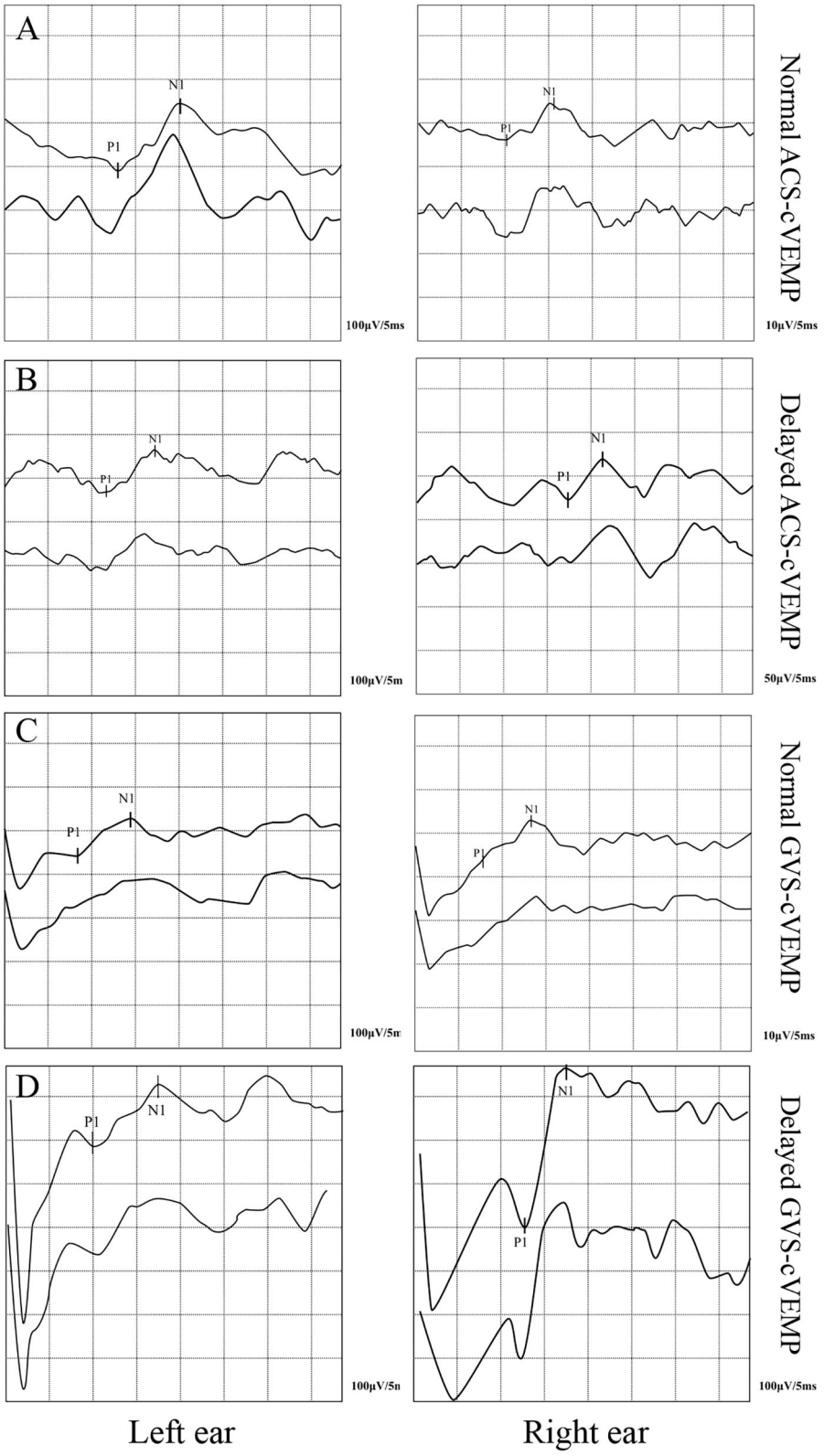

FIGURE 1
Typical double-trace records of cVEMPs. **(A)** Normal ACS-cVEMP. **(B)** Delayed ACS-cVEMP. **(C)** Normal GVS-cVEMP. **(D)** Delayed GVS-cVEMP.

TABLE 2 Comparison of oVEMP elicit rates between the RVC group and the control group.

Group	ACS-oVEMP				GVS-oVEMP			
	Elicite (ears)	Not elicite (ears)	χ^2	P	Elicite (ears)	Not elicite (ears)	χ^2	P
RVC	38	4	1.205	0.272	40	2	1.588	0.208
Control	48	10			51	7		

RVC group was longer than that in the control group, with statistical significance in the comparison ($P < 0.05$). But the interval of ACS-cVEMP was similar between the two groups, with no statistical significance in the comparison ($P > 0.05$).

Comparison of latencies and intervals of oVEMP

The oVEMP P1 latencies, N1 latencies, and intervals of the two groups are shown in Figure 4. The N1 latency of ACS-oVEMP in the RVC group was statistically shorter than that in the control group ($P < 0.05$), while the P1 latency was not statistically different from that in the control group ($P > 0.05$). The interval of ACS-oVEMP in the RVC group was statistically longer than that in the control group ($P < 0.05$). The N1 latency, P1 latency, and interval of GVS-oVEMP in the RVC group were not statistically different from those in the control group ($P > 0.05$).

Comparison of amplitudes and AARs of cVEMP

The amplitudes and AARs of the two groups are shown in Table 5. The amplitude of ACS-cVEMP in the RVC group was significantly higher than that in the control group ($P < 0.05$). However, there was no significant difference in the AAR of ACS-cVEMP, the amplitude, and the AAR of GVS-cVEMP between the two groups ($P > 0.05$).

Comparison of amplitudes and AAR values of oVEMP

The amplitudes and AARs of the two groups are shown in Table 6. The amplitude of ACS-oVEMP in the RVC group was not significantly different from that in the control group ($P > 0.05$). The AAR value of ACS-oVEMP in the RVC group was higher than that in the control group ($P < 0.05$). The amplitude of GVS-oVEMP in the RVC group was significantly higher than that in the control group ($P < 0.05$). The AAR value of GVS-oVEMP in the RVC group was not significantly different from that in the control group ($P > 0.05$).

Discussion

Epidemiological studies have shown that RVC is the most common cause of dizziness or vertigo in children (15–17), and the etiology and pathogenesis of the disease are still not well understood and were even controversial.

Eviatar first found in a study of 24 children with vertigo as their chief complaint that vestibular damage could be a peripheral vestibular system lesion (18). However, Finkelhor concluded that the most likely etiology of RVC is a transient ischemic disturbance of the central vestibular system secondary to a vascular disturbance of the posterior circulation after summarizing the previous literature and analyzing five cases he encountered (19). Lanzi examined the clinical aspects of RVC in infancy and its most common differential diagnosis, particularly the analogies and differences with the later onset form of "migraine", and concluded that RVC can be interpreted as a migraine precursor and MV as a migraine equivalent (20). Salami et al. investigated the diagnostic role of the visual vestibular interaction test for vertigo in children and suggested that the visual system of newborns is immature at birth and continues to develop until maturity in childhood and that this transient "abnormality" during development may lead to a failure of binocular information pooling and thus to vertigo in children (21). The latest review on "Prevalence and diagnosis of vestibular disorders in children" concluded that most of the current theories on the pathogenesis of RVC are still based on clinical studies assessing the vestibular system (22).

VEMP is often used to evaluate the function of the saccule and the integrity of the saccule–colic reflex (SCR) pathway (23). oVEMP is often applied to evaluate the function of the utricle and the integrity of the vestibulo-ocular reflex (VOR) pathway (23). ACS-VEMPs depend on the integrity of the otolith, while GVS directly stimulates the vestibular nerve endings to elicit VEMPs (24, 25). Therefore, different VEMPs can be compared to locate intra-labyrinthine and retro-labyrinthine lesions (26). If GVS-VEMPs can be elicited and ACS-VEMPs cannot be elicited, then the lesion is located in the otolith. If both ACS-VEMPs and GVS-VEMPs cannot be elicited, it is likely to be a retro-labyrinthine lesion.

The results of our study showed that there was no statistical difference in the elicit rates of cVEMP and oVEMP under ACS and GVS stimulation in the RVC group, suggesting that the function of the peripheral otolithic end receptors and

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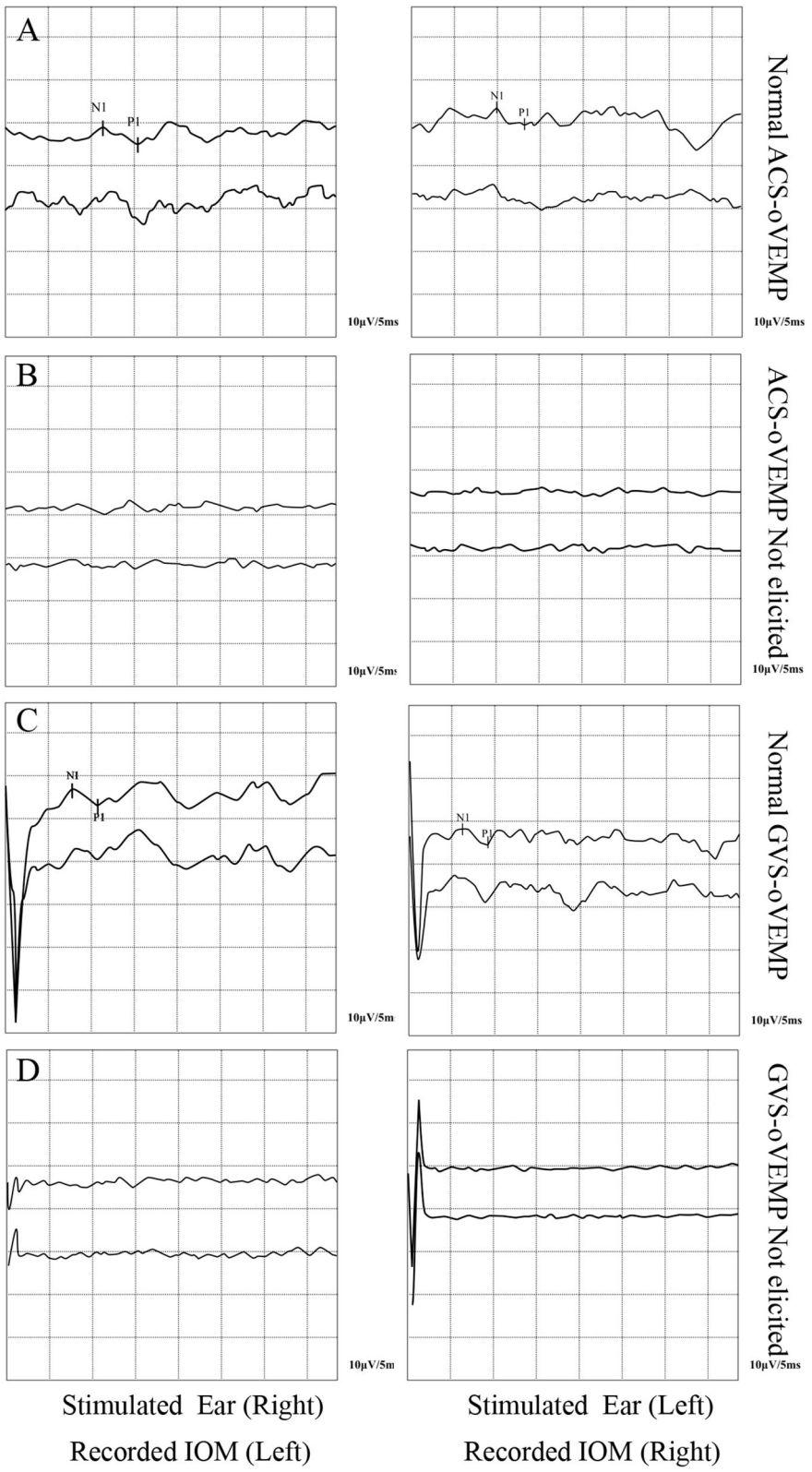

FIGURE 2
Typical double-trace records of oVEMPs. **(A)** Normal ACS-oVEMP. **(B)** Not elicited ACS-cVEMP. **(C)** Normal GVS-oVEMP. **(D)** Not elicited GVS-oVEMP.

TABLE 3 Self-comparison of cVEMP and oVEMP elicit rates in the control group.

VEMPs	ACS				GVS			
	Elicite (ears)	Not elicite (ears)	χ^2	P	Elicite (ears)	Not elicite (ears)	χ^2	P
cVEMP	56	2	5.949	0.015	54	4	0.904	0.342
oVEMP	48	10			51	7		

TABLE 4 Self-comparison of cVEMP and oVEMP elicit rates in the RVC group.

VEMPs	ACS				GVS			
	Elicite (ears)	Not elicite (ears)	χ^2	P	Elicite (ears)	Not elicite (ears)	χ^2	P
cVEMP	41	1	1.914	0.167	41	1	0.346	0.556
oVEMP	38	4			40	2		

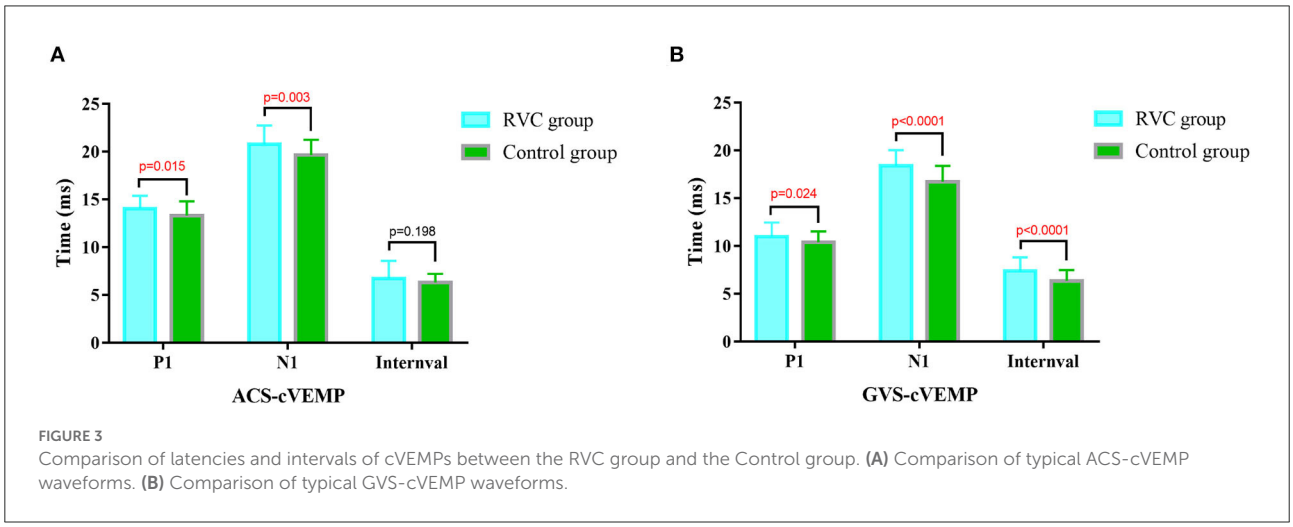

FIGURE 3
Comparison of latencies and intervals of cVEMPs between the RVC group and the Control group. **(A)** Comparison of typical ACS-cVEMP waveforms. **(B)** Comparison of typical GVS-cVEMP waveforms.

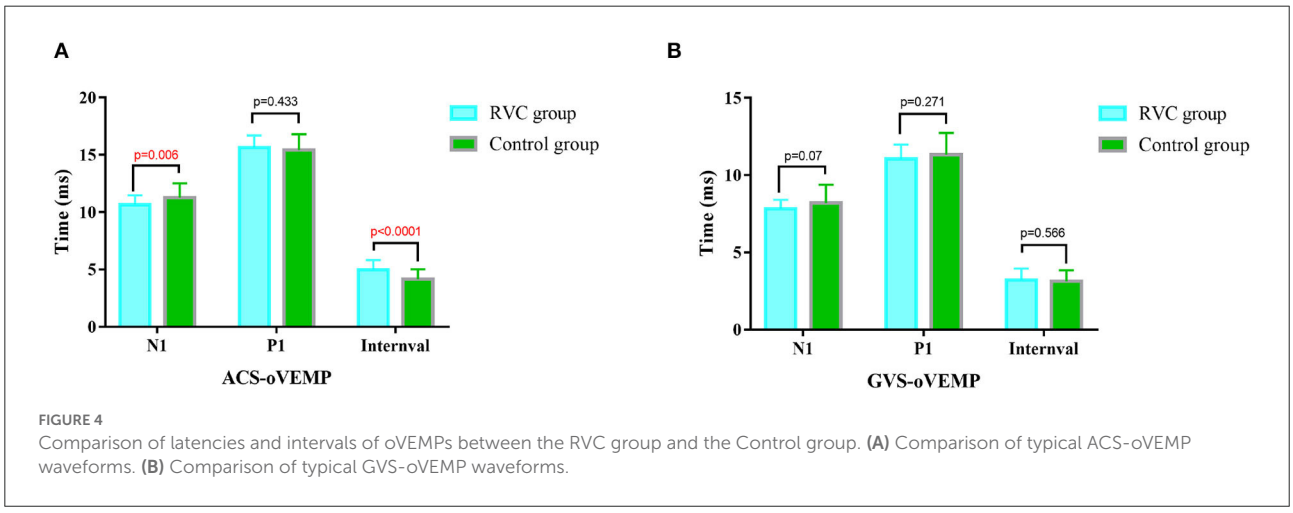

FIGURE 4
Comparison of latencies and intervals of oVEMPs between the RVC group and the Control group. **(A)** Comparison of typical ACS-oVEMP waveforms. **(B)** Comparison of typical GVS-oVEMP waveforms.

their pathways is complete in children with RVC. The P1 and N1 latencies of ACS-cVEMP and GVS-cVEMP in children with RVC were longer than those in the control group, while the N1 latency of ACS-oVEMP was shorter than that in the control group, and no prolongation was seen in the P1 latency of ACS-oVEMP or in the latencies of GVS-oVEMP. Among

TABLE 5 Comparison of latencies and intervals of cVEMP between the RVC group and the control group.

Group	ACS-cVEMP		GVS-cVEMP	
	Amplitude (μV)	AAR (%)	Amplitude (μV)	AAR (%)
RVC	182.08 ± 71.21	13.04 ± 12.11	145.46 ± 54.41	23.07 ± 25.14
Control	102.83 ± 64.34	15.86 ± 13.14	129.19 ± 64.54	19.48 ± 15.99
T	−5.727	0.751	−1.3	−0.596
P	<0.0001	0.457	0.197	0.554

TABLE 6 Comparison of latencies and intervals of oVEMP between the RVC group and the control group.

Group	ACS-oVEMP		GVS-oVEMP	
	Amplitude (μV)	AAR (%)	Amplitude (μV)	AAR (%)
RVC	4.94 ± 2.51	20.01 ± 10.74	7.32 ± 6.16	17.51 ± 17.09
Control	4.44 ± 3.30	11.67 ± 10.15	4.61 ± 2.36	18.49 ± 12.35
T	−0.776	−2.491	−2.631	−0.21
P	0.4405	0.017	0.011	0.834

them, P13 shortening did not have much clinical significance but was more of a statistical difference. The prolongation of P13 has clinical significance, suggesting that there might be impairment in the saccule and the inferior vestibular nerve conduction pathway in children with RVC, while the utricle and the superior vestibular nerve conduction pathway are not affected. Lin et al. (6) found that among 15 children with RVC, 73% had prolonged ACS-cVEMP latencies, which was significantly different from healthy children, while ACS-oVEMPs were all elicited normally and did not differ from healthy children. Therefore, they hypothesized that the VOR pathway and upper brainstem were functioning normally, while the vestibulospinal reflexes of the saccule–inferior vestibular pathway may have abnormal lesions. Chang et al. (5) performed the caloric test and cVEMP tests in children with RVC and normal children and found that the rate of abnormal cVEMP was significantly higher in children with RVC than that in the caloric test, which led to the assumption that there might be some lesions in the inferior vestibular conduction pathway in children with RVC. The caloric test detects the response of the horizontal semicircular canal to low-frequency stimuli and assess the superior vestibular conduction pathway. Although previous studies have proposed a mechanism of damage in the inferior vestibular conduction pathway in patients with RVC, they have not been able to define whether this abnormality originates from the saccule or in retro-labyrinthine. Our study further investigated the possibility of intra-labyrinthine or retro-labyrinthine vestibular damage in children with RVC based on ACS-VEMPs and GVS-VEMPs. Combined with these findings, we speculated that the retro-labyrinthine portion and lower brainstem along the SCR pathway were impaired in children with RVC.

Murofushi et al. (27, 28) proposed a "neuritis pattern" as a theoretical mechanism for retro-labyrinthine injury of the inferior vestibular nerve conduction pathway, including the inferior vestibular nerve, lateral vestibular nucleus, medial vestibulospinal tract, paracentral nucleus, and paracentral nerve. In addition, in a study of investigating the diagnostic value of vestibular test and the high stimulus rate auditory brainstem response (ABR) test and the possible mechanism responsible for RVC, Zhang et al. (7) proposed that the vascular mechanism might be involved in the pathogenesis of RVC, that is, the ischemia of vestibular nuclei and vestibular pathway was one of the causes, and the inferior vestibular nerve pathway was more vulnerable than the superior vestibular nerve pathway. Batuecas-Caletrío et al. (29) observed a higher prevalence of migraine in patients with RVC than in the general population and suggested that RVC is a precursor to migraine in childhood. Marcelli et al. (30) further reported their 10-year follow-up study of 17 children with RVC, with 10 of them with migraine.

However, as reviewed by Lempert et al. (31), genetic, neurochemical, and inflammatory mechanisms may be involved in the pathophysiological mechanisms of VM. The patients' genetic susceptibility leads to a more excitable and vulnerable cerebral cortex, which produces a local neurogenic inflammatory response when relevant triggers are present in the environment, resulting in increased sensitivity of peripheral and central afferent nerve conduction pathways, thereby activating migraine-related loops and the trigeminal innervated vascular system (32). Most neurotransmitters involved in the pathogenesis of migraine, such as calcitonin gene-related peptides, 5-hydroxytryptamine, norepinephrine, and dopamine, also modulate the activity of central and peripheral vestibular neurons and may be involved in the pathogenesis of VM (31).

Aseptic inflammation of intracranial vessels, such as lesions of the vascular striatum trigeminal, cochlear spiral cochlear axial artery, and dark cell area of the jugular crest, causes inner ear damage, which leads to the appearance of vertigo (31, 32). Therefore, more in-depth research is needed to explore the pathogenesis of RVC and its correlation with VM in the follow-up. We will also conduct a systematic follow-up study of this group of children with RVC in this study to further investigate the prognosis of the disease and the changes of the parameters of VEMPs.

Several studies have shown (33, 34) that the amplitude of VEMPs fluctuates greatly, which is related to the subjects' muscle tone. To avoid the influence of muscle tone on the results, we further compared the AARs of the subjects' binaural VEMPs in our study. Statistical analysis revealed that the AAR values of ACS-cVEMPs and GVS-VEMPs in the RVC group were similar to those in the control group. The AAR value of ACS-oVEMP in the RVC group was significantly higher than that in the control group. But the mean AAR value in the RVC group was still within the normal range, suggesting that the function of the bilateral utricle and superior vestibular nerve conduction pathway in children with RVC was affected to some extent but not impaired. At the same time, the reasons of poor cooperation in the oVEMP test, the relatively insensitivity of young children to stimulation sounds, testing errors, and so on cannot be ruled out.

Conclusion

The elicit rates of VEMPs in children with RVC are the same as those in healthy children, with no significant reduction in amplitude, and the bilateral AAR is still within the normal range. Both ACS-cVEMP and GVS-cVEMP latencies were significantly prolonged in children with RVC; however, the elicit rate is no different from that in the control group, suggesting that there might be potential impairment in the inferior vestibular nerve and the subsequent nerve conduction pathway in them without affecting the utricle and the superior vestibular nerve conduction pathway.

Data availability statement

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

Ethics statement

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

Author contributions

JC and JY contributed to the study design. JS and LW preformed VEMP tests. XS and DG contributed to statistical analysis and manuscript draft. All authors helped to perform the analysis and to revise the manuscript with constructive discussions. All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline.

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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

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EDITED BY
Widdershoven Josine,
Maastricht University Medical Centre, Netherlands

REVIEWED BY
Daogong Zhang,
Shandong Provincial ENT Hospital, China
Kristen Leigh Janky,
Boys Town, United States

*CORRESPONDENCE
Qing Zhang
zhangqing03@xinhuamed.com.cn
Yulian Jin
yulianjin66@163.com
Jun Yang
yangjun@xinhuamed.com.cn

†These authors have contributed equally to this work

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Effects of acoustic stimulation intensity on air-conducted vestibular evoked myogenic potential in children

Qianwen Xiao[1,2,3†], Qin Zhang[1,2,3†], Qiong Wu[1,2,3], Jiali Shen[1,2,3], Lu Wang[1,2,3], Yanfei Chen[4], Jingrong Lv[1,2,3], Jun Yang[1,2,3*], Yulian Jin[1,2,3*] and Qing Zhang[1,2,3,4*]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China, [4]Department of Otolaryngology, Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Objective: To investigate the effects of acoustic stimulation intensity on ocular and cervical vestibular evoked myogenic potential (oVEMP and cVEMP) responses elicited by air-conducted sound (ACS) in healthy children.

Methods: Thirteen healthy children aged 4–10 years and 20 healthy adults aged 20-40 years with normal hearing and tympanometry were enrolled in this study. All subjects received oVEMP and cVEMP tests under different acoustic stimulation intensities (131, 126, 121, 116, 111 and 106 dB SPL). Mean n1 latency, p1 latency, interpeak latency, amplitude and response rate were investigated and analyzed.

Results: As the acoustic stimulation intensity decreased, for oVEMP, the response rate of children decreased from 100% (131, 126 and 121 dB SPL) to 57.69% (116 dB SPL), 26.92% (111 dB SPL) and 11.54% (106 dB SPL). The response rate of adults decreased from 100% (131 and 126 dB SPL) to 95% (121 dB SPL), 55% (116 dB SPL), 12.5% (111 dB SPL) and 2.5% (106 dB SPL). There were lower n1 latency, p1 latency and higher amplitude in children when comparing by acoustic stimulation intensities ($p < 0.05$). Regarding cVEMP, the response rate of children decreased from 100% (131, 126 and 121 dB SPL) to 88.46% (116 dB SPL), 53.85% (111 dB SPL) and 26.92% (106 dB SPL). The response rate of adults decreased from 100% (131 and 126 dB SPL) to 95% (121 dB SPL), 85% (116 dB SPL), 37.5% (111 dB SPL) and 7.5% (106 dB SPL). A statistically significant difference was found in amplitude at different acoustic stimulation intensities in both children and adults ($p < 0.05$). When stimulated by 131 dB SPL acoustic stimulation, there were lower n1 latency, p1 latency and higher amplitude in children in oVEMP and cVEMP compared with adults ($p < 0.05$).

Conclusion: The response rate and amplitude of oVEMP and cVEMP in children and adults presented significant differences with a decrease in

acoustic stimulation intensity. In this study, using 121 dB SPL for children and 126 dB SPL for adults during VEMP test could be regarded as safer stimulation intensities and thus reduced sound exposure.

KEYWORDS

acoustic stimulation intensity, air-conducted sound, ocular vestibular evoked myogenic potential, cervical vestibular evoked myogenic potential, children

Introduction

Vestibular evoked myogenic potential (VEMP) has been utilized in neuro-otology clinics as a test for evaluation of otolith function and vestibular nerves (1, 2). It is elicited by modulated electromyographic signals either from the inferior oblique muscle for the ocular VEMP (oVEMP) or the sternocleidomastoid muscle for the cervical VEMP (cVEMP) (3). There are usually three types of stimuli eliciting VEMPs, including air-conducted sound (ACS), bone-conducted vibration (BCV) and galvanic vestibular stimulation (GVS), among which ACS has been regarded as the primary and widely used stimulus (4, 5). Previous studies have demonstrated that, when evoked by ACS, the oVEMP could evaluate utricle function and the crossed vestibulo-ocular reflex (VOR) and the cVEMP could evaluate saccular function and the vestibulo-collic reflex (VCR) pathway (2, 4, 6, 7).

Vestibular loss often resulted in delayed motor development and reduced quality of life in children with normal hearing (8). The prevalence of childhood balance disorders is uncertain and mainly depends on the method of data collection. It is estimated that about 0.45% children aged from newborns to 18 years are diagnosed with balance disturbances (9). However, the prevalence may be even higher and the underestimation can be attributed to difficulties in describing vertigo, obtaining detailed medical history and establishing clear diagnosis (8). Therefore, vestibular loss in children is in need of attention, and clinicians are supposed to search for a valid and reliable tool to increase the diagnostic rate in children.

The oVEMP and cVEMP tests *via* ACS are objective, non-invasive and safe to perform in children as long as a safe acoustic stimulation is maintained (10, 11). The test has been widely used in adults and the normal values have been identified (12). Previous study had only focused on the effects of simple acoustic stimulation intensity on VEMPs. However, few studies on the sets of normative data in children have been reported, especially the investigation on the effects of different acoustic stimulation intensity on ACS-VEMPs in children. Thus, more researches are necessary and critical to determine the appropriate acoustic stimulation intensity in the tests. The aim of this study is to investigate different acoustic stimulation intensities on VEMPs elicited by ACS in healthy children.

Abbreviations: VEMP, vestibular evoked myogenic potential; oVEMP, ocular VEMP; cVEMP, cervical VEMP; ACS, air-conducted stimulation; BCV, bone-conducted vibration; GVS, galvanic vestibular stimulation; VOR, vestibulo-ocular reflex; VCR, vestibulo-collic reflex; SCM, sternocleidomastoid muscle; DPOAE, distortion product otoacoustic emission; ECV, ear canal volume.

Materials and methods

Subjects

Thirteen healthy children (6 males and 7 females, aged from 4 to 10 years, mean 7.23 ± 2.01 years) and 20 healthy adults (9 males and 11 females, aged from 20 to 40 years, mean 24.95 ± 5.16 years) were enrolled in this study. All subjects had no history of any ear disorders and vestibular disorders, and were further checked with pure tone audiometry, acoustical immittance and otoscope tests. Each subject underwent oVEMP and cVEMP elicited by ACS. This study was approved by the institutional review board of the Xinhua Hospital of Shanghai Jiaotong University School of Medicine. Each child's parent and each adult signed the informed consent to take part in the study.

Equipment and recordings

A sound-proof and comfortable examination room was employed for tests. The electromyographic signals were amplified through the ICS Chartr EP 200 Evoked Potential System (Otometrics, Denmark) for further analysis.

ACS with 500 Hz short tone burst (rise/fall time = 1ms, plateau time = 2ms) was delivered through the inserted earphone. The band-pass filter was set at 1–1000 Hz, and the responses to 50 stimuli were averaged twice. The stimulation rate was 5 Hz, and the analysis window of each response was 50 ms. The initial acoustic stimulus used was a short tone burst, with an intensity of 131 dB SPL. The stimulation intensity was then decreased in steps of 5 dB SPL until no oVEMP or cVEMP were present. A clear and repeatable biphasic waveform comprised of peaks n1 and p1 was considered positive response, and

unrepeatable biphasic waveform was considered no response. The length of time between 0 ms and the peak n1 or p1 was regarded as n1 latency or p1 latency, respectively. The duration between peaks n1 and p1 was recorded as interpeak latency, which includes n1-p1 latency and p1-n1 latency. We regarded the vertical distance of voltage between peaks n1 and p1 as the amplitude.

oVEMP test

Each subject was in the supine position during the test. Before attaching electrodes, the skin of all subjects should be cleaned with abrasive paste. Two active electrodes were positioned around 1 cm below the center of the two lower eyelids. Two reference electrodes were placed around 1–2 cm below the two active electrodes, and the ground electrode was placed on the middle of the forehead. The electrode impedance was kept below 5 kΩ. Each subject was asked to look upward at a small fixed target above 1 m from the eyes when hearing the sound through the inserted earphone (13). Response rate, n1 and p1 latencies, n1-p1 latency and amplitude were measured under different acoustic stimulation intensities.

cVEMP test

Each subject was in the supine position during the test. Before attaching electrodes, the skin of all subjects was cleaned with abrasive paste. Two active electrodes were placed on the middle and upper third of the sternocleidomastoid (SCM) muscle, and the two reference electrodes were positioned on jugular notch. The ground electrode was placed on the middle of the forehead. The electrode impedance was kept below 5 kΩ. Each subject was instructed to raise his/her head off the pillow in order to increase the tension of the SCM when the sound was presented through the inserted earphone (14). Response rate, p1 and n1 latencies, p1-n1 latency and amplitude were measured under different acoustic stimulation intensities.

Statistical methods

Data were analyzed using IBM SPSS Statistics 26.0.0. Kruskal-Wallis test was used for comparisons of n1 latency, p1 latency, interpeak latency and amplitude of oVEMP or cVEMP among different acoustic stimulation intensities. All data were expressed as mean ± standard deviation. A significance of $p < 0.05$ is considered significant.

Results

Acoustic stimulation intensity impacts on ACS-oVEMP in children

All healthy children completed ACS-oVEMP test following different acoustic stimulation intensities, which included 131, 126, 121, 116, 111 and 106 dB SPL (Table 1, Figure 1A). Regarding oVEMP, the response rates were 100% (26/26) under 131, 126 and 121 dB SPL acoustic stimulations. However, the response rate decreased gradually (57.69, 26.92 and 11.54%, respectively) under 116, 111 and 106 dB SPL acoustic stimulations. As acoustic stimulation intensity decreased, the mean n1 latencies increased (9.97 ± 0.75 ms, 10.29 ± 0.69 ms, 10.56 ± 1.01 ms, 10.78 ± 0.86 ms, 11.88 ± 0.75 ms and 11.96 ± 0.18 ms, respectively) and the mean p1 latencies increased (14.41 ± 1.18 ms, 14.89 ± 0.93 ms, 15.16 ± 1.09 ms, 15.37 ± 0.99 ms, 15.70 ± 0.93 ms and 16.71 ± 0.30 ms, respectively) and the mean amplitudes decreased (8.32 ± 5.71 μV, 6.53 ± 3.57 μV, 3.99 ± 2.70 μV, 2.90 ± 1.44 μV, 2.65 ± 0.86 μV and 2.37 ± 1.39 μV, respectively). Comparisons of parameters showed prolonged latencies of n1 ($p < 0.0001$) and p1 ($p = 0.010$) and decreased amplitude ($p < 0.0001$) significantly. Whereas, no significant difference was observed in the n1-p1 latency ($p = 0.418$).

Acoustic stimulation intensity impacts on ACS-cVEMP in children

All healthy children completed ACS-cVEMP test under 131, 126, 121, 116, 111 and 106 dB SPL acoustic stimulation intensities (Table 2, Figure 2A). Regarding cVEMP, the response rates were 100% (26/26) under 131, 126 and 121 dB SPL acoustic stimulations. Whereas, the response rate decreased from 88.46, 53.85 to 26.92% under 116, 111 and 106 dB SPL acoustic stimulations, respectively. With the decrease of acoustic stimulation intensity, the mean amplitudes were 369.60 ± 177.90 μV, 402.80 ± 163.90 μV, 271.60 ± 155.60 μV, 228.70 ± 118.00 μV, 177.80 ± 96.56 μV and 150.80 ± 81.22 μV, indicating decreasing acoustic stimulation intensity was accompanied by a significant decrease of amplitude ($p < 0.0001$). However, statistically significant differences were not found in terms of p1 latency ($p = 0.310$), n1 latency ($p = 0.542$) and p1-n1 latency ($p = 0.826$).

Acoustic stimulation intensity impacts on ACS-oVEMP in adults

All healthy adults presented ACS-oVEMP test induced by 131, 126, 121, 116, 111 and 106 dB SPL acoustic stimulation

TABLE 1 The ACS-oVEMP with decreasing acoustic stimulation intensity in children.

Intensity (dB SPL)	N (ears)	Response rate	n1 latency (ms)	p1 latency (ms)	Interpeak latency (ms)	Amplitude (μV)
131	26	100%	9.97 ± 0.75	14.41 ± 1.18	4.45 ± 1.10	8.32 ± 5.71
126	26	100%	10.29 ± 0.69	14.89 ± 0.93	4.60 ± 0.83	6.53 ± 3.57
121	26	100%	10.56 ± 1.01	15.16 ± 1.09	4.61 ± 1.17	3.99 ± 2.70
116	15	57.69%	10.78 ± 0.86	15.37 ± 0.99	4.59 ± 0.92	2.90 ± 1.44
111	7	26.92%	11.88 ± 0.75	15.70 ± 0.93	3.82 ± 0.58	2.65 ± 0.86
106	3	11.54%	11.96 ± 0.18	16.71 ± 0.30	4.75 ± 0.11	2.37 ± 1.39
Kruskal-Wallis test			$p < 0.0001$	$p = 0.010$	$p = 0.418$	$p < 0.0001$

Data are expressed as mean ± SD.

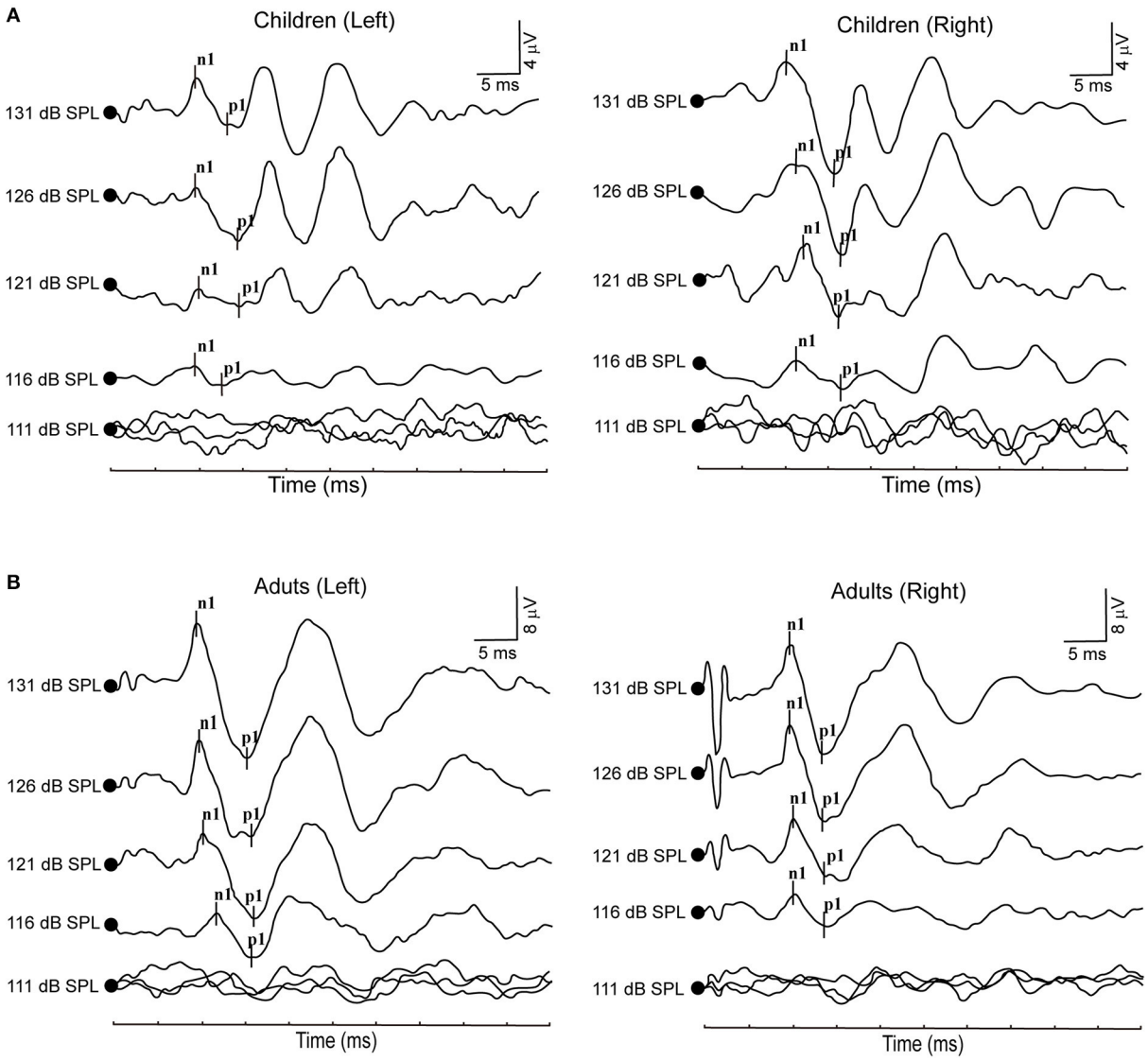

FIGURE 1
(A) Clear oVEMP waveform in a child in response to ACS stimuli. **(B)** Clear oVEMP waveform in an adult in response to ACS stimuli.

TABLE 2 The ACS-cVEMP with decreasing acoustic stimulation intensity in children.

Intensity (dB SPL)	N (ears)	Response rate	n1 latency (ms)	p1 latency (ms)	Interpeak latency (ms)	Amplitude (μV)
131	26	100%	21.45 ± 1.58	14.96 ± 1.08	6.52 ± 1.00	369.60 ± 177.90
126	26	100%	22.15 ± 1.76	15.67 ± 1.27	6.49 ± 1.01	402.80 ± 163.90
121	26	100%	22.08 ± 1.89	15.47 ± 1.34	6.61 ± 1.35	271.60 ± 155.60
116	23	88.46%	21.66 ± 1.48	15.40 ± 1.29	6.27 ± 1.12	228.70 ± 118.00
111	14	53.85%	21.70 ± 1.44	14.99 ± 0.77	6.69 ± 1.11	177.80 ± 96.56
106	7	26.92%	21.00 ± 1.14	14.82 ± 0.92	6.18 ± 1.40	150.80 ± 81.22
Kruskal-Wallis test			$p = 0.542$	$p = 0.310$	$p = 0.826$	$p < 0.0001$

Data are expressed as mean ± SD.

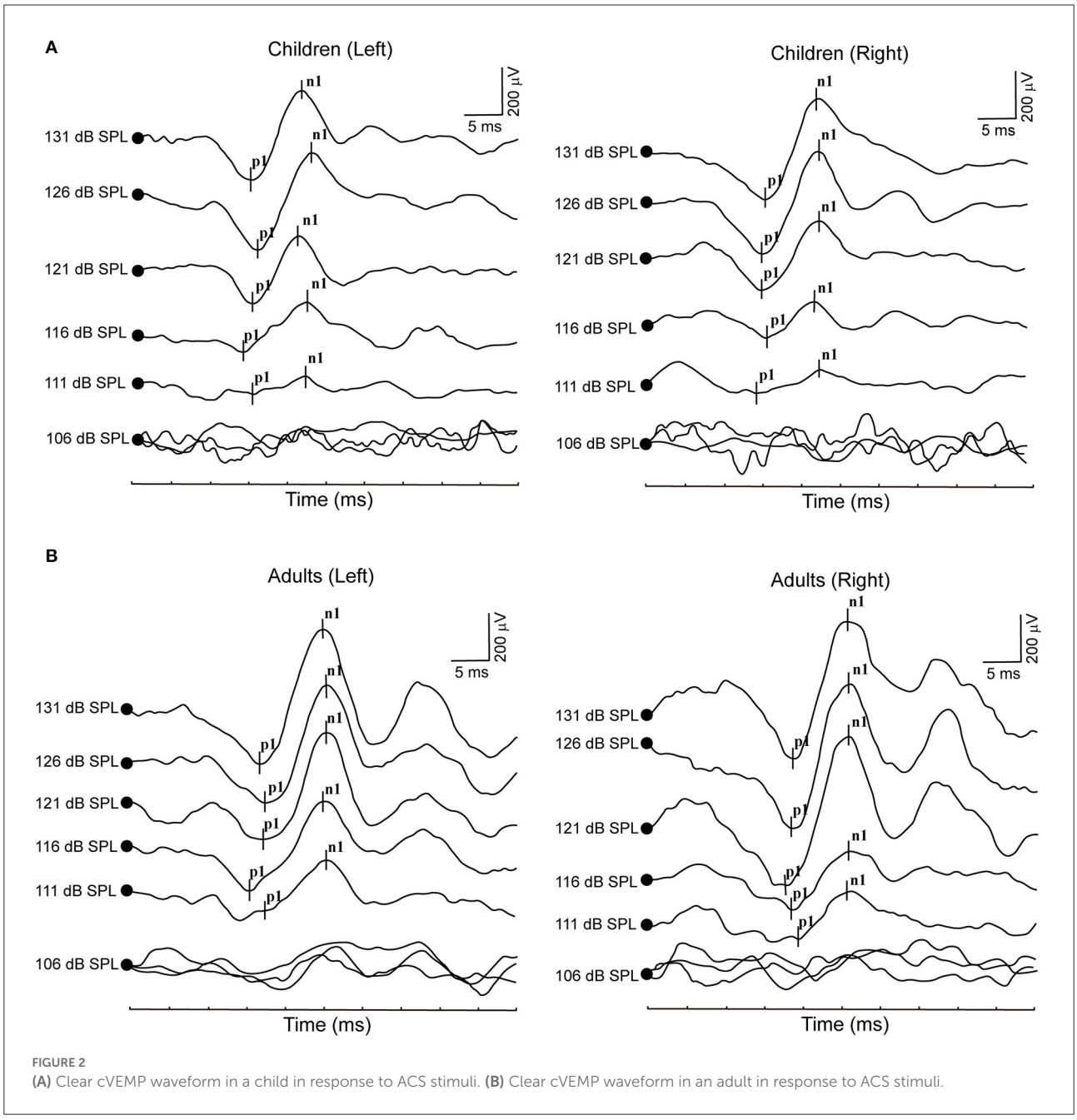

FIGURE 2
(A) Clear cVEMP waveform in a child in response to ACS stimuli. **(B)** Clear cVEMP waveform in an adult in response to ACS stimuli.

TABLE 3 The ACS-oVEMP with decreasing acoustic stimulation intensity in adults.

Intensity (dB SPL)	N (ears)	Response rate	n1 latency (ms)	p1 latency (ms)	Interpeak latency (ms)	Amplitude (μV)
131	40	100%	10.26 ± 0.68	14.76 ± 1.31	4.50 ± 1.07	7.29 ± 3.60
126	40	100%	10.43 ± 0.78	14.94 ± 1.40	4.51 ± 1.19	5.82 ± 3.38
121	38	95%	10.74 ± 0.84	15.25 ± 1.17	4.51 ± 1.13	3.85 ± 2.16
116	22	55%	11.38 ± 1.09	15.79 ± 0.98	4.55 ± 1.03	3.52 ± 2.03
111	5	12.50%	12.12 ± 1.27	16.00 ± 0.94	3.88 ± 0.83	3.23 ± 0.67
106	1	2.50%	12.58 ± 0.00	16.00 ± 0.00	3.42 ± 0.00	3.21 ± 0.00
Kruskal-Wallis test			$p < 0.0001$	$p = 0.015$	$p = 0.690$	$p < 0.0001$

Data are expressed as mean ± SD.

TABLE 4 The ACS-cVEMP with decreasing acoustic stimulation intensity in adults.

Intensity (dB SPL)	N (ears)	Response rate	n1 latency (ms)	p1 latency (ms)	Interpeak latency (ms)	Amplitude (μV)
131	40	100%	24.97 ± 1.87	17.15 ± 1.94	7.82 ± 1.37	279.50 ± 151.20
126	40	100%	25.08 ± 2.10	17.30 ± 2.14	7.78 ± 1.37	253.80 ± 128.50
121	38	95%	25.23 ± 2.13	17.82 ± 2.34	7.39 ± 1.41	230.80 ± 110.90
116	34	85%	25.02 ± 2.31	17.64 ± 2.33	7.39 ± 1.95	179.10 ± 80.38
111	15	37.50%	24.90 ± 2.32	18.27 ± 2.45	6.63 ± 1.67	155.30 ± 57.60
106	3	7.50%	24.64 ± 1.76	17.25 ± 1.08	7.39 ± 1.06	142.40 ± 44.49
Kruskal-Wallis test			$p = 0.974$	$p = 0.277$	$p = 0.190$	$p = 0.002$

Data are expressed as mean ± SD.

intensities (Table 3, Figure 1B). The response rates were 100% (40/40) when simulated by 131 and 126 dB SPL acoustic stimulations. However, the response rate decreased from 95, 55, 12.5% to 2.5% under 121, 116, 111 and 106 dB SPL acoustic stimulations, respectively. As the acoustic stimulation intensity decreased, the mean n1 latencies were 10.26 ± 0.68 ms, 10.43 ± 0.78 ms, 10.74 ± 0.84 ms, 11.38 ± 1.09 ms, 12.12 ± 1.27 ms and 12.58 ± 0.00 ms, and the mean p1 latencies were 14.76 ± 1.31 ms, 14.94 ± 1.40 ms, 15.25 ± 1.17 ms, 15.79 ± 0.98 ms, 16.00 ± 0.94 ms and 16.00 ± 0.00 ms, and the mean amplitudes were 7.29 ± 3.60 μV, 5.82 ± 3.38 μV, 3.85 ± 2.16 μV, 3.52 ± 2.03 μV, 3.23 ± 0.67 μV and 3.21 ± 0.00 μV. Comparisons of parameters revealed that there were significant differences in the n1 latency ($p < 0.0001$), p1 latency ($p = 0.015$) and amplitude ($p < 0.0001$), but not in the n1-p1 latency ($p = 0.690$).

Acoustic stimulation intensity impacts on ACS-cVEMP in adults

All healthy adults completed ACS-cVEMP test induced by 131, 126, 121, 116, 111 and 106 dB SPL acoustic stimulation intensities (Table 4, Figure 2B). The response rates were 100% (40/40) under 131 and 126 dB SPL acoustic stimulations. Whereas, the response rate gradually decreased (95, 85, 37.5 and 7.5%, respectively) when induced by 121, 116, 111 and 106 dB SPL acoustic stimulations. With the decrease of acoustic stimulation intensity, the mean amplitudes were 279.50 ± 151.20 μV, 253.80 ± 128.50 μV, 230.80 ± 110.90 μV, 179.10 ± 80.38 μV, 155.30 ± 57.60 μV and 142.40 ± 44.49 μV, respectively. Although there was a significant difference in the amplitude ($p = 0.002$), no statistically significant differences were not found in terms of p1 latency ($p = 0.277$), n1 latency ($p = 0.974$) and p1-n1 latency ($p = 0.190$).

oVEMP and cVEMP: Children vs. adults

All children and adults presented VEMPs following 131 dB SPL acoustic stimulation (Table 5). Regarding oVEMP, mean n1 latency, p1 latency, n1-p1 latency and amplitude for children were 9.97 ± 0.75 ms, 14.41 ± 1.18 ms, 4.45 ± 1.10 ms and 8.32 ± 5.71 μV, respectively, and 10.26 ± 0.68 ms, 14.76 ± 1.31 ms, 4.50 ± 1.07 ms and 7.29 ± 3.60 μV for adults, respectively, indicating that latencies were shorter in children than that in adults. There was a significant difference in the n1 latency between children and adults ($p = 0.007$), but not in the p1 latency ($p = 0.288$), n1-p1 latency ($p = 0.752$) and amplitude ($p = 0.807$). For cVEMP, mean p1 latency, n1 latency, p1-n1 latency and amplitude were 14.96 ± 1.08 ms, 21.45 ± 1.58 ms, 6.52 ± 1.00 ms and 369.6 ± 177.9 μV for children, while 17.15 ± 1.94 ms, 24.97 ± 1.87 ms, 7.82 ± 1.37 ms and 279.5 ± 151.2 μV for adults, respectively, indicating that children had shorter latencies and lower amplitudes than that in adults. A significant

TABLE 5 oVEMP and cVEMP under 131 dB SPL stimulation in children vs. adults.

	oVEMP		*p*	cVEMP		*p*
	Children	Adults		Children	Adults	
n1 latency (ms)	9.97 ± 0.75	10.26 ± 0.68	0.007	21.45 ± 1.58	24.97 ± 1.87	<0.0001
p1 latency (ms)	14.41 ± 1.18	14.76 ± 1.31	0.288	14.96 ± 1.08	17.15 ± 1.94	<0.0001
Interpeak latency (ms)	4.45 ± 1.10	4.50 ± 1.07	0.752	6.52 ± 1.00	7.82 ± 1.37	<0.0001
Amplitude (μV)	8.32 ± 5.71	7.29 ± 3.60	0.807	369.6 ± 177.9	279.5 ± 151.2	0.021

Data are expressed as mean ± SD.

difference existed between children and adults in terms of p1 latency ($p < 0.0001$), n1 latency ($p < 0.0001$), p1-n1 latency ($p < 0.0001$) and amplitude ($p = 0.021$).

Discussion

VEMPs have been widely utilized in children suspected with peripheral vestibular disorders due to early maturation of the crossed VOR and the VCR (15). Though there are several types of stimuli eliciting VEMPs, ACS is presumed to be the most commonly used in the clinical setting (16). To our knowledge, the risk for ACS-VEMPs test in children and adults is the increased sound exposure on account of the number of tests required in order to obtain a response. Previous studies have observed adverse effects on cochlear function resulted from VEMPs test in adults, including sudden sensorineural hearing loss, decreased distortion product otoacoustic emission (DPOAE) amplitudes and other symptoms (17–19). Compared to the adults, there are few investigations concerning the effect of acoustic stimulation intensity on ACS-VEMPs in children. In the article, we therefore investigated the characteristics of ACS-VEMPs induced by different acoustic stimulation intensities in children for searching for an appropriate acoustic stimuli level and avoiding the potential risk of acoustic trauma associated with VEMPs test.

In the current study, our results revealed that the response rates were 100% when stimulated by 131, 126 and 121 dB SPL acoustic stimulations in children. Compared to children, the response rates of adults were 100% under 131 and 126 dB SPL acoustic stimulations. Based upon these results, 121 and 126 dB SPL were regarded as the appropriate initial acoustic stimulation intensity for VEMPs test in children and adults, respectively. This indicated that VEMPs stimuli for children may not need to be presented adopting adults stimulation levels. As reported by Rodriguez et al., children receive around 3 dB higher peak equivalent SPL in the ear in response to acoustic stimulation due to the smaller equivalent ear canal volumes (ECV) of children compared to adults. Therefore, a 120 dB SPL acoustic stimulation intensity is recommended for VEMPs test in children with ECV below 0.8 cm, which is similar to our results (20). In addition, we also found the amplitude significantly attenuated in both children and adults with the reduction in acoustic stimulation intensity, indicating a close relationship existed between acoustic stimulation intensity and the amplitude (21). Interestingly, oVEMP showed significantly prolonged n1 and p1 latencies with the decrease of acoustic stimulation intensity not only in children but also in adults. Taken together, our findings supported the notion that different acoustic stimulation intensities had significantly impacts on the n1 latency, p1 latency, amplitude of oVEMP and the amplitude of cVEMP in both children and adults.

On the other hand, we investigated the characteristics of VEMPs induced by 131 dB SPL acoustic stimulation between children and adults. Regarding oVEMP, since the conduction velocity increased with age to compensate for increasing brainstem circumference, Hsu et al. have demonstrated that significant differences in oVEMP parameters were not found between children and adults (22). Whereas, the current data revealed that children had shorter oVEMP n1 latencies compared to adults. This needs to be further verified through increasing the number of samples. Additionally, our results showed that cVEMP p1 and n1 latencies were significantly shorter in children under 131 dB SPL acoustic stimulation compared to adults, which may be ascribed to several factors consisting of VCR pathways development, neck length and head size in children (23). We detected the cVEMP amplitude for adults attenuated compared to that for children, which is different from previous view (24, 25). We speculated that different acoustic stimulation intensities and the increased number of trials resulted in fatigue of the sternocleidomastoid muscle.

Children may be at higher risk for noise-induced hearing loss from sound exposure. Previous studies in animal models demonstrated that young mice are more prone to neural degeneration through the cochlear when exposed to high acoustic stimulations compared to older mice (26). Though there are no available human data, the corresponding findings in mice made us aware of the importance of children's acoustic exposure from VEMPs stimulations. Apart from acoustic stimulation intensity, VEMPs response depends on frequency, rise/fall and plateau time and duration, and these parameters can affect the total sound pressure level (SPL) delivered to children's ears in ACS-VEMPs test (27). This study is dedicated

to investigating the characteristics of acoustic stimulation intensity on ACS-VEMPs in healthy children. However, certain populations with some disorders in clinical practice, including tinnitus or hyperacusis, third-window phenomena and high susceptibility to noise-induced hearing loss, should also be taken into consideration to avoid potential acoustic trauma in VEMPs test (28). We could collect medical history, make hearing test and vestibular function examinations and do imaging test to exclude those diseases. Moreover, in this article, there are some limitations we should take into consideration. Since the children coordination is worse that of adults during VEMPs test, the sample size of children and age ranges were small, and EMG monitoring was not completed. Therefore, clinicians must be mindful of all factors associated with potential acoustic trauma, and further studies are needed to search for an appropriate acoustic stimulation intensity protocol to minimize the risk of unsafe sound exposure during VEMPs test in children.

Conclusion

Findings from the study showed significant differences in the response rate and amplitude in VEMPs in both children and adults when stimulated by different acoustic stimulation intensities. We suggested that 121 and 126 dB SPL were considered as the appropriate initial acoustic stimulation intensity for VEMPs test in children and adults, respectively.

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 Xinhua Hospital of Shanghai Jiaotong University School of Medicine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

QX, QinZ, QW, JS, LW, and YC contributed to the data collection. QX wrote the manuscript. YJ, QingZ, JY, and JL provided the idea and edited the manuscript. All authors contributed to manuscript revision 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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EDITED BY
Jose Antonio Lopez-Escamez,
Universidad de Granada, Spain

REVIEWED BY
Patricia Pérez-Carpena,
Hospital Universitario Virgen de las Nieves, Spain
Teru Kamogashira,
The University of Tokyo, Japan
Daogong Zhang,
Shandong Provincial ENT Hospital, China
Ruben Hermann,
Hospices Civils de Lyon, France

*CORRESPONDENCE
Qing Zhang
zhangqing03@xinhuamed.com.cn
Jun Yang
yangjun@xinhuamed.com.cn
Yulian Jin
jinyulian8548@xinhuamed.com.cn

†These authors have contributed equally to this work and share first authorship

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Vestibular dysfunction in pediatric patients with cochlear implantation: A systematic review and meta-analysis

Qiong Wu[1,2,3†], Qin Zhang[1,2,3†], Qianwen Xiao[1,2,3], Yuzhong Zhang[4], Zichen Chen[4], Shuyun Liu[5], Xueyan Wang[6], Yong Xu[4], Xin-Da Xu[7], Jingrong Lv[1,2,3], Yulian Jin[2,3,8*], Jun Yang[1,2,3*] and Qing Zhang[2,3,8*]

[1]Department of Otolaryngology Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Ear Institute, Shanghai Jiaotong University School of Medicine, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine in Ear and Nose Diseases, Shanghai, China, [4]Department of Otolaryngology Head and Neck Surgery, Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shanxi, China, [5]Department of Otolaryngology Head and Neck Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China, [6]Department of Otolaryngology Head and Neck Surgery, The Affiliated Hospital of Yanbian University, Yanji, Jilin, China, [7]Department of Otolaryngology, Eye and ENT Hospital, Fudan University, Shanghai, China, [8]Diagnosis and Treatment Center of Hearing Impairment and Vertigo, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Objective: Vestibular dysfunction may delay the achievement of balance and perception milestones in pediatric patients after cochlear implantation (CIM).

Methods: A strategic literature search was done following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched the PubMed, Medline, Embase, Web of Science, and Cochrane Library databases from inception to July 2022. Studies were included on the otoliths, semicircular canals, and balance function changes in children after CIM. Two reviewers independently assessed the level of evidence, methodological limitations, risk of bias, and characteristics of the cases. Matched pre- and postoperative vestibular functional test data, including ocular and cervical vestibular-evoked myogenic potential (oVEMP and cVEMP), caloric test, video head impulse test (vHIT), and Bruininks-Oseretsky Test 2 (BOT-2), were used to calculate the relative risk of vestibular disorders. Subgroup analyses were performed according to surgical approach, CIM device status, and etiology.

Results: Twenty studies that met the inclusion criteria were selected for the meta-analysis. We observed significant vestibular dysfunction in pediatric patients with CIM. The results showed a statistically significant increase in abnormal cVEMP response (RR = 2.20, 95% CI = 1.87, 2.58, $P < 0.0001$), abnormal oVEMP response (RR = 2.10, 95% CI = 1.50, 2.94, $P < 0.0001$), and abnormal caloric test results (RR = 1.62, 95% CI = 1.20, 2.19, $P = 0.0018$) after implantation. Statistically significant differences were not found in the vHIT test results of all three semicircular canals before and after the operation ($P > 0.05$). Regarding static and dynamic balance, we found significantly poorer BOT-2 scores in children with CIM than in the normal group (mean difference = −7.26, 95% CI = −10.82, −3.70, $P < 0.0001$).

Conclusion: The results showed that vestibular dysfunction might occur after CIM in pediatric patients. Some children experience difficulties with postural control and balance. Our results suggest that a comprehensive evaluation of vestibular function should be performed before and after CIM.

KEYWORDS

cochlear implantation, vestibular function test, vestibular-evoked myogenic potentials, vestibular disorders, pediatric patients

Introduction

Cochlear implantation (CIM) is the gold standard for treating severe to profound unilateral or bilateral sensorineural hearing loss (SNHL) in pediatric patients. CIM significantly improves hearing levels, speech intelligibility, and sound localization in quiet and noisy environments (1, 2). Thus, implantation should be performed in children with congenital SNHL as early as possible once confirmatory diagnostics are reliably completed.

Although CIM is a safe and conventional surgical procedure, the possible consequences and risks posed by CIM should be evaluated (3). As the importance of vestibular preservation has been widely acknowledged, an increasing number of studies have found that CIM can increase the risk of vestibular dysfunction (4–12). Congenital or acquired vestibular dysfunction in infants and children normally leads to impaired postural control, gait disturbances, and delayed locomotion development (13–15). Thus, the development, status, and damage to vestibular function in pediatric patients after CIM have been widely studied by researchers.

The vestibular function can be measured based on the cervical vestibular-evoked myogenic potential (cVEMP), ocular VEMP (oVEMP), caloric test, and video head impulse test (vHIT) (16, 17), and the symptoms of vestibular dysfunction commonly manifest as dizziness or postural imbalance (18).

Vestibular ramifications in adults after CIM have been documented (19–21). In a meta-analysis, Ibrahim et al. (22) observed that CIM surgery had a significant negative effect on the results of cVEMP and caloric tests, while Hänsel et al. (23) reported a notable increase in postoperative subjective vertigo and vestibular dysfunction. Nevertheless, assessing vestibular function in children seems difficult due to the difficulty and non-compliance in testing pediatric patients and the lack of available equipment. A few related studies of pre- and postoperative vestibular function focused on CIM in children. A recent systematic review showed subjective and objective vestibular changes following pediatric CIM. Due to the lack of quantitative data in some vestibular and balance function measurements, we only detected vestibular function by analyzing cVEMP and caloric test results (24).

The innovation of the current meta-analysis is that it demonstrated the difference in vestibular function between the pre- and postoperative statuses of pediatric patients by comprehensively comparing various vestibular function tests, including the cVEMP, oVEMP, caloric, and vHIT tests. We also evaluated the balance function in children using the Bruininks-Oseretsky Test of Motor Proficiency 2 (BOT-2) balance subtest. Thus, we aimed to systematically clarify the alterations in vestibular function following CIM in pediatric patients and the factors that may influence these results.

Materials and methods

Data retrieval

The specifications for this systematic review were formulated in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (25). The PRISMA checklist is shown in Supplementary Table S1.

Search strategy

Online databases, including PubMed, Medline, Embase, Web of Science, and the Cochrane Library, were searched by two independent authors (QW and QZ). Observational cohort studies of vestibular function changes after CIM were retrieved

Abbreviations: ASC, anterior semicircular canal; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency 2; CI, confidence interval; CIM, cochlear implantation; CMV, cytomegalovirus; cVEMP, cervical vestibular-evoked myogenic potential; EVA, enlarged vestibular aqueduct syndrome; Extended, extended RW; HSC, horizontal semicircular canal; IAC, Internal auditory canal; LVAS, large vestibular aqueduct syndrome; MD, mean diffusivity; oVEMP, ocular vestibular-evoked myogenic potential; PSC, posterior semicircular canal; RR, relative risk; RW, round window; SMD, standardized mean difference; SNHL, sensorineural hearing loss; VEMP, vestibular-evoked myogenic potential; vHIT, video head impulse test; and VOR, vestibulo-ocular reflex.

TABLE 1 PICOS model.

Population	Pediatric patients with unilateral or bilateral sensorineural hearing loss
Intervention	After CIM
Comparison	Before CIM
Outcomes	The results of cVEMP, oVEMP, caloric tests, vHIT, and BOT-2 balance subtest
Study design	Observational studies (prospective and retrospective cohort studies)

from the establishment of the database until July 9, 2022. Specific keywords consisted of Medical Subject Headings (MeSH) and free-text terms: "vestibular system," "vestibular evoked myogenic potentials," "vestibular function test," "vestibular diseases," "vertigo," "vestibular, labyrinth," "proprioception," "reflex, vestibular-ocular," "saccule and utricle," "vestibular disorders," "vestibular dysfunction," "vestibular impairment," "cochlear implants" or "cochlear implantation," and "all child." In addition, correlative references from eligible publications were examined. The disagreements regarding the exclusion or inclusion of specific studies were resolved by the third author (QZ) after discussion with all the research group members.

Eligibility criteria

We systematically retrieved the literature using the PICOS model (Population, Intervention, Comparison, Outcomes, Study design) (Table 1).

Inclusion criteria

(1) Prospective or retrospective cohort studies comparing vestibular function before and after CIM;
(2) Studies including pediatric patients (age $<$ 18 years);
(3) Necessary results of various vestibular function tests are available in the manuscript, including the results of cVEMP, oVEMP, caloric, and vHIT tests;
(4) Studies reporting BOT-2 balance subtest results;
(5) Studies including children with unilateral or bilateral CIM regardless of the surgical method used;
(6) Selection of studies with the largest number of participants in the case of overlapping samples.

Exclusion criteria

(7) Studies not published in English;
(8) Studies that focused only on pre- or post-CIM;
(9) Case reports, editorials, and commentaries;
(10) Publications do not report appropriate data for performing a meta-analysis.

Data extraction

Microsoft Excel (Microsoft, Redmond, WA, USA) was used to independently perform data extraction and literature screening by two researchers (QWX and SYL). Disagreements were resolved by cross-checking and discussion. The extracted data included (1) family name of the first author and publication year. (2) study design. (3) patient country. (4) sample size. (5) age of patients. (6) etiology of SNHL. (7) specific surgical measures for CIM. (8) unilateral or bilateral CIM. (9) time of vestibular function test postoperatively. (10) vestibular function test methods, and (11) references list. We evaluated the heterogeneity and external validity of the selected studies using this information.

Quality assessment

The Newcastle-Ottawa scale, which is comprehensive and has been partially validated to assess the quality of observational research in meta-analyses, was used to estimate the quality of the included studies. The Newcastle-Ottawa scale is a checklist that evaluates the quality of literature based on three categories: selection (composed of four items with a maximum score of 4 points), comparability of the study groups (composed of one item with a maximum score of 2 points), and ascertainment of exposure or outcome of interest (composed of three items with a maximum score of 3 points). A "star system" (ranging from 0 to 9) has been developed for evaluation. A score of $<$ 7 was designated as low quality; higher scores indicated high-quality studies. Quality evaluations were performed independently by two authors (YZ and ZC). According to statistics, all the 20 documents included in the meta-analysis meet the conditions.

Heterogeneity

Methodological and clinical heterogeneity were assessed by inspecting the characteristics of the studies, outcomes, the similarity between the types of participants, and interventions as specified in the inclusion criteria. The chi^2 test and I^2 statistic were used to evaluate statistical heterogeneity. $I^2 \geq 50\%$ indicated substantial heterogeneity, and the meta-analysis recommended the random-effects model. $I^2 < 50\%$ demonstrated notable homogeneity, and the fixed-effects model was used. Low, moderate, and significant heterogeneity were determined according to I^2 values of 25, 50, and 75%, respectively. Sensitivity analysis was used to check whether any single study accounted for the heterogeneity.

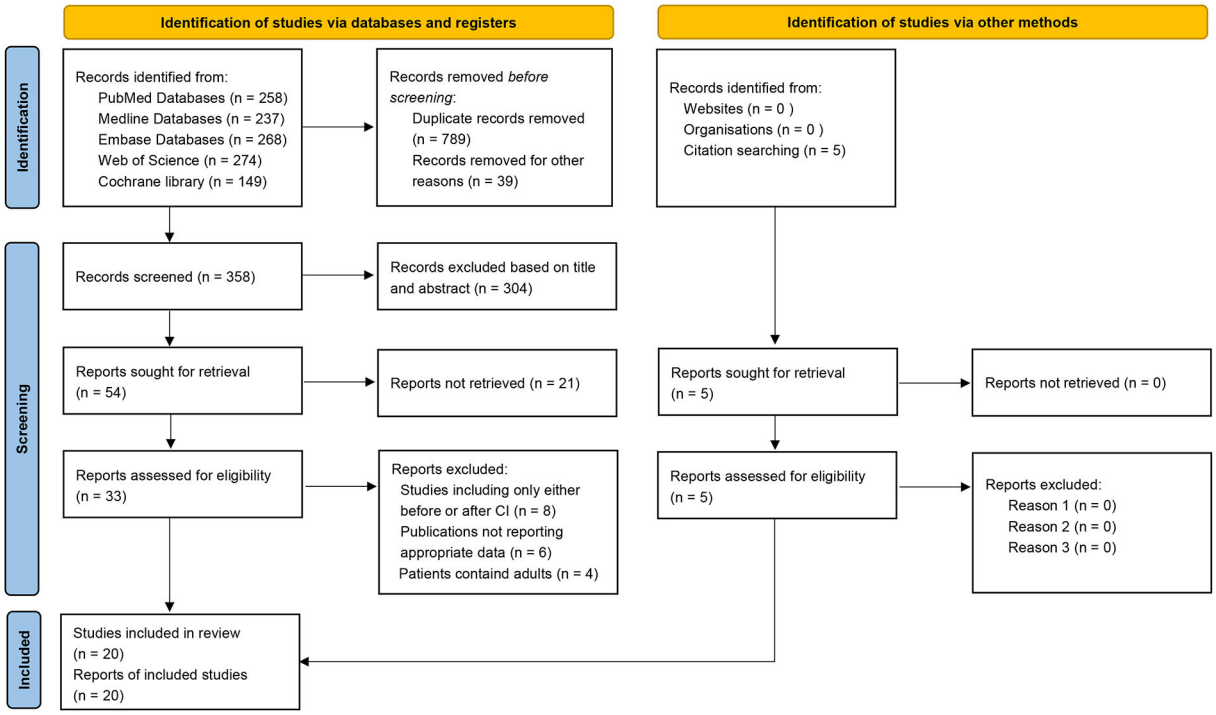

FIGURE 1
PRISMA flow diagram of the systematic literature search process.

Data analyses

Major outcomes included differences in vestibular function test results between the pre- and postoperative periods in children with CIM. The results of the cVEMP, oVEMP, caloric, vHIT, and BOT-2 tests were examined as major parameters. For performing the meta-analysis, in the case of binary variables, we calculated the relative risk (RR) and 95% confidence interval (95% CI) as the effect size using the maximum likelihood method; for continuous variables, the effect size was measured using the mean difference and standardized mean difference in scores of the normal and CIM groups.

Regarding statistical analysis, all data processing and graph plotting in the meta-analysis were performed with R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), using the R-package (metagen). Statistical significance was set at $P < 0.05$.

Results

Literature search

The systematic review identified 1,186 studies *via* databases and registers. After manually removing 789 duplicate studies and 39 studies that were irrelevant to the subject, 358 records were screened. After title and abstract screening, 304 studies were excluded. The remaining 54 studies were retrieved for full-text appraisal. We eliminated 21 reports for which the full text was unavailable, eight studies that only considered the pre- or post-CIM period, six studies without appropriate data, and four studies with adults (age $\geq$ 18 years). After reviewing the research references, five additional studies were identified. Thus, 20 studies were finally selected for the meta-analysis (7, 15, 26–43) (Figure 1).

Included study characteristics

The specific characteristics of the 20 selected studies are summarized in Table 2. Their publication dates ranged from 2006 to 2022. Five studies had unknown study designs, eight had a prospective study design, five had a retrospective study design, and two were only observational studies without a specific study design. Most of the 20 studies were performed in Asia (10 studies from China, Japan, India, and Iran, with a total of 299 patients), followed by North America (five studies from Canada and the USA; a total of 215 patients), Europe (four studies from France, Romania, Belgium, and Greece; a total of 131 patients), and Africa (one study from Egypt with 40 patients). The detailed etiologies of 687 patients (age range 1–18 years) are shown in Table 2. The surgical approach for electrode insertion was a

TABLE 2 Study demographics.

Study	Design	Country	Sample size	Age	Etiology	Surgical approach	CI side	Follow up	Test method
Wang et al. (26)	Retrospective	China	34	4–15 years	LVAS 18 Normal CT 16	RW/ Extended RW	Unilateral	9 months	cVEMP oVEMP caloric test vHIT
Koyama et al. (7)	Not specified	Japan	73	10.58 years	Genetic mutation 31 Virus infection 11 Syndrome 5 Inner ear malformations 5 Other 2 Unknown 19	RW/ Extended RW /Cochleostomy	Bilateral	33 months	cVEMP
Wang et al. (27)	Retrospective	China	16	5–18 years	EVA 16	RW/ Extended RW	Unilateral	12 months	Cvemp oVEMP
Guan et al. (28)	Retrospective	China	22	6–17 years	Hereditary 5 Drug–induced 1 viral infection 5 Unknown 11	RW	Unilateral and bilateral	1 month	cVEMP oVEMP caloric test vHIT
Wolter et al. (29)	Not specified	Canada	52	6–18 years	Usher syndrome 7 Meningitis 4 Cochleovestibular anomaly 3 Unknown etiology 3 CMV 1 Normal 34	Not specified	Bilateral	Not specified	BOT−2
Reynard et al. (30)	Retrospective	France	15	1.67–6 years	Mondini malformation 3 Pendred syndrome 2 LC malformation 1 Enlarged IAC 1 Nomal CT 8	RW	Bilateral	6 months	cVEMP vHIT
Wolter et al. (31)	Prospective	Canada	26	6–18 years	Usher syndrome 7 Unknown 5 Meningitis 3 Cochleovestibular anomalies 2 Nomal 10	Not specified	Bilateral	Not specified	BOT−2
Li et al. (32)	Prospective	China	35	3–18 years	EVA 14 Normal CT 21	RW	Unilateral	5 days, 1 month, 2 months	cVEMP oVEMP

(Continued)

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TABLE 2 (Continued)

Study	Design	Country	Sample size	Age	Etiology	Surgical approach	CI side	Follow up	Test method
Cozma et al. (33)	Prospective	Romania	80	4.35 years	Not specified	RW/Cochleostomy	Unilateral and bilateral	3 months	cVEMP
Gupta et al. (34)	Prospective	India	25	3–7 years	Profound SNHL 23 Severe SNHL 2	Cochleostomy	Not specified	6 weeks	Caloric test
Ajalloueyan et al. (35)	Prospective	Iran	27	1–4.67 years	Not specified	RW	Unilateral	6–8 weeks	Cvemp caloric test
Hazzaa et al. (36)	Not specified	Egypt	40	3–14 years	Heredofamilial 16 Unknown 13 Heredofamilial + Postfebrile 3 Heredofamilial+ Neonatal insult 2 Waardenberg syndrome 2 Ototoxicity 2 Perinatal insult 1	Not specified	Not specified	1 months 6 months	cVEMP oVEMP
Devroede et al. (15)	Retrospective	Belgium	26	6.75 years	Clinical syndrome 7 Genetic mutations 7 Postmeningitis 1 CMV infection 1 Auditory neuropathy spectrum disorder 2 Unknown 8	Cochleostomy	Sequentially implanted	3 months	Cvemp caloric test
Xu et al. (37)	Prospective	China	31	3–12 years	Not specified	Cochleostomy	Unilateral	4 weeks	Cvemp oVEMP
Psillas et al. (38)	Prospective	Greece	10	1.5–4 years	Congenital idiopathic deafness without inner ear dysplasia or syndrome 10	Cochleostomy	Unilateral	10 days, 6 months	cVEMP
Eustaquio et al. (39)	Observational	USA	64	8.16 years	Nonimplanted 26 Unilateral implant 12 Bilateral implants 26	Not specified	Unilateral and bilateral	Not specified	BOT−2

(Continued)

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TABLE 2 (Continued)

Study	Design	Country	Sample size	Age	Etiology	Surgical approach	CI side	Follow up	Test method
Licameli et al. (40)	Prospective	Boston	19	8 years	Not specified	Not specified	Unilateral	4–6 weeks	cVEMP
Cushing et al. (41)	Observational	Canada	56	4–17 years	Cochlear implant 41 Normal 14	Not specified	Unilateral	4.8 years	BOT−2
Jin et al. (42)	Not specified	Japan	24	2–14 years	Not specified	Not specified	Not specified	Not specified	cVEMP
Jin et al. (43)	Not specified	Japan	12	2–7 years	Mondini 2 one branch of vestibulocochlear nerve 1 EVA 1 Normal 8	Not specified	Not specified	Not specified	cVEMP

BOT−2, Bruininks–Oseretsky Test 2; cVEMP, cervical vestibular–evoked myogenic potential; CMV, cytomegalovirus; EVA, enlarged vestibular aqueduct syndrome; Extended, extended RW; IAC, Internal auditory canal; LSC, lateral semicircular canal; LVAS, large vestibular aqueduct syndrome; oVEMP, ocular vestibular–evoked myogenic potential; RW, round window; SNHL, sensorineural hearing loss; vHIT, video head impulse test.

round window (RW) or extended RW in 6 studies, cochleostomy in four studies, both RW and cochleostomy in two studies, and no specified approach in eight studies. In addition, the study also determined the methods of vestibular function tests, the implanted side, and the time of postoperative vestibular function tests.

Results of the otolith function tests

cVEMP, which is produced from the saccule and transmitted through the ipsilateral inferior vestibular nerve, induces the ipsilateral sternocleidomastoid to produce an inhibitory potential. The cVEMP test is an established technique for evaluating saccular function. The present meta-analysis defined weak or disappearing cVEMP response as otolith organ dysfunction. Statistical analysis demonstrated significant impairment of saccular function after CIM in children (fixed-effects model, RR = 2.20, 95% CI = 1.87, 2.58, $P < 0.0001$) (Figure 2A). In addition, cVEMP response parameters showed significantly reduced P1-N1 amplitudes in the postoperative period (fixed-effects model, SMD = −0.29, 95% CI = −0.52, −0.06, $P = 0.0118$), while no significant changes in P1 (random-effects model, SMD = −0.34, 95% CI = −1.25, 0.57, $P = 0.4670$) and N1 latencies (fixed-effects model, SMD = 0.27, 95% CI = −0.01, 0.54, $P = 0.0633$) were observed (Figures 2B–D).

oVEMP, mainly induced by the utricle, is transmitted through the superior vestibular nerve to induce the excitatory potential of the contralateral musculus obliquus inferior bulbi. oVEMP reflects the function of the utricle-superior vestibular nerve reflex pathway. Similar to the results of cVEMP, significant damage to utricle function in postoperative pediatric patients was found (random-effects model, RR = 2.10, 95% CI = 1.50, 2.94, $P < 0.0001$) (Figure 3A). Additionally, by analyzing the response parameters of oVEMP, a significant weakening of the P1-N2 amplitude after CIM in children was identified (fixed-effects model, SMD = −0.37, 95% CI = −0.69, −0.05, $P = 0.0250$). There were no significant differences in P1 (random-effects model, SMD = −0.15, 95% CI = −0.69, 0.40, $P = 0.5952$) and N1 (fixed-effects model, SMD = 0.00, 95% CI = −0.31, 0.32, $P = 0.9808$) latencies in oVEMP after CIM (Figures 3B–D).

Results of the tests for semicircular canal function

The caloric test detects the vestibulo-ocular reflex (VOR), which reflects the function of the left and right horizontal semicircular canals (HSCs), evaluating the status of vestibular function at ultralow frequencies. The results of the caloric test analysis are shown in the forest plot (Figure 4A). By comparing

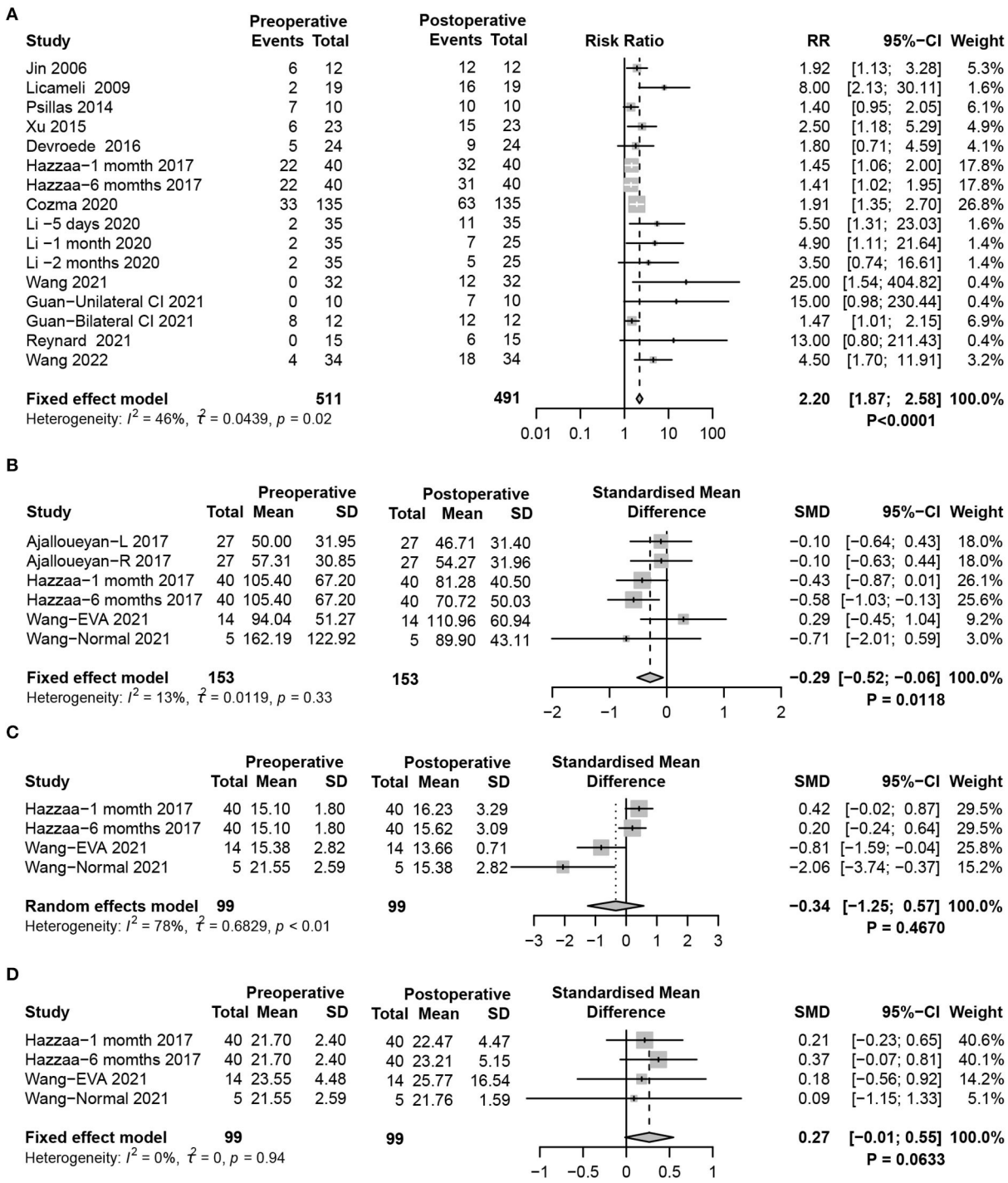

FIGURE 2
Forest plots showing the saccular function test results between pre- and post-surgery groups. **(A)** Response to the cVEMP test. **(B–D)** Response of cVEMP parameters including **(B)** P1-N1 amplitude, **(C)** P1 latency, and **(D)** N1 latency. Study, included studies for Research on meta-analysis; Preoperative, results of vestibular function test before operation; Postoperative, results of vestibular function test after operation; Events, number of people with abnormal vestibular function test results; Total, total number of patients in the study; Mean, arithmetic mean; SD, standard deviation; RR, relative risk; 95%-CI, 95% confidence interval; SMD, standardized mean difference; Weight, weight of each study in statistics.

the collection of nystagmus pre- and postoperatively, statistical analysis revealed a significant effect of CIM on the caloric test results. The increased risk of abnormal reactions in the caloric test demonstrated that HSC function was seriously damaged

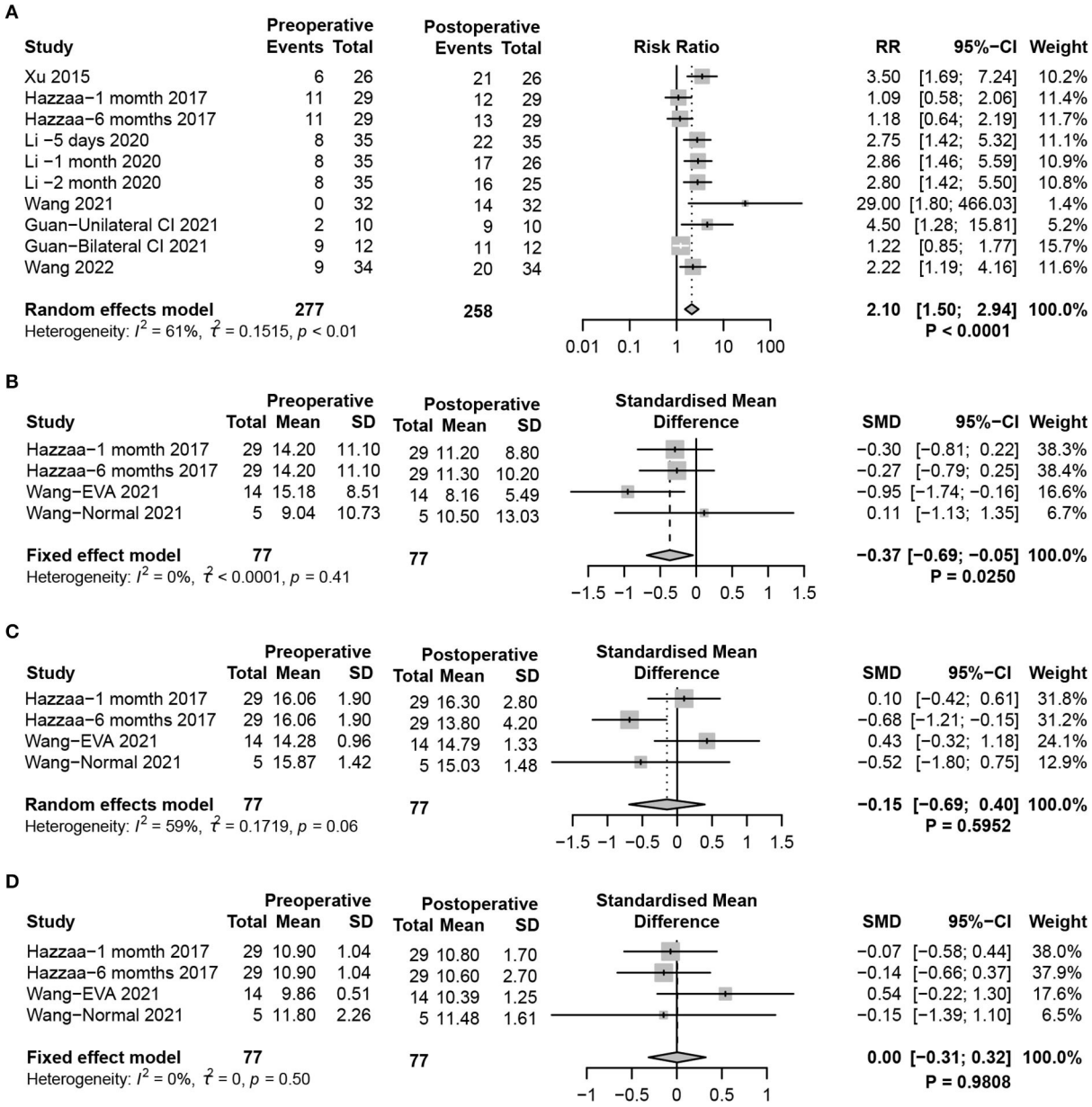

FIGURE 3
Forest plots showing utricle function test results between pre- and post-surgery groups. **(A)** Response to the oVEMP test. **(B–D)** Response of oVEMP parameters including **(B)** P1-N1 amplitude, **(C)** P1 latency, and **(D)** N1 latency. Study, included studies for Research on meta-analysis; Preoperative, results of vestibular function test before operation; Postoperative, results of vestibular function test after operation; Events, number of people with abnormal vestibular function test results; Total, total number of patients in the study; Mean, arithmetic mean; SD, standard deviation; RR, relative risk; 95%-CI, 95% confidence interval; SMD, standardized mean difference; Weight, weight of each study in statistics.

after CIM in children (fixed-effects model, RR = 1.62, 95% CI = 1.20, 2.19, $P = 0.0018$).

In recent years, vHIT has become a comprehensive examination method to assess the function of the semicircular canals [HSC, posterior semicircular canal (PSC), and anterior semicircular canal (ASC)]. In contrast to the caloric test, vHIT completes the examination of three pairs of semicircular canals to evaluate vestibular function status at high frequencies. VOR gain was used to determine the function of the semicircular canals (VOR < 0.8 considers HSC dysfunction, while the dysfunction of PSC and ASC was VOR < 0.7). The fixed-effects meta-analysis did not indicate any significant differences after CIM in VOR gain detection for HSC and PSC, demonstrating that normal function might be preserved in HSC (RR = 2.23, 95% CI = 0.95, 5.23, $P = 0.0650$), PSC (RR = 2.64, 95% CI = 0.81, 8.56, $P = 0.1059$), and ASC (RR = 4.70, 95% CI = 0.84, 26.36, $P = 0.0788$ (Figures 4B–D).

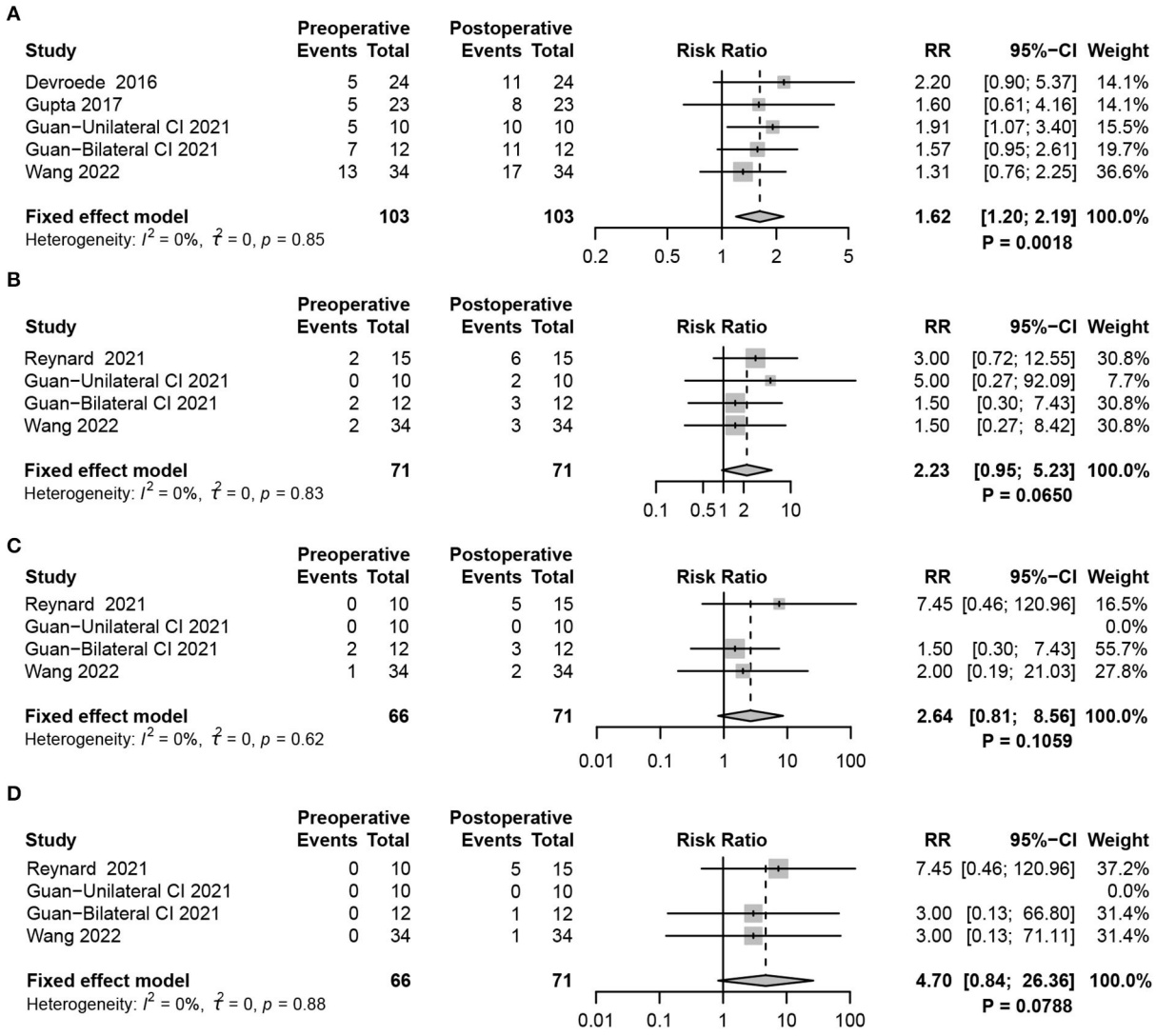

FIGURE 4
Forest plots showing semicircular canal function test results between pre- and post-surgery groups. **(A)** Response to the caloric test. **(B–D)** vHIT, including **(B)** HSC **(C)** PSC, and **(D)** ASC function tests. Study, included studies for Research on meta-analysis; Preoperative, results of vestibular function test before operation; Postoperative, results of vestibular function test after operation; Events, number of people with abnormal vestibular function test results; Total, total number of patients in the study; RR, relative risk; 95%-CI, 95% confidence interval; Weight, weight of each study in statistics.

Results of the balance function test

The balance subtest of BOT-2 evaluates static and dynamic balance functions by scoring nine balance tasks, with higher scores indicating better overall static and dynamic balance. The results revealed that balance was significantly worse in children with SNHL who received CIM than in children with typical hearing (random-effects model, MD = −7.26, 95% CI = −10.82, −3.70, $P < 0.0001$) (Figure 5A). Interestingly, when the CIM device was on, the BOT-2 score slightly improved compared with when the CIM device was off, which suggested that providing sound inputs through implants positively affects balance in children with SNHL (fixed-effects model, MD = 1.76, 95% CI = 0.52, 3.00, $P = 0.0053$) (Figure 5B).

Factors affecting changes in vestibular function

Considering the benefit of maintaining balance in children with CIM devices, the meta-analysis compared the results of tests assessing objective vestibular function using cVEMP between CIM devices on and off. However, no significant

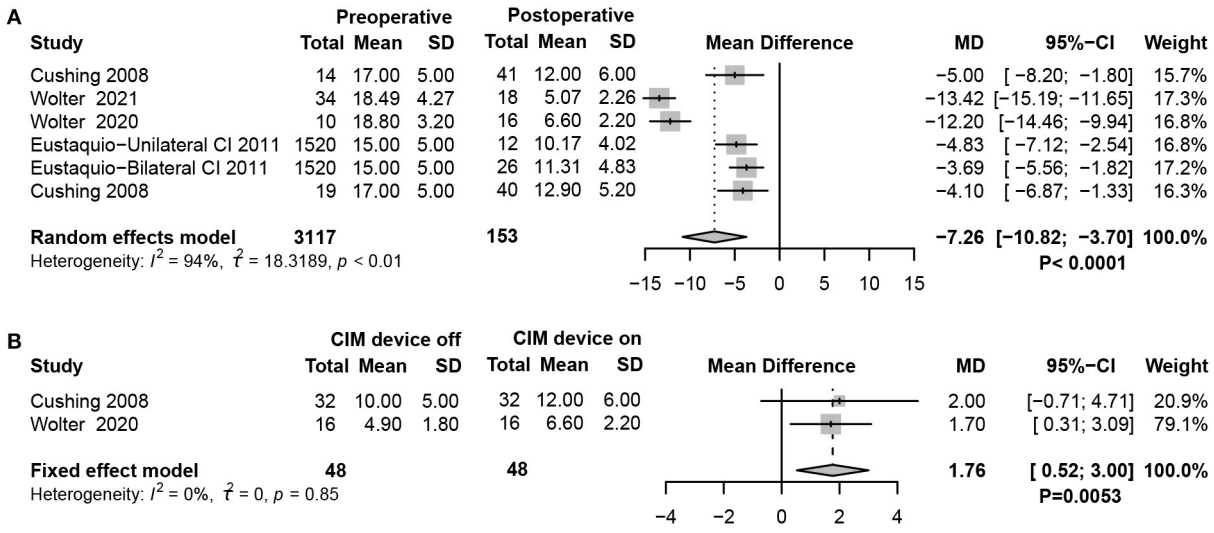

FIGURE 5
Forest plots showing balance function test results between pre- and post-surgery groups. **(A)** BOT-2 test scores. **(B)** Comparison of the balance function between CIM devices switched on and off. Study, included studies for Research on meta-analysis; Preoperative, results of vestibular function test before operation; Postoperative, results of vestibular function test after operation; CIM device off, postoperative results of vestibular function test with CIM devices off; CIM device on, postoperative results of vestibular function test with CIM devices on; Total, total number of patients in the study; Mean, arithmetic mean; SD, standard deviation; MD, mean difference; 95%-CI, 95% confidence interval; Weight, weight of each study in statistics.

difference was found between the two groups (random-effects model, RR = 0.83, 95% CI = 0.63, 1.10, P = 0.1898) (Figure 6A).

RW and cochleostomy are the two most common surgical approaches for CIM port electrode insertion. Although both caused vestibular dysfunction, the meta-analysis revealed that children receiving RW acquired more severe damage (P = 0.0101) (Figure 6B). While directly contrasting the effect of vestibular function between the two methods, no statistically significant difference was found (fixed-effects model, RR = 0.74, 95% CI = 0.45, 1.23, P = 0.2471) (Figure 6C).

Vestibular dysfunction occurred in about half of the children with profound SNHL before CIM. The likelihood was highly dependent on their individual etiologies. In the absence of specific aetiological data from the included literature, we only compared whether a difference in the degree of vestibular dysfunction would occur between children with LVAS and normal children after CIM. Although the abnormality rate of cVEMP after CIM was higher in normal patients than in those with LAVS, subgroup analysis showed no statistically significant difference between the two groups (P = 0.0819) (Figure 6D).

Risk of bias across studies

The risk of bias when comparing the studies was deemed low. No concerns were identified regarding the selective reporting of data because patients in the reviewed studies were generally accounted for in the results.

Discussion

Background

Cochlear implantation may also lead to vestibular dysfunction. In studies involving adults, Hansel et al. (23) observed a significantly increased postoperative risk of imbalance, vertigo, and falls as well as a significant impairment of otolithic organs and canal function. Similar results were observed in pediatric patients. A significant reduction in cVEMP response was observed after CIM in children (24). Inadequate labyrinth protection is considered a major cause of vestibular symptoms (44). Specifically, several potential mechanisms of surgical injuries include serous labyrinthitis induced by the opening of the membranous labyrinth (45, 46), permanent damage in the endolymphatic system caused by the direct injury caused by electrode array insertion in the implantation process (47), mechanical disruption of inner ear structures (48–53), or temporary lymph flow obstruction caused by blood, fibrous tissue, and bone powder (54).

Due to the challenges in accomplishing vestibular tests in the pediatric population, few studies, especially systematic and comprehensive analyses, have reported vestibular function changes pre- and postoperatively in children who receive CIM.

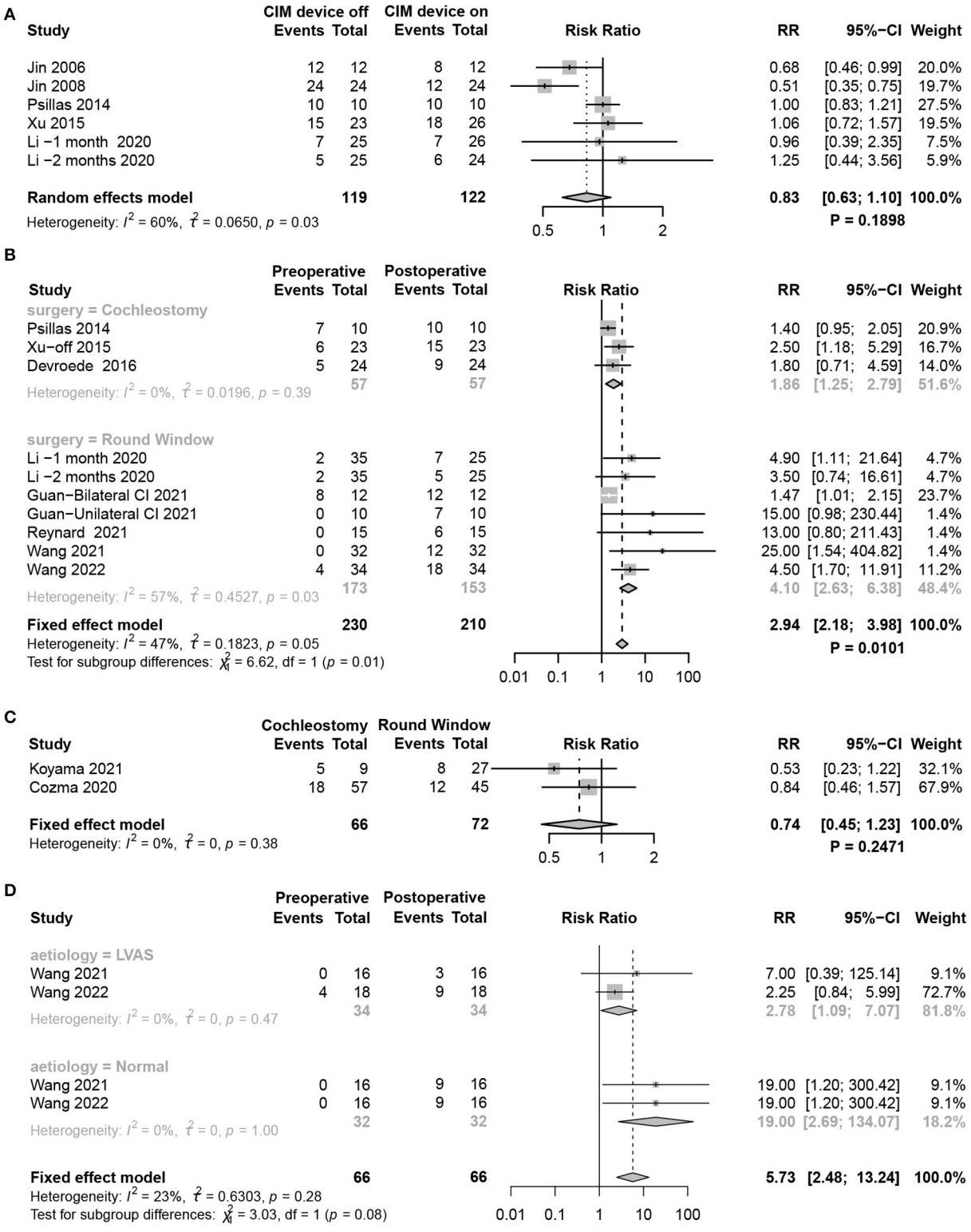

FIGURE 6
Forest plots showing factors affecting vestibular function changes. **(A)** cVEMP test comparing CIM devices on and off. **(B)** Subgroup analysis of patients using RW and cochleostomy. **(C)** Comparison of the effect of RW and cochleostomy on vestibular function. **(D)** Subgroup analysis comparing the effect of LAVS and normal patients on vestibular function. Study, included studies for Research on meta-analysis; CIM device off, postoperative results of vestibular function test with CIM devices off; CIM device on, postoperative results of vestibular function test with CIM devices on; Preoperative, results of vestibular function test before operation; Postoperative, results of vestibular function test after operation; Cochleostomy, cochleotomy implantation group; Round Window, round window implantation group; Events, number of people with abnormal vestibular function test results; Total, total number of patients in the study; RR, relative risk; 95%-CI, 95 confidence interval; Weight, weight of each study in statistics.

Therefore, to measure the specific impact of CIM surgery on vestibular function in children, our meta-analysis confirmed that the vestibular function of the pediatric population was significantly damaged after CIM by comparing the function of the otoliths, semicircular canals, and balance.

Otolith function after CIM

Previous evidence has reported that the abnormal response or parameters of the VEMPs are present in pediatric patients with CIM (15, 26, 28, 30, 32, 33, 36–38, 40, 43). The statistical analysis of the VEMPs' responses showed that the abnormal response of VEMPs significantly increased after CIM, which proved that CIM could potentially cause damage to both utricle and saccular functions in pediatric patients. Due to the lack of literature on the results of VEMP parameters, we only found lower amplitudes in the postoperative cVEMP and oVEMP tests (27, 35, 36). Only two studies have reported specific P1 and NI latency data, and inconsistent results were presented. Comprehensive analysis showed that the difference was not statistically significant in the P1 and NI latencies of cVEMP and oVEMP (27, 36).

Because the saccule is closer to the electrode insertion pathway anatomically, some studies have considered that the saccule is more susceptible to damage than the utricle (55, 56). However, some studies have reported divergent results. Li et al. (32) showed significant differences between the response rates of cVEMP and oVEMP after CIM, highlighting that the utricle may be more vulnerable to surgery. In addition, no significant difference between the response rates of cVEMP and oVEMP after CIM was found by Xu et al. (37). Therefore, we compared the meta-analysis results of cVEMP and oVEMP to verify which one is more easily damaged, and the outcome demonstrated no significant difference between the two tests. Further in-depth studies with larger sample sizes are needed to confirm this conclusion.

Semicircular canals function after CIM

In addition to otoliths, vestibular organs include three pairs of semicircular canals. To comprehensively evaluate vestibular function in pediatric patients after surgery, we evaluated all three pairs of semicircular canal function under high-frequency impulse stimulation by integrating the vHIT results. Meanwhile, a caloric test assessed HSC function under a low-frequency stimulus. Practically, these vestibular function tests are quite difficult to perform in children. Increased abnormal rates from pre- to post-implantation in caloric tests, but not in vHIT, suggested that the detection of calorie tests was more sensitive than vHIT in pediatric patients. Similar results from Nassif et al. (57) showed no significant difference in HSC VOR gain between the implanted and non-implanted-implanted sides in unilaterally implanted children; the function on both sides was similar to that in children with normal hearing. The deterioration risk ratio was increased in HSC tested by caloric testing (RR=1.62, $P = 0.0018$), while HSC tested by vHIT showed no significant difference. The vHIT and caloric tests measured two extreme frequency ranges of the HSC VOR. The vHIT uses a physiological stimulus with higher testing frequencies (>1 Hz), close to the physiological stimuli of daily life, whereas the caloric test applies a non-physiological stimulus (< 0.003 Hz), and the parallel recovery processes in vestibular function between the two tests were different (58). The other evidence, attempting to validate the caloric test compared with vHIT, discovered that HSC VOR gain in high-frequency stimulus results is abnormal only when vestibular impairment on caloric testing of the semicircular canals is higher than 40% (59). These two measures should be performed together to comprehensively assess semicircular canal function.

Balance function after CIM

Although CIM improves hearing and speech perception in SNHL, this technique can also cause balance deficiencies or increase existing balance dysfunction (60). BOT-2 has become the most widely standardized method for assessing motor proficiency. It is a clinical test battery comprising several subtests, one of which was designed to evaluate the overall balance function (61). As expected, with lower BOT-2 scores, balance ability was significantly worse in children with SNHL requiring CIM than in typically developing children with hearing impairment. Nevertheless, when pediatric patients received any sound with their implant device, the rising BOT-2 score indicated that the postural balance function slightly improved. Postural stability can also be measured using posturography and center-of-pressure variation as a function of time (62–64). The same conclusion was reached even with other evaluation methods (65). Stabilizing postural control requires the optimal integration of information from somatosensory, visual, vestibular, and other sensory systems (hearing, tactile, etc.) (66). Thus, auditory information can improve postural stability in children with balance disorders (31, 41).

Factors affecting changes in vestibular function

We also compared the changes in vestibular function when the cochlear implant device was turned on or off. Some research results indicated that although the saccular function was damaged before surgery, the VEMP response was elicited again upon activation of the CIM device (32, 42, 43). For instance, the study demonstrated that 11 out of 12 children

showed no response in cVEMPs when the cochlear implant was turned off, whereas four children had reproducible cVEMPs when switched on (43). A comparison of the cVEMP parameters found that lower thresholds on the implanted sides and wider amplitudes on the contralateral side were achieved with the CIM device (32). The possible reason is that galvanic stimulation from the CIM device may evoke a myogenic response in the sternocleidomastoid muscle (67, 68). However, other studies have not supported this conclusion. In the study by Psillas et al. (38), the VEMPs remained absent irrespective of device activation. Therefore, we conducted a summary analysis of relevant studies and found no significant difference in vestibular function changes between CIM devices on and off. Evidently, our findings were based on a small sample, and there was great variability among these studies. Further research is necessary for an in-depth understanding of vestibular changes with CIM devices on and off.

The surgical approach is an important consideration affecting the preservation of the vestibular neurosensory epithelium and cochlea. RW and cochleostomy are widely used to enrich the intracochlear space. Clinically and histopathologically, previous studies have identified that RW is better than cochleostomy, especially in effectively preserving vestibular functions (43, 69–72). For example, Todt et al. (73) reported hypofunction of postoperative cVEMP in 13% of patients who underwent RW, while 50% underwent cochleostomy. The reason port electrode insertion by cochleostomy induces a risk of vestibular loss is probably due to the drilling, which produces mechanical and thermal aggression.

Additionally, the bony drilling residue may penetrate the inner ear and even produce ossifications (33). However, electrode insertions through the RW membrane resulted in deep atraumatic insertions into the scala tympani. Thus, previous studies suggested that to preserve vestibular functions to the greatest extent, RW is the better technique (74). In our study, we calculated the RR to directly compare the differences in vestibular function damage between the two surgical methods. Compared with cochleostomy, Koyama et al. (7) and Cozma et al. (33) reported that the risk of vestibular loss was reduced by 47 and 16%, respectively, when performing RW. Nevertheless, no significant difference was observed. A subgroup analysis involving the indirect comparison of the results of different studies showed the opposite results; compared with cochleostomy, RW increased the risk of vestibular dysfunction. We inferred that although cochleostomy produces greater surgical trauma and bone scarring, the RW membrane is closer to the saccule anatomically. Furthermore, previous studies were mainly based on adult patients, and pediatric implantation surgeries in the included cohorts were performed by different surgeons using distinct techniques. Consequently, the degree of vestibular function damage caused by RW and cochleostomy in pediatric patients is difficult to define; further verification is needed to clarify this conclusion. Follow-up research should focus on this aspect through a comprehensive assessment of hearing and vestibular function in pediatric patients before surgery, carefully confirming the differences in anatomical structures of different patients and determining the eligible surgical method.

The likelihood of vestibular dysfunction is highly dependent on etiology, with meningitis and cochleovestibular anomalies having the highest rates of severe dysfunction (75). LAVS is the most common abnormal radiologic finding in pediatric patients with SNHL (76), and it has a high rate of vestibular pathology (77). Comparing the extent of vestibular dysfunction between children with LVAS and normal children after CIM revealed a significant increase in the overall abnormality rate of the VEMP from pre- to post-CIM in normal patients but no significant change in children with LVAS. This could be because, in children with LVAS, the pressure generated during electrode insertion could be released through the enlarged vestibular aqueduct or into the endolymphatic fluid, resulting in less impairment (26). Besides the vestibular dysfunction, peripheral mechanical changes were considered. However, the subgroup analysis found no statistical significance between the two groups, most likely due to insufficient sample size and corresponding cohort studies. The effect of etiology on vestibular function is significant, and our future work will collect more relevant data for statistical analyses. We propose that more attention should be paid to the detailed assessment of pre- and postoperative vestibular function in pediatric patients with the underlying condition of vestibular dysfunction.

Comprehensive evaluation of vestibular function before and after CIM

In addition, about half of pediatric cochlear implant candidates already suffer from vestibular deficits, and 51% of cochlear implants result in changes in existing preoperative vestibular function. Given the high prevalence of vestibular dysfunction after CIM in our meta-analysis, any implantation should be preceded by functional testing of the semicircular canals and otolith. Preoperative vestibular function testing is not only useful to check for vestibular dysfunction associated with congenital SNHL, but it can also determine the side of CIM. If only one functional vestibule is present, the least functional vestibule should be selected as the side for the CIM to limit the likelihood of bilateral vestibular loss, except in cases where audiological or anatomical criteria are important (40). Similarly, a vestibular assessment should be performed before bilateral simultaneous or sequential implantation to prevent complete bilateral vestibular areflexia and its potential consequences.

The postoperative test is also indispensable. It is better suited to comprehensively assessing the changes in vestibular function. The vestibular function should be evaluated not

only when the pediatric patients show symptoms related to vestibular disorders, such as dizziness or vertigo, but in all patients that underwent CIM. It should be kept in mind that the subjects are children who may have difficulty describing their symptoms clearly. If vestibular function tests were only conducted after the onset of obvious symptoms, this would lead to an increased diagnosis rate and delayed treatment. We conclude that CIM can lead to vestibular dysfunction. Thus, assessing vestibular function after surgery is vital to assure early diagnosis and treatment.

To sum up, we should not only pay attention to the degree of hearing restoration after CIM but also to the vestibular dysfunction in pediatric patients to detect and treat it in time.

Limitations

Most studies classified abnormal VEMP response as hyporeflexia or areflexia. Only some studies reported specific VEMP response parameters. Additionally, the CIM device state, etiologies of SNHL, and the surgical approach may affect the vestibular function of the pediatric population. Most children are unable to accurately describe their symptoms. This makes it difficult to assess their subjective perception of dizziness or vertigo. The Dizziness Handicap Inventory is often used to evaluate the quality of life of adults, but this questionnaire is not suited for children. Consequently, we did not analyze the occurrence of dizziness and vertigo in pediatric patients after CIM. We will further collect the latest articles in the future, which also validates our analysis results.

Conclusions

The present study confirmed that the disappearance and impairment of cVEMP, oVEMP, and caloric response could be observed after CIM in pediatric patients, reflecting damage to the utricle, saccule, and HSC caused by CIM. In addition, the patients' balance ability significantly decreased after the operation. All the evidence indicates that vestibular dysfunction is common in pediatric patients with SNHL after CIM, suggesting that apart from audiological or anatomical criteria being the main concern of CIM in pediatric patients, vestibular function should be considered.

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.

Author contributions

QW designed the study, screened the literature, conducted statistical analyses, and drafted the manuscript. QZ assisted in drafting the protocol, collecting data and processing, and editing the manuscript. YZ and ZC assessed the quality of inclusion research. QX and SL performed data extraction and literature screening. YX, XW, and X-DX prepared the figures and revised the manuscript. JL, YJ, JY, and QZ critically evaluated the manuscript. All authors reviewed and approved the final version of the manuscript.

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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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.996580/full#supplementary-material

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Jun Yang,
Shanghai Jiaotong University School of Medicine, China

REVIEWED BY
Nahid Olfati,
University of California, San Diego, United States
Nils Guinand,
Hôpitaux universitaires de Genève (HUG), Switzerland

*CORRESPONDENCE
Filipp Maximilian Filippopulos
filipp.filippopulos@med.uni-muenchen.de

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Episodic ataxias in children and adolescents: Clinical findings and suggested diagnostic criteria

Filipp Maximilian Filippopulos[1,2]*, Lutz Schnabel[1,2], Konstanze Dunker[1], Ralf Strobl[1] and Doreen Huppert[1,2]

[1]German Center for Vertigo and Balance Disorders (DSGZ), University Hospital, Ludwig-Maximilians-Universität, Munich, Germany, [2]Department of Neurology, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany

Background: The main clinical presentation of episodic ataxias (EAs) consists of vertigo and dizziness attacks lasting for minutes to hours with widely varying accompanying symptoms. The differentiation of EA and episodic vertigo/dizziness syndromes in childhood and adolescence such as vestibular migraine (VM) and recurrent vertigo of childhood (RVC) can be challenging. Furthermore, only few prospective studies of children/adolescents with EA are available.

Objective: This study aims to characterize clinical and instrument-based findings in EA patients under 18 years of age, to delineate the clinical and therapeutic course in EA, and to present potentially new genetic mutations. Furthermore, the study aims to differentiate distinct characteristics between EA, VM, and RVC patients.

Methods: We prospectively collected clinical and instrument-based data of patients younger than 18 years, who presented at the German Center for Vertigo and Balance Disorders (DSGZ) at the LMU University Hospital in Munich with EA, VM, or RVC between January 2016 and December 2021. All patients underwent a comprehensive evaluation of neurological, ocular-motor, vestibular and cochlear function, including video-oculography with caloric testing, video head impulse test, vestibular evoked myogenic potentials, posturography, and gait analysis.

Results: Ten patients with EA, 15 with VM, and 15 with RVC were included. In EA the main symptoms were vertigo/dizziness attacks lasting between 5 min and 12 h. Common accompanying symptoms included walking difficulties, paleness, and speech difficulties. Six EA patients had a previously unknown gene mutation. In the interictal interval all EA patients showed distinct ocular-motor deficits. Significant differences between EA, VM, and RVC were found for accompanying symptoms such as speech disturbances and paleness, and for the trigger factor "physical activity". Furthermore, in the interictal interval significant group differences were observed for different pathological nystagmus types, a saccadic smooth pursuit, and disturbed fixation suppression.

Conclusion: By combining clinical and ocular-motor characteristics we propose diagnostic criteria that can help to diagnose EA among children/adolescents and identify patients with EA even without distinct genetic findings. Nevertheless, broad genetic testing (e.g., next generation sequencing) in patients fulfilling the diagnostic criteria should be conducted to identify even rare or unknown genetic mutations for EA.

KEYWORDS

episodic ataxia, spinocerebellar ataxia 27, ocular motor disturbances, children, adolescents, vertigo, dizziness

Introduction

The diagnoses behind recurrent vertigo attacks in children and adolescents are manifold and often pose a major diagnostic challenge even for experienced clinicians. The most common diagnoses include vestibular migraine (VM) and the associated disorder of "Recurrent Vertigo of Childhood" (RVC), whereas central causes such as episodic ataxia (EA) are less frequent (1–3). The core features of these diseases may be very much alike and include recurrent attacks of vertigo (sensation of spinning of the environment)/dizziness (various sensations of body orientation and position), headaches, and different trigger-factors, as well as an inconclusive clinical examination, at least in early stages. Furthermore, overlap syndromes between e.g., migraine and EA (4, 5), epilepsy and EA (6), or progressive and episodic ataxias (e.g., spinocerebellar ataxia type 27 and EA 9) (7) have been described. Especially diseases with a rare occurrence such as EA are sometimes difficult to diagnose. Nevertheless, due to the direct therapeutic relevance (e.g., acetazolamide or 4-aminopyridine for EA, magnesium for VM), different prognosis (often progressive in EA, benign in RCV and VM), and impact on family planning (EA mostly has an autosomal dominant inheritance pattern), it is important not to miss such differential diagnoses of episodic vertigo syndromes.

Episodic ataxias are hereditary chanellopathies with symptoms mainly attributable to a cerebellar dysfunction, that are genetically and phenotypically heterogeneous (8), which further complicates the diagnostic approach. To date, nine phenotypes and genotypes of EA have been described (EA 1–9) (7, 9), with EA 2 being most common (10). EA 1 is typically caused by mutations of the potassium channel Kv1.1-encoding gene KCNA1 on chromosome 12q13 (11), and EA 2 by mutations in the CACNA1A gene on chromosome 19p13 which encodes the Cav2.1 subunit of the P/Q-type voltage-gated calcium channel (5). Although EAs usually have an autosomal-dominant inheritance pattern (7–9), spontaneous mutations have been described (4, 12), so that affected children/adolescents might not always have a positive family history, again complicating the correct diagnosis. The age of onset, disease characteristics, and symptom constellation during and between attacks is highly variable even in patients with the same gene mutation causing the EA (6, 10). No causative treatments are available for any EA syndrome, but there are some symptomatic treatment options available for EA 1 and 2 such as acetazolamide and 4-aminopyridine (10), that may have a significant impact on the patients' quality of life.

Since the knowledge of the clinical spectrum as well as typical instrument-based findings in patients with EA are the key for early diagnosis and specific treatment, we prospectively examined ten children/adolescents with episodic ataxia syndromes. We describe clinical and instrument-based findings, treatment response, and clinical course. Furthermore, to depict the most important features for diagnosing EA, we compared clinical and instrument-based findings between EA patients and patients with the most common episodic vertigo syndromes in children/adolescents, namely VM and RVC.

Methods

Subjects and clinical/instrument-based evaluation

All children/adolescents younger than 18 years of age who presented at the German Center for Vertigo and Balance Disorders (DSGZ) at the LMU University Hospital in Munich between January 2016 and December 2021 were screened for inclusion. All patients with an episodic ataxia syndrome were included in the study. Furthermore, patients younger than 18 years with the final diagnosis of vestibular migraine (VM) or RVC according to the diagnostic criteria of the Bárány Society (13) were included in the study as comparative groups. All patients who were recruited before the publication of the diagnostic criteria in 2021 were reevaluated and only included for further analysis, if the diagnostic criteria for VM or RVC were fulfilled. Written informed consent was obtained from all participants included in the study.

Due to the lack of evidence on distinct clinical and instrument-based findings in patients with EA, an extensive,

standardized work-up was designed to broadly evaluate clinical features and instrument-based findings these patients. The work-up was comprised to include most of the available neuro-otological examinations for the assessment of the peripheral and central vestibular system. Following examinations were performed:

A) Medical history (including duration and quality of symptoms, accompanying symptoms, trigger factors, family history, medication).
B) Clinical examination of the vestibular function including neuro-otological and neuro-ophthalmological examination (including head impulse test, test for spontaneous nystagmus, provocation nystagmus, positional nystagmus, skew deviation, smooth pursuit, saccades, gaze-holding, fixation suppression of the vestibulo-ocular reflex, hearing).
C) Neurological status (including motor, sensory, coordination, cranial nerve, cognitive function assessment).
D) Instrument-based assessment:

a. Video-oculography with caloric irrigation was conducted with cold (30°C) and worm (44°C) water on both sides to evaluate the low frequency function of the vestibular system
b. Video-Head-Impulse-Test (vHIT) was performed on a standard commercial v-HIT system to evaluate the high frequency function of the vestibular system
c. Ocular and cervical Vestibular-Evoked Myogenic Potentials (c/o VEMP's) were analyzed for the evaluation of utricular and saccular function respectively
d. Auditory-Evoked Potentials (AEP's) for the evaluation of the hearing function
e. Posturography and gait analysis was performed to measure body sway and gait patterns
f. Testing of subjective visual vertical, and fundus photography.

D) Clinical follow-up for patients with EA syndrome.

Statistical analysis

We report mean and standard deviation for continuous variables, and absolute frequency and the relative frequency as percentages for categorical variables. Group comparison is based on the chi-squared test for categorical data and on the likelihood ratio test for continuous variables.

Two-tailed p-values <5% were considered as statistically significant. As this is an exploratory study, no correction for multiple testing was done. R 4.1.2 was used for statistical analyses (14).

Results

Between January 2016 and December 2021, 336 patients under the age of 18 were screened for inclusion. Of all screened children/adolescents, ataxia syndromes represented the fifth most common diagnosis following VM, functional dizziness, RVC, and orthostatic hypotension. A total of 18 children/adolescents with ataxia syndromes presented in the period mentioned, 10 of whom had an episodic ataxia syndrome and were included in the present study (see Figure 1). Furthermore, 15 age- and gender- matched children and adolescents with VM and RVC were included in the comparative groups.

EA characteristics

Of the 10 children/adolescents with EA, seven had a genetically confirmed EA 2, one had a genetically confirmed EA 1, one a genetically confirmed EA 9, and one child had a suspected EA 1. In the latter child, a mutation in the CACNA1A gene was ruled out; further testing for mutations e.g., in the KCNA1 gene was not possible due to insurance restrictions (Table 1). Nevertheless, the child was included in the EA group due to the distinct clinical and instrument-based findings (see Tables 2, 3), as well as due to the fact, that in a considerable amount of children and adolescents with EA, no mutation at all is found (8). Of the 10 children/adolescents five had a spontaneous mutation defined as no genetic marker in tested family members nor a positive family history (including the suspected EA 1 child). Six children/adolescents (five with EA 2, one with EA 1) had a new mutation, that has not been described in common gene databases such as the University of California Santa Cruz (UCSC) genome browser, the human gene mutation database (HGMD), ClinVar at the National Center for Biotechnology Information (NCBI), and global variome shared Leiden Open Variation Database (LOVD) (see Table 1).

The mean age at symptom presentation in children/adolescents with EA was 7.4 ± 4.3 years. The earliest symptom manifestation was in the ninth month in one child with EA 2 and the latest at the age of 12 years and 6 months, also in an adolescent with EA 2.

Attack frequency varied between daily attacks (in EA 9 and suspected EA 1) and attacks once a month (mean ± sd = 9.3 ± 11.2). The Scale for the Assessment and Rating of Ataxia (SARA) in the attack-free interval was increased in three children/adolescents (for details see Table 1).

In a vertigo/dizziness attack, the most common accompanying symptoms were "nausea/vomiting" (80%) and experiencing "walking difficulties" (80%), which were often described as the "inability to walk" and "having to lie down" until the attack is over. Furthermore, "paleness" (50%) and "oscillopsia" (40%) were commonly described.

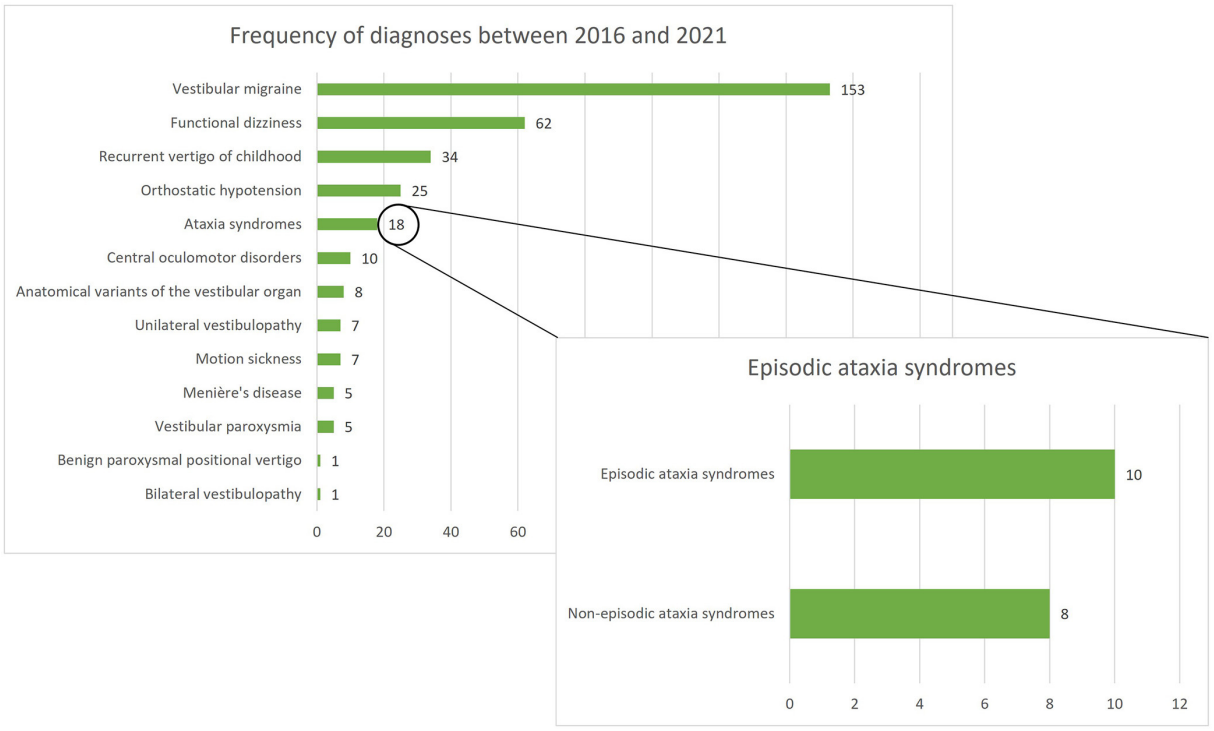

FIGURE 1
Frequency of diagnoses among 336 children/adolescents presenting at the German Center for Vertigo and Balance Disorders (DSGZ) between 2016 and 2021. Ataxia syndromes are the fifth most frequent diagnosis with episodic ataxias being the leading subgroup.

The most frequent trigger for an attack was physical activity ("sport", 80%), followed by psychosocial stress (30%), while two children/adolescents (20%) did not report any trigger factors. Detailed findings are listed in Tables 2, 3.

The broad ocular-motor evaluation showed in all patients with EA an impaired smooth pursuit, in most cases with a medium to highly reduced smooth pursuit gain at 0.1 and 0.2 Hz (Hertz). Furthermore, 70% of the patients had a pathological finding in the nystagmus examination (see Table 3). The optokinetic nystagmus was impaired in 60% of patients and fixation suppression in 50%. Overall, 70% of patients had more than one ocular-motor abnormality. No pathological findings were detected in additional instrument-based examinations such as caloric irrigation, VEMPS, AEPs, and audiogram.

EA disease course

The mean follow up of the patients with EA was 2.7 years. Seven children/adolescents received treatment with at least one medication, two declined treatment and one with genetically not confirmed EA 1 was not offered any specific medication. Medical treatment was administered for at least 6 weeks and then changed or discontinued if no therapeutic effect was noted. Initial treatment was chosen according to the side-effect profile of each substance and according to patient/parents' wishes; dosage was adapted to weight for acetazolamide (8–30 mg/kg), 4-aminopyridine was restricted to a maximum of 2 doses of 10 mg per day. In four cases acetazolamide was prescribed but led to a reduction of the frequency or duration of the vertigo attacks in only one case. 4-Aminopyridine was administered in three children/adolescents (the youngest being 1 year and 6 months old) and led to a decrease in attack frequency and duration in two cases. Magnesium which was administered in three patients did not influence vertigo attacks. In the adolescent with EA 9, especially the behavioral recommendations (in combination with magnesium) led to a significant decrease in attack frequency and severity, but also to a reduced SARA score (see Table 1).

Comparison of EA with VM and RVC

Table 4 shows the results of the comparison between EA, VM, and RCV in detail. A positive family history of genetically determined EA and delayed motor and/or mental development occurred significantly more often ($p = 0.0012$) in EA patients compared to patients with VM and RVC (40 vs. 0%). The attack characteristics (type of vertigo, attack frequency, attack duration) did not differ between the three diagnoses. Accompanying symptoms such as "speech disturbances" and

TABLE 1 Genetic and clinical course characteristics of 10 children/adolescents with episodic ataxia.

Nr.	EA	Symptom onset	Genetic mutation	Previously unknown mutation	Spontaneous mutation	Developmental delay	SARA score (attack free interval)	Attack frequency/month before treatment	Treatment (in order of prescription)	Attack frequency/month after treatment	Other treatment response
1	1	5 yrs	c.555C>g in the KCNA1 gene	Yes	Yes	No	0	4	Acetazolamide, Magnesium	4	None
2	(1)	4 yrs 7 mos	Yet Unknown, no mutation in the CACNA1A gene		Probably (no family history)	No	0	30	None	-	-
3	9	11 yrs 8 mos.	Microdeletion 13q33 in the first Exon of the FGF14 gene	No	Yes	Yes	8	30	Magnesium, behavioral recommendations	6	reduced SARA score (4)
4	2	8 yrs	c.5035C>T; p.(Arg1679Cys) in the Exon 32 of the CACNA1A gene	No	Yes	No	0	2	4-Aminopyridine	1	None
5	2	0 yrs 9 mos	c.4300C>T; p.Arg1434Trp in the CACNA1A gene	Yes	No	Yes	0	1	Acetazolamide	1	None
6	2	12 yrs	c.1949delA; p.Asn650Thrfs*9 in the CACNA1A gene	Yes	Yes	No	0	1	None	-	-
7	2	12 yrs 6 mos	c.5570G>A (p.Arg1857Gln) in the CACNA1A gene	Yes	No	No	0	5	None	-	-
8	2	10 yrs	c.3370G>A; p.(Ala1124Thr) **AND** c.1011delG; p.(Trp337Cysfs*16), both in the CACNA1A gene	Yes / Yes	Yes	Yes	3	8	Acetazolamide, 4-Aminopyridine	4	Reduced SARA score (1)
9	2	1 yr 6 mos	c.4095_4096delGT (Stop-Kodon) in the CACNA1A gene	Yes	No	Yes	1,5	4	Magnesium, Acetazolamide, 4-Aminopyridine		None
10	2	8 yrs	c.5419-1G>A in the CACNA1A-Gen	No	No	No	0	8	Acetazolamide	1	attack duration ↓ (60 → 5 min)

Six children/adolescents showed a novel disease-causing mutation. Five children/adolescents had a spontaneous mutation. Not all patients responded to treatment with acetazolamide or 4-Aminopyridine.
EA, Episodic ataxia type; SARA, Scale for the Assessment and Rating of Ataxia.

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TABLE 2 Detailed clinical characteristics of the vertigo/dizziness attacks of children and adolescents with episodic ataxia.

Nr.	EA	Main symptom	Attack freq.	Attack dur.	Accompanying symptoms									Trigger	
		Vert. (V) Dizz. (D)	*per month*	*in min.*	Head-ache	Speech disturb	Limb ataxia	Walking difficulties	Photo-/Phono-phobia	Double vision	Oscill-opsia	Nausea/ Vomiting	Paleness	Sport	Stress
1	1	D	4	20	n	y	n	y	n	n	y	y	n	y	y
2	(1)	V	30	10	n	n	n	y	n	n	y	y	y	y	n
3	9	V	30	30	y	n	n	n	y	y	n	y	y	y	n
4	2	V	2	120	n	n	n	y	n	n	n	y	y	y	y
5	2	V	1	5	n	n	n	y	n	y	y	n	n	y	n
6	2	D	1	30	y	n	n	y	y	n	n	y	n	n	n
7	2	V/D	5	40	n	y	n	y	n	n	n	y	n	y	n
8	2	V	8	720	y	y	n	y	n	n	y	y	y	y	y
9	2	D	4	150	n	n	y	n	n	n	n	y	y	n	n
10	2	D	8	60	n	n	y	y	n	n	n	n	n	y	n

Attack frequency varied between 1 to 30 times per month, attack duration from 5 to 720 min. The most frequent accompanying symptom "walking difficulties" was often described as "having to lie down" or "not being able to stand up". Physical activity ("sport") was the most common trigger factor.
D, Dizziness; V, Vertigo; n, no, y, yes.

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TABLE 3 Ocular-motor and instrument-based findings in the attack-free (interictal) interval in children and adolescents with episodic ataxia.

Ocular-motor findings

Nr.	EA	Strabismus	Nystagmus				Saccadic smooth pursuit		Optokinetic nystagmus	Fixation suppression
		-phoria	Provocation	Gaze holding	Down-/Up-beat	Rebound	Horizontal	Vertical		
1	1	Exo-	n	n	n	n	+++	+++	norm	norm
2	(1)	Eso-	n	y	n	n	+++	+++	norm	path
3	9	Eso-	y	y	D	y	+++	+++	path	path
4	2	Eso-	y	y	D	y	+++	+	path	path
5	2	Exo-	y	n	D	y	+++	+++	path	path
6	2	Exo-	y	y	U	n	+	+	path	norm
7	2	n	n	n	n	n	+	+	norm	norm
8	2	Eso-/Exo-	n	y	D	n	+	+++	path	path
9	2	n	n	n	U	n	+++	++	path	norm
10	2	n	n	n	n	n	norm	+	norm	norm

Instrument-based findings

Nr.	EA	Gait analysis	Caloric irrigation	VEMP's	AEP	Audio	Posturography	MRI
1	1	-	-	norm	-	-	norm	-
2	(1)	-	norm	norm	norm	norm	functional	norm
3	9	atactic	-	-	-	-	norm	norm
4	2	functional	-	-	-	-	norm	norm
5	2	atactic	norm	norm	norm	norm	functional	norm
6	2	-	norm	norm	-	norm	functional	norm
7	2	-	norm	norm	norm	norm	-	-
8	2	-	norm	-	norm	-	functional	norm
9	2	-	-	-	-	-	functional	-
10	2	-	-	norm	-	-	norm	norm

The most frequent findings were the presence of a nystagmus and a saccadic smooth pursuit. Except atactic and functional patterns in the gait analysis and posturography, no distinct pathological findings were recorded in the instrument-based examinations.
VEMPS, vestibular evoked myogenic potentials; AEP, acoustic evoked potentials; Audio, audiogram; MRI: magnetic resonance imaging; n, no; y, yes; U, up-beat; D, down-beat; +, gain 0.65–0.85; ++ = gain 0.45–0.65; + + +, gain < 0.45; norm, normal; path, pathological.

"paleness" differed significantly ($p = 0.0429$ and $p = 0.0212$ respectively) between groups, with the highest frequency observed in EA patients (30 and 50% respectively), while "headache" ($p < 0.0001$) and "photo-/phonophobia" ($p < 0.0001$) were most often observed in children/adolescents with VM (80% each). Furthermore, physical activity ("sport") as a trigger factor occurred more often in EA patients (60%, $p = <0.0001$). Provocation, gaze-holding, and down-beat nystagmus were more frequently observed in EA, but also occurred, in a milder form, in some patients with VM, but no patients with RVC. Similarly, an impaired smooth pursuit was observed in all EA patients, in 47% of VM patients, and in 7% of RVC patients, significantly differing between the groups ($p < 0.0001$). In all VM and RVC patients with an impaired smooth pursuit, the gain was only slightly reduced (gain between 0.65 and 0.85) in contrary to the EA patients (see above).

Discussion

EA syndromes

Episodic ataxia syndromes are rare genetic disorders, but as demonstrated here, in a specialized vertigo/dizziness clinic they might be present in about 5% of patients under the age of 18 years (see Figure 1). The most common EA syndrome was EA type 2 followed by EA type 1. Of the seven patients with EA type 2 included in the study, five had mutations that have not been described before (patients 5–9). Additionally, the mutation of the EA type 1 patient (patient 1) also constitutes a novel description (details presented in Table 1). According to criteria suggested by Jen 2008 (8) these new mutations were considered disease-causing, as all newly described mutations were heterozygous and caused a premature stop or altered amino acid residues. The high number of spontaneous mutations in

TABLE 4 Comparison of clinical and instrument-based findings between children and adolescents with episodic ataxia, vestibular migraine, and recurrent vertigo of childhood.

	Episodic Ataxia ($n = 10$)	Vestibular Migraine ($n = 15$)	Recurrent vertigo of childhood ($n = 15$)	*p*-value
Age at diagnosis [years; (min.; max.)]	11 (3.75; 15.8)	11.5 (5.5; 17)	7.0 (2,75; 10,6)	**<0.0001**
Years to diagnosis	3.7 ± 2.74 (0.3; 7.8)	1. ± 1.8 (0.3; 5.8)	1.2 ±0.8 (0.2; 3.6)	0.0017
Gender (f:m)	7:3	10:5	9:6	0.8637
Delayed motoric/cognitive development	4 (40%)	0 (0%)	0 (0%)	**0.0098**
Family history for EA	4 (40%)	0 (0%)	0 (0%)	0.0013
Family history for migraine	2 (20%)	10 (67%)	7 (47%)	0.0726
Attack characteristics				
Form of vertigo (dizziness: vertigo)	5:5	4:11	3:12	0.2271
Mean attack frequency [days/month; (min.; max.)]	9.3 ± 11.2 (1; 30)	19 ± 17.8 (1; 60)	12.6 ± 17.2 (0.5; 60)	0.3154
Mean attack duration [minutes; (min.; max.)]	118.5 ± 216.7 [10; 720]	184.3 ± 249.2 (2; 720)	34.1 ± 48.3 (1; 180)	0.0933
Accompanying symptoms				
Headache	3 (30%)	12 (80%)	0 (0%)	**<0.0001**
Speech disturbance	3 (30%)	1 (7%)	0 (0%)	**0.0429**
Limb ataxia	1 (10%)	0 (0%)	0 (0%)	0.2147
Walking difficulties	6 (60%)	6 (40%)	6 (40%)	0.5455
Photo-/Phonophobia	2 (20%)	12 (80%)	0 (0%)	**<0.0001**
Nausea/Vomiting	8 (80%)	9 (60%)	7 (47%)	0.2494
Double vision	2 (20%)	0 (0%)	1 (7%)	0.1752
Oscillopsia	4 (40%)	4 (27%)	2 (13%)	0.3149
Paleness	5 (50%)	2 (13%)	1 (7%)	**0.0212**
Falls	2 (20%)	2 (13%)	2 (13%)	0.8775
Trigger				
Sport	6 (60%)	0 (0%)	0 (0%)	**<0.0001**
Stress	3 (30%)	3 (20%)	0 (0%)	0.0951
Position change	0 (0%)	1 (7%)	0 (0%)	0.4254
Loud noise	0 (0%)	1 (7%)	0 (0%)	0.4252
Weather change	0 (0%)	2 (13%)	0 (0%)	0.1730
Clinical exam				
Finger nose test	0 (0%)	0 (0%)	0 (0%)	-
Finger chase test	2 (22%)	0 (0%)	0 (0%)	**0.0298**
Dysdiadochokinesis	2 (20%)	1 (7%)	0 (0%)	0.0728
Knee shin test	1 (12%)	0 (0%)	0 (0%)	0.1458
Romberg test	2 (20%)	0 (0%)	0 (0%)	**0.0425**
Ocular-motor findings				
Strabismus	7 (70%)	7 (47%)	8 (53%)	0.4349
Spontaneous nystagmus	0 (0%)	0 (0%)	0 (0%)	-
Provocation nystagmus	4 (40%)	2 (13%)	0 (0%)	**0.0226**
Gaze holding nystagmus	5 (50%)	4 (27%)	0 (0%)	**0.0120**
Downbeat nystagmus	4 (40%)	1 (7%)	0 (0%)	**0.0085**
Upbeat nystagmus	2 (20%)	2 (13%)	0 (0%)	0.2273
Rebound nystagmus	3 (30%)	0 (0%)	0 (0%)	**0.0077**
Smooth pursuit saccadic	10 (100%)	7 (47%)	1 (7%)	**<0.0001**
Optokinetic nystagmus path.	6 (60%)	0 (0%)	0 (0%)	**0.0017**
Fixation suppression path.	5 (50%)	1 (7%)	1 (7%)	**0.0076**
Ocular counter-roll	1 (11%)	1 (7%)	0 (0%)	0.4616

(Continued)

TABLE 4 (Continued)

	Episodic Ataxia ($n = 10$)	Vestibular Migraine ($n = 15$)	Recurrent vertigo of childhood ($n = 15$)	p-value
Instrument-based findings				
Video HIT path.	0 (0%)	0 (0%)	0 (0%)	-
Caloric irrigation path.	0 (0%)	0 (0%)	0 (0%)	-
AEP path.	0 (0%)	0 (0%)	0 (0%)	-
VEMPS path.	0 (0%)	0 (0%)	0 (0%)	-
Audio path.	0 (0%)	0 (0%)	0 (0%)	-
Posturography functional	5 (56%)	1 (14%)	7 (64%)	0.1070

Delayed motoric/cognitive development was considered when children did not achieve the gross motor developmental or cognitive (including language development and intellectual growth) milestones respectively. Statistically significant p-values (<0.05) are displayed in bold.

the present study supports the suggestion to consider EA also in children and adolescents with a negative family history.

The patient included here with a mutation in the FGF14 gene is to our knowledge the thirteenth case described with the clinical syndrome of episodic ataxia (7, 15, 16). FGF14 mutations are considered a rare cause of spinocerebellar ataxia type 27 (SCA 27) and show a broad phenotypic spectrum (17–20). The case presented here showed recurrent attacks of vertigo and dizziness lasting between a few minutes and 2 h, accompanied by severe walking difficulties partly leading to falls. Furthermore, the patient had a developmental delay (mental and motor) and psychiatric comorbidity. Further characteristics are presented in Tables 1–3. Overall, this case extends the phenotypic spectrum of EA related to a mutation in the FGF14 gene and further supports the previous suggestion to characterize such patients as EA type 9 (7).

A high genotype-phenotype variability has been shown especially in patients with EA type 2 and EA type 1 (6, 17, 21, 22). Furthermore, mutations in the most common genes associated with EA, namely in the CACNA1A gene (associated with EA type 2) and KCNA1 (associated with EA type 1) might lead to different clinical entities without episodes of vertigo/ataxia, such as epilepsy, paroxysmal dyskinesia, or hemiplegic migraine (4, 6, 21, 23). Also, in a considerable number of patients with a clinical syndrome of EA, no disease-causing mutation might be found (4, 24–26).

EA phenotype, instrument-based findings, and treatment

Since a broad clinical spectrum has been described in patients with different types of EA, a precise clinical evaluation of patients suspected of suffering from EA is of the utmost importance in order to reach a correct diagnosis and initiate appropriate therapeutic measures including medical treatment option with acetazolamide or 4-aminopyridin.

In the present study, all the EA children/adolescents included suffered from vertigo or dizziness attacks lasting between 5 min and 12 h, in the mean 2 ± 3.6 h The lowest attack frequency was one attack per month, the highest was daily attacks. All children/adolescents had accompanying symptoms, such as paleness, speech disturbances, and walking difficulties. Walking difficulties were often described as the "inability to walk straight" or children/adolescents "lying down and not being able to stand up". Many children/adolescents reported trigger factors, most frequently physical exercise ("sports"), but two children did not report any triggers. Physical exercise leading to an attack most commonly was described while participating in school sports, but also in lighter activities such as climbing a few stairs. These findings seem to constitute the core symptoms of EA children/adolescents. This is also in line with findings from previous studies and case descriptions of patients with EA (4, 6, 7, 22, 26–35).

In the interictal interval only three children/adolescents had clinical signs of ataxia, two with EA type 2 and the above-described adolescent with EA type 9. As expected, in the latter, ataxia was much more pronounced (see Table 1), since patients with an FGF14 mutation show an overlap between episodic and chronic progressive ataxia (7). No pathological findings were found in any child/adolescent in the instrument-based findings such as vHIT, caloric irrigation, AEP's, VEMPs, or the audiogram (see Table 3).

To our knowledge, this is the first prospective study to evaluate the ocular-motor function of children/adolescents with EA in detail. One previous study retrospectively reported on neuro-ophthalmological findings in chronic ataxia, which included 7 patients with EA and described the presence of nystagmus in these patients, however without further differentiation (36). A second study retrospectively analyzed eye movement disorders in children with CACNA1A mutations, most frequently describing paroxysmal tonic upgaze, saccade dysmetria, and strabismus (37). Strabismus was also present in most children/adolescents (7/10, see Table 3) of our cohort.

The prevalence of strabismus among children/adolescents varies between different countries in the world between <1% and 8.6% (38), thus suggesting a much higher prevalence among children/adolescents with EA. Paroxysmal tonic upgaze and saccade dysmetria were not present in our cohort. The most common finding in all patients in the present study was a pathological smooth pursuit, either horizontally, vertically, or in both directions. Furthermore, most children/adolescents showed a nystagmus in the interictal interval, either a vertical spontaneous nystagmus (4/10 down-beat, 2/10 up-beat) and/or a gaze-holding nystagmus (5/10, see Table 3). The optokinetic nystagmus was disrupted in 6/10 children/adolescents and a pathological fixation suppression was found in half of the children/adolescents. These findings are in line with a study describing ocular-motor findings in nearly only adults with EA type 2 (39, 40), so it can be assumed that ocular-motor disturbances are also distinct clinical findings in children and adolescents with EA.

Treatment with acetazolamide or 4-aminopyridine improved attack frequency and duration in some, but not all patients, which is in line with previous findings (8, 24, 28). Both treatments are not approved for use in patients with EA, so it is an individual treatment that children/adolescents and parents must be made aware of. Additionally behavioral recommendations (e.g., reducing physical activity and stress) should not be underestimated, since they might reduce EA attacks.

Distinction of EA among dizzy patients

The most common differential diagnoses of EA are RVC and more importantly VM. These diseases can show similar vertigo/dizziness attacks and accompanying symptoms such as headaches (see Table 4), so that a distinct differentiation in order to reach the correct diagnosis and subsequently initiate the correct treatment is merited.

Attack frequency was similar in all three patient groups, while attack duration was shorter in RVC with a maximum of 3 h compared to a maximum of 12 h in EA and VM patients. The most common accompanying symptoms of VM attacks were headache, photo-/phonophobia, and nausea/vomiting, which was expected in accordance with the diagnostic criteria (13). EA patients in our cohort showed typical clinical attack features (i.e. sport or stress induced ataxia or vertigo, accompanied by walking-difficulties, oscillopsia, and paleness) as previously described (9, 28). The two included EA type 1 patients had no evidence of myokymia which is often reported in EA type 1 (41, 42). As EA type 9 overlaps with SCA 27, this patient had a high SARA score, while the SARA score was slightly increased in only two EA type 2 patients and none of the EA type 1 patients. Furthermore, RVC patients more frequently showed a functional sway pattern in posturography, which may indicate a higher risk of secondary psychosomatic development, similarly to VM and migraine-related disorders (43, 44).

Ocular-motor findings in children with VM have to our knowledge not been reported previously. However, the most common finding of a slight saccadic smooth pursuit in the present VM cohort is similar to findings in adult VM populations (45, 46). In contrast, ocular-motor deficits were rarely noted in RVC (see Table 4). All EA patients showed considerable ocular-motor deficits compared to only slight deficits in VM. Especially EA type 1 is typically reported to not show any interictal nystagmus (41, 42); however, ocular-motor deficits have to our knowledge not been examined in detail before. In our study we find a clearly saccadic smooth pursuit in both EA type 1 patients, as well as a pathological fixation suppression in one of them (see Table 3). The present findings suggest, that distinct interictal ocular-motor findings are present in the most frequent EA types, nevertheless the number of EA type 1 patients in the present study is low and further evaluation of a larger EA type 1 cohort is needed.

In summary, the findings of the present study suggest that EA patients more often report speech disturbances and paleness as accompanying symptoms during the attacks, while VM patients more often report headaches and photo-/phonophobia. Regarding trigger factors, only patients with EA reported physical activity (sport) as an attack trigger. Pathological findings in the clinical evaluation were almost exclusively found in EA patients. The most striking differences between these groups though are the ocular-motor findings, especially various types of spontaneous nystagmus and/or a pathological smooth pursuit in patients with EA. Nevertheless, ocular-motor disturbances, such as gaze-holding nystagmus and a pathological smooth pursuit might also be found in some patients with VM and only rarely in RVC, but overall to a much lesser extent and scarcely with more than one ocular-motor abnormality.

Proposed diagnostic criteria for EA in children/adolescents

Besides the recommendations by Jen 2004 (4), diagnostic criteria for EA have not been defined. Defining criteria for EA syndromes is especially important, since genetic findings in patients with EA might be negative or inconclusive (4, 24–26). In Figure 2, we propose diagnostic criteria for identifying children/adolescents with "probable EA" according to the findings of the present study, considering a broad literature review (4–12, 15, 16, 22, 24–30, 32–35, 39–42, 47) and our expert opinions. The diagnosis of a "definite EA" should additionally include a pathological genetic finding with a "disease-causing mutation" as characterized by Jen 2008 (8).

The diagnostic criteria include data from medical history such as details on the duration of vertigo attacks and

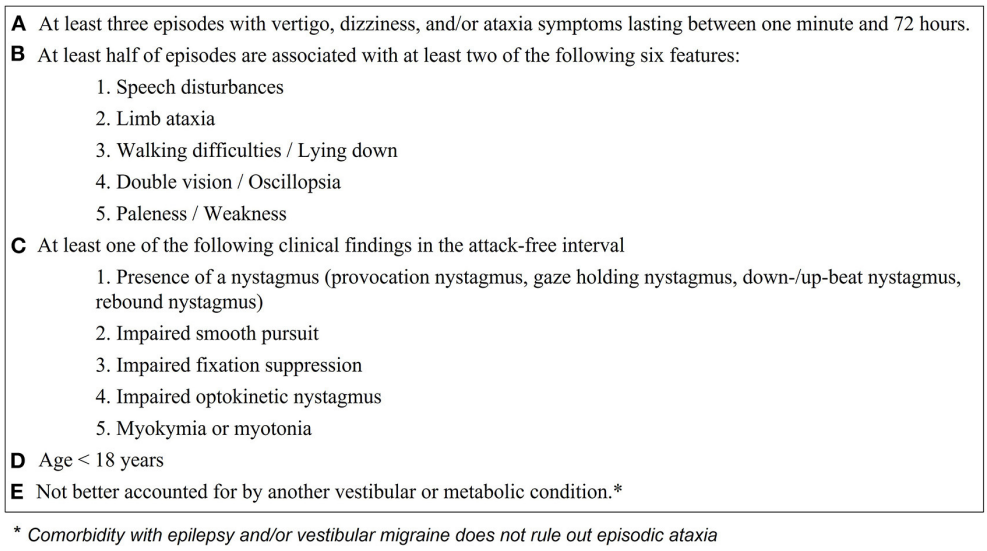

FIGURE 2
Proposed clinical and ocular-motor criteria for diagnosing children and adolescents with episodic ataxia. With the fulfillment of all criteria **(A–E)** the diagnosis of "probable episodic ataxia" can be made and genetic testing should be initiated. A positive genetic finding confirms the diagnosis of episodic ataxia.

accompanying symptoms (see Figure 2 points A. and B.) as well as ocular-motor findings (see Figure 2, point C). Because ocular-motor findings in EA in some cases might be subtle and only distinguishable by experienced physicians (mostly early in the disease course), we suggest performing a standardized orthoptic examination conducted by a trained orthoptician to evaluate the ocular-motor system. Except gait analysis, which may show an atactic gait in the attack free interval of EA patients, all instrument-based examinations (VEMP's, AEP's, audiometry, posturography, MRI) were unremarkable in EA children, but are necessary to rule out other vestibular conditions (see Figure 2, point E.). We therefore suggest a basic vestibulo-cochlear work-up in all children suspected to suffer from EA comprising of a caloric irrigation, one examination of the auditory function (either AEP's or audiometry), and an MRI. Latter is suggested, since anatomical variants of the vestibular/cochlear organ and central pathologies are not uncommon in childhood (see Figure 1).

When applying the proposed criteria to the present findings, all patients could be identified. Furthermore, the diagnostic criteria were applied on patient descriptions from previous studies of EA including types 1–9 (see Supplementary Table 1). Only studies including a clinical characterization of the attacks as well as interictal findings, at least regarding the presence of nystagmus and/or myokymia/myotonia, were used for analysis. Sensitivity was calculated as the number of correctly identified EA patients (173; including the children of the present study) divided by the number of all EA patients included (223) and reached 78% (Supplementary Table 1). The most frequent reason to not fulfill the proposed diagnostic criteria was a missing interictal clinical finding (see Figure 2, point C.). This might be due to the lack of reported broad ocular-motor findings such as smooth pursuit, optokinetic nystagmus, and fixation suppression, which were only reported in one study (33). Therefore, and according to the present findings, where all EA patients showed considerable ocular-motor deficits, the above reported sensitivity might be underestimated.

Specificity could only be calculated according to the control group defined in the present study (including children with RVC and VM) and reached 90% (3 children with VM fulfilled the here suggested diagnostic criteria). These three children suffered from headache attacks, which might segregate EA from VM. However, we decided not to use "headache attacks" as an exclusion criterium for the suggested diagnostic criteria, since headaches (irrespective of the fulfillment of the diagnostic criteria of VM or other ICHD diagnoses) are commonly present in EA children/adolescents (4, 22, 28). Overall, this suggests a good sensitivity and specificity for the suggested criteria for children with EA; nevertheless the applicability and accuracy must be further evaluated in larger cohorts of precisely characterized children with vertigo, dizziness, or ataxia attacks.

Conclusion

EA is a rare genetic disorder, but might be present in a considerable amount of children and adolescents presenting with episodic vertigo and/or dizziness. Six new genetic

mutations are presented, five for EA type 2 and one for EA type 1, so that a broad genetic testing (e.g., next generation sequencing) in suspected EA patients is recommended. Clinical and instrument-based findings that help to differentiate EA from VM and RVC include attacks triggered by physical activity and accompanied by speech disturbances and paleness. Furthermore, a pathological smooth pursuit and the presence of a nystagmus in the interictal interval seem to be indicative for EA, especially type 1, 2, and 9. In accordance with the findings of the present study, we propose diagnostic criteria for EA, which should be further evaluated as to their sensitivity and specificity for detecting EA in future research.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of the LMU (414-15). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

FF: patient recruitment, data acquisition, statistical analysis, interpretation of data, and drafting the manuscript. LS and KD: patient recruitment and data acquisition. RS: statistical analysis and interpretation of data. DH: patient recruitment, data acquisition, interpretation of data, and drafting the manuscript. All authors approved the final version of the manuscript.

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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.2022.1016856/full#supplementary-material

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EDITED BY
Jose Antonio Lopez-Escamez,
Universidad de Granada, Spain

REVIEWED BY
Julia Dlugaiczyk,
University Hospital Zürich, Switzerland
Alfarghal Mohamad,
National Guard Hospital, Saudi Arabia

*CORRESPONDENCE
Maoli Duan
maoli.duan@ki.se
Jianyong Chen
chenjianyong@xinhuamed.com.cn
Jun Yang
yangjun@xinhuamed.com.cn

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Evaluating children with vestibular migraine through vestibular test battery: A cross-sectional investigation

Fan Zhang[1], Jiali Shen[1], Qi Zhu[2], Lu Wang[1], Xiaobao Ma[1], Baihui He[1], Yang Yang[1], Wei Wang[1], Xiangping Chen[1], Qing Zhang[1], Yulian Jin[1], Maoli Duan[3]*, Jianyong Chen[1]* and Jun Yang[1]*

[1]Department of Otorhinolaryngology-Head and Neck Surgery, School of Medicine, Xinhua Hospital, Shanghai Jiaotong University, Shanghai, China, [2]Department of Otorhinolaryngology-Head and Neck Surgery, Yuyao People's Hospital, Yuyao, China, [3]Division of Ear, Nose and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

Objective: The present study aimed to investigate the status of vestibular function in children with vestibular migraine of childhood (VMC) reflected by vestibular function test battery and explore the pathophysiological implication of these instrument-based findings.

Methods: The clinical data of 22 children (mean age 10.7 ± 2.9 years) with VMC who met the diagnostic criteria of the Barany Society were collected from September 2021 to March 2022. A vestibular function test battery on these children included a caloric test, video head impulse test (vHIT), cervical vestibular-evoked myogenic potential (cVEMP), and ocular vestibular-evoked myogenic potential (oVEMP); these parameters were triggered by air-conducted sound (ACS) and galvanic vestibular stimulation (GVS). The subjects were further divided into two groups: <3 months and >3 months according to the disease duration from symptom onset. The functional abnormalities and their characteristics reflected by the vestibular test battery, as well as the outcomes in children with or without aura, were analyzed.

Results: (1) The abnormal rate of the caloric test was 15.8% and that of vHIT was 0%. The response rates of ACS-cVEMP and ACS-oVEMP were 100% and 90.5%, respectively. The response rates of GVS-cVEMP and GVS-oVEMP were 100% and 88.9%, respectively. (2) No statistical difference was observed in the abnormal rate of the caloric test ($P = 0.55$) and the response rate of ACS-oVEMP ($P = 0.21$) between the two groups, irrespective of the course duration. (3) No statistical difference was detected in the abnormal rate of the caloric test ($P = 0.53$) and the response rate of ACS-oVEMP ($P = 1.00$) in children with or without aura.

Conclusion: Vestibular function status comprehensively reported by the vestibular test battery did not show an aggravation with the disease duration in children with VMC. Also, it was not affected by the existence of aura in children with VMC. The high abnormal rates of the caloric test and oVEMPs (ACS-oVEMP and GVS-oVEMP) suggested that the lateral semicircular canal (low-frequency

function component), the utricle, and the superior vestibular conduction pathway might be involved in VMC.

KEYWORDS

vestibular migraine of childhood, vestibular end organs, vestibular test battery, caloric test, video head impulse test, vestibular evoked myogenic potential, pathogenesis

Introduction

The International Headache Society (IHS) and the Barany Society revised and published the diagnosis of vestibular migraine (VM) and probable vestibular migraine (pVM) in 2012 (1). Benign paroxysmal vertigo of childhood and VM are the most frequent pathologies leading to vertigo and dizziness during childhood (2). Previous studies have focused on the epidemiological causes of dizziness in children or initiation of the symptoms and the physical and laboratory examination and treatment in children with vestibular migraine. Studies showed that vestibular testing might have abnormal results in pediatric patients but with high variability (3–7).

Although VM is considered to be a central vestibular disorder (8, 9), peripheral vestibular end organs could also be involved (10). However, the functional abnormalities and the characteristics of the vestibular end organs in this etiological entity are not well-documented.

In 2021, the definition of vestibular migraine of childhood (VMC) and probable VMC (pVMC) was proposed based on the frequency of vestibular symptoms and the clinical signs of migraine. The diagnostic criteria of VMC are as follows (2):

A. At least five episodes with vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 h.
B. Current status or history of migraine with or without aura.
C. About 50% of the episodes are associated with at least one of the following three migraine features:

    1. Headache with at least two of the following four characteristics:

        a) One-sided location.
        b) Pulsating quality.
        c) Moderate or severe pain intensity.
        d) Aggravation by routine physical activity.

    2. Photophobia and phonophobia
    3. Visual aura.

D. Age <18 years
E. Not better accounted for by another headache disorder, vestibular disorder, or other condition.

Moreover, the applications of galvanic vestibular stimulation-vestibular-evoked myogenic potentials (GVS-VEMPs) in children are being explored. This could help in locating the lesions combined with air-conducted sound (ACS)-VEMPs; however, there are no reports on the GVS-VEMP results in children with VM.

In this study, we conducted the vestibular test battery to explore the putative vestibular pathway involved in patients with VMC according to the new diagnostic criteria.

Patients and methods

The present study was approved by the Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University, School of Medicine (No. XHYY-2021-039), and informed consent was obtained from the children's guardians. The clinical data of 22 children with dVMC who visited the Department of Otorhinolaryngology-Head and Neck Surgery of Xinhua Hospital, Shanghai Jiao Tong University, School of Medicine, were collected from September 2021 to March 2022 and analyzed retrospectively.

The inclusion criteria for VMC were as follows: (1) children who met the diagnostic criteria of the Barany Society in 2021 (2); (2) children who had completed the vestibular test battery.

The exclusion criteria were as follows: (1) external or middle ear diseases; (2) other definite vestibular diseases; (3) structural abnormalities on brain magnetic resonance imaging (MRI) and/or electroencephalogram (EEG) findings indicative of vertiginous epilepsy; (4) vertigo-related diseases of other systems, such as neurological and psychiatric.

The parents were asked to provide their medical history in detail. All patients completed pure-tone audiometry, cranial MRI, electroencephalogram, and vestibular test battery including caloric test, video head impulse test (vHIT), cervical VEMP (cVEMP), and ocular VEMP (oVEMP), triggered by ACS and GVS, respectively.

In terms of technical feasibility, the cVEMP test can be conducted in newborns, whereas oVEMP is not performed until the age of 3 years (11, 12). vHIT can be performed in infants >3 months old, while the caloric test is routinely conducted in children >6 or 7 years old due to less impact of fear and focus at that age (13, 14). Therefore, all tests in the vestibular test battery are suitable for children in the age range in this study.

Audiometry

Pure-tone audiometry was conducted in a soundproof room using an audiometer (Type Astera, Madsen, Denmark). The pure-tone average (PTA) is the average of the 0.5, 1, 2, and 4 kHz air-conduction thresholds. PTA <20 dB HL is considered normal (15). The air-bone gap (ABG) is calculated as the air-conduction threshold minus the bone-conduction threshold at the same pure-tone frequency (16).

Vestibular testing

Caloric test

The patients lay supine in a dark room and looked straight ahead with their heads elevated 30° to keep the horizontal semicircular canal vertical to the ground. Any spontaneous nystagmus was recorded by video-nystagmography (Interacoustics). Cold (24°C) and hot (50°C) air irrigations were completed in both external auditory canals, both for 60 s sequentially (13, 17). Then, the nystagmus was recorded, and the percentage of canal paresis (CP%) and dominant preponderance (DP%) was calculated using Jongkees' formula. The caloric test was defined as abnormal if CP was >25% and/or bithermal peak slow phase velocity (SPV) on each side was <6°/s or DP was >30% (5, 18).

Video head impulse test

A video head impulse test was performed using a video head pulse instrument (Interacoustics, EyeSeeCam, Denmark). The patients were seated in a chair, looked straight ahead at a fixed visual target 1 m in front of their eyes, avoided blinking, and relaxed their neck muscles. An experienced technician delivered at least 20 high-acceleration, sudden, and unpredictable head impulses per side (10–20°, duration 150–200 ms, peak velocity of >150°/s for horizontal head impulses, and >100°/s for vertical head impulses) (13, 19). An instantaneous vestibulo-ocular reflex (VOR) gain was automatically calculated using the equipment software, which is eye velocity (°/s)/head velocity (°/s). Abnormal vHIT was defined when the instantaneous VOR gain at 60 ms for the horizontal canal was <0.8 or the regression VOR gain for vertical canals was <0.7 or showed corrective saccades in each semicircular canal (20).

ACS-cVEMP

ACS-VEMP test was examined using Neuropack MEB-9404C (NIHON KOHDEN, Japan). Short pure tones (500 Hz, 105 dB nHL intensity, rise/fall time 1 ms, plateau period 2 ms, superposition 50 times, window opening time 0–60 ms, stimulation rate 5.1 times/s, impedance <10 kΩ) were presented monaurally through a calibrated headphone TDH-39. The recording electrodes were placed on the upper third of the bilateral sternocleidomastoid muscles (SCMs). The reference electrode was placed between the clavicle joints. Then, the ground electrode was placed in the middle of the forehead. The patients were in a supine position and asked to raise their heads 30° upon the horizon to keep the SCM tense from the start of a single stimulus sound until the end. The electromyographic monitoring limited the variability and guaranteed bilateral muscle tones in case the children could not cooperate during the test.

For better observation of the waveforms, each grid represented 5 ms on the horizontal axis and 100 or 200 μV on the vertical axis. A positive wave of 13 ms after stimulation was labeled as p1, and a negative wave of 23 ms was labeled as an n1 wave. cVEMP was defined if reproducible p1 and n1 waveforms could be elicited, and no response was defined as the absence of meaningful p1 and n1 waveforms. Latency of p1 and n1 waves and amplitudes of p1-n1 were obtained, defined as the vertical distance between the highest point of the p1 wave and the lowest point of the n1 wave. The asymmetry ratio (AR) was calculated using the large p1-n1 amplitude (AL) and the small p1-n1 amplitude (AS) and the following formula: AR (%) = (AL-AS)/(AL+AS)×100%. A difference of >40% between two ears is considered significant, while no response or AR (%) of >40% was considered abnormal in this study (13, 21).

ACS-oVEMP

The parameter settings of ACS-oVEMPs were similar to those ACS-cVEMP, while electromyographic monitoring was not required. The recording electrode was placed 1 cm below the middle of the contralateral eyelid, the reference electrode was placed 2 cm below the recording electrode, and the ground electrode was placed in the middle of the forehead. The patients were asked to maintain eye gaze upward for 25–30° after hearing a single acoustic stimulus and minimize blinking to maintain tension in the inferior oblique muscle until the stimulation stops. As for the waveforms, each grid represented 5 ms on the horizontal axis and 5 or 10 μV on the vertical axis. A negative wave occurring about 10 ms after stimulation was labeled as an n1 wave, and a positive wave at about 16 ms was labeled as a p1 wave. Then, oVEMP was confirmed to be induced if reproducible n1 and p1 waveforms could be elicited. No response or AR (%) >40% was considered abnormal (13, 21).

GVS-cVEMP

GVS-cVEMP was examined using an electrophysiological recorder (Neuropack MEB-9404C, NIHON KOHDEN, Japan). The recording electrodes were placed at the upper third of the

bilateral SCMs, the reference electrode was placed between the clavicle joints, and the ground electrode was at the nasal root. The cathode of the direct current stimulation was placed at the mastoid process, and the anode was placed at the midpoint of the forehead hairline. The initial stimulation (3.0 mA, stimulation rate 5 Hz, band-pass filter 20–2,000 Hz, superposition 50 times, and time window 50 ms) was direct current, and the waveform was recorded using an electromyographic amplifier. The waveform under muscle contraction was subtracted from the waveform under muscle relaxation to eliminate the artifacts of mechanical waves (22–24). If the reproducible waveform could not be elicited at 3.0 mA, the stimulation could rise according to the patient's tolerance, typically at ≤5.0 mA. Then, the latency of p1 and n1 waves, amplitudes of p1-n1, and AR% were recorded.

GVS-oVEMP

The recording electrode was placed 0.5–1.0 cm below the eyelid, the reference electrode was placed 2.0 cm below the recording electrode, and the ground electrode was placed at the nasal root. The cathode of the direct current stimulation was placed at the mastoid process and the anode at the midpoint of the forehead hairline. The waveform obtained from eye gaze upward for 25–30° was subtracted from the waveform obtained from eye gaze downward to eliminate mechanical wave artifacts (22, 23).

Data analysis

All data were analyzed using SPSS v.22 statistical software. The categorical variables were expressed as a ratio, while the continuous variables were expressed as mean ± standard deviation. The abnormal rates and response rates of vestibular testing were compared by Fisher's exact test. $P < 0.05$ was considered statistically different.

Results

Characteristics

The clinical and demographical data of the 22 children included in this study are listed in Table 1. The average age of the cohort was 10.7 ± 2.9 (range: 6–17) years. A subset of the children with VMC presented migraine features in the episodes: aura occurred in 5, headache aggravated by routine physical activity or stress in 3, photophobia and/or phonophobia in 8, motion sickness in 7, and a family history of migraine in 7. All had auditory thresholds within normal range, with PTA <20 dBHL and no ABG. EEG did not find any spikes and sharp waves or other epileptiform discharges, and two patients showed mild abnormalities. Brain MRIs were normal.

Rates of abnormal vestibular tests

Not all children completed the entire test battery but most of the tests in the protocol were completed. The results showed that the abnormal rates of the caloric test and vHIT were 15.8% (3/19) and 0% (0/22), respectively. Among them, one patient showed CP >25% (Figure 1), two showed DP >30%, and three had spontaneous nystagmus with SPV = 1, 1, and 2°/s, respectively (<3°/s). The typical normal caloric test and vHIT testing are shown in Figures 2 and 3.

The response rates of ACS-cVEMP and ACS-oVEMP were 100% (20/20) and 90.5% (19/21), respectively. The response rates of GVS-cVEMP and GVS-oVEMP were 100% (18/18) and 88.9% (16/18), respectively. No statistically significant difference was observed between the two groups ($P = 0.48$, 0.49). The response rates of ACS-cVEMP, ACS-oVEMP, GVS-cVEMP, and GVS-oVEMP are listed in Tables 2 and 3. The typical normal ACS-cVEMP and GVS-cVEMP are shown in Figures 4 and 5.

In one patient, ACS-oVEMP was not elicited bilaterally, and GVS-oVEMP was not elicited on the left side. In another patient, ACS-oVEMP was not elicited on the left side (Figure 6), but GVS-oVEMP was elicited bilaterally. Another patient showed bilaterally elicited ACS-oVEMP, but GVS-oVEMP was not elicited on the left at 3.0 mA (Figure 7).

In addition, one child showed AR > 40% in ACS-oVEMP, and thus, the abnormal rates of ACS-cVEMP and ACS-oVEMP were 0% and 14.3% (3/21), respectively.

Course duration, aura, and vestibular tests

The mean duration of the disease was 667 ± 1,061 days, ranging from 6 days to 10 years. The children were divided into <3 months and >3-month groups according to the disease duration from symptom onset. The former consisted of 10 patients and the mean disease duration was 27.4 ± 16.1 days, while the latter had 12 patients and the mean duration was 1,146 ± 1,209 days. The comparison of the abnormal or the response rates of vestibular test battery between the two groups, irrespective of the course duration, is shown in Table 4. No statistical difference was found in the abnormal rate of the caloric test ($P = 0.55$) and the response rate of ACS-oVEMP ($P = 0.21$) and GVS-oVEMP ($P = 1.00$) between the two groups.

The vestibular test battery results in children with aura ($n = 5$) were normal, and the comparison with children with no aura is shown in Table 5. No statistical difference was found in the abnormal rate of the caloric test ($P = 0.53$) and the response

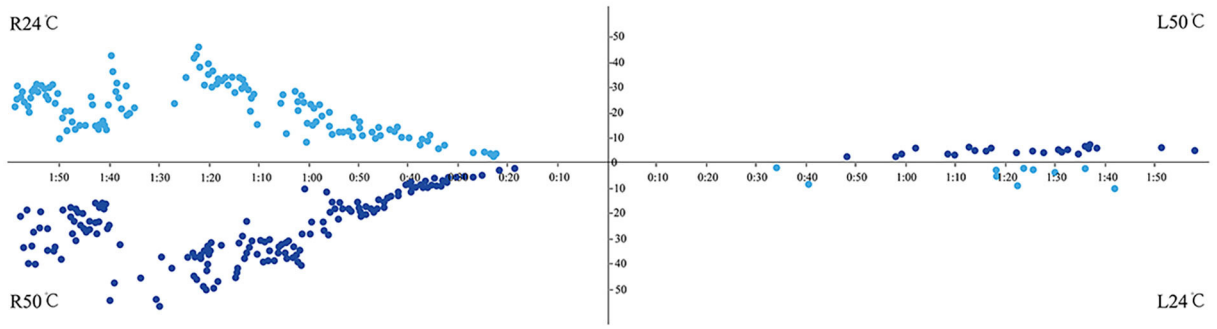

FIGURE 1
Abnormal caloric test showed attenuation on the left side.

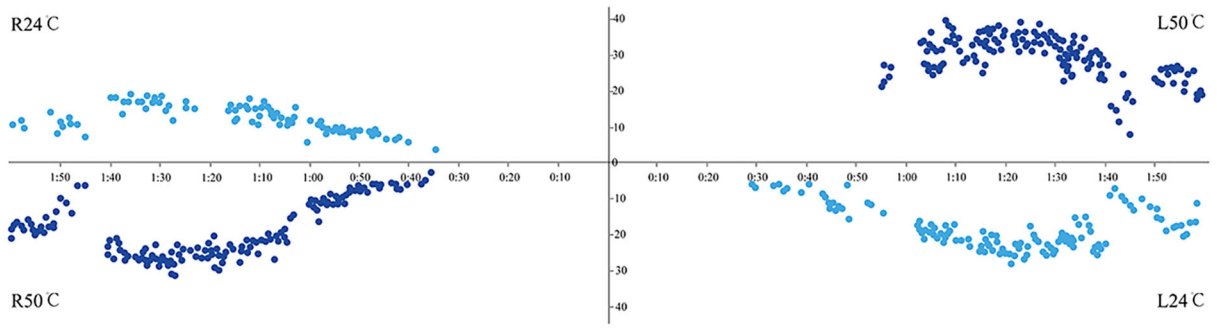

FIGURE 2
Normal caloric test showed bilateral symmetry and no absolute caloric hypofunction.

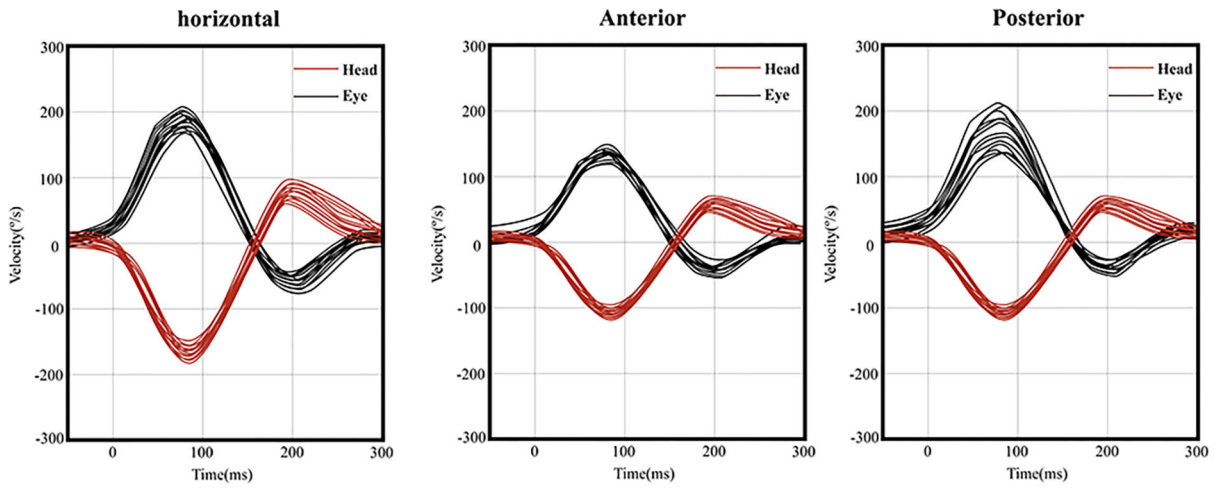

FIGURE 3
Normal vHIT on the right side of one patient. **(left)** Instantaneous VOR gain at 60 ms for the horizontal canal was 1.02 and showed no corrective saccades. **(middle)** Regression VOR gain for the anterior canal was 1.06 and showed no corrective saccades. **(right)** Regression VOR gain for the posterior canal was 1.45 and showed no corrective saccades.

rate of ACS-oVEMP ($P = 1.00$) and GVS-oVEMP ($P = 1.00$) between the two groups.

Discussion

The prevalence of vestibular disorders in the pediatric population is 0.7–15% (7, 25, 26). Migraine-related vertigo is the most common diagnosis in 7–12-year-old children (7). The mean age of the patients in our study was 10.7 ± 2.9 years, which was similar to the previous study. In a study of child migraine sufferers with vestibular symptoms, many children reported "the home is moving" or "the picture is moving" already at 3–4 years of age (10). We also reported vestibular symptoms at an early age in children, with a duration of 667 ± 1,061 days.

The putative pathophysiological mechanism of VM

Currently, the pathophysiological mechanism of VM is unclear. Nonetheless, many similarities have been detected in the mechanisms underlying VM and migraine; animal experiments have demonstrated that the brain stem is involved in the pathophysiological mechanism of migraine (10). The persistent brain stem activation after injecting sumatriptan supports the explanation of an imbalance in the activity between brain stem nuclei regulating antinociception and vascular control in migraine (27). Another hypothesis is that the triggering of the trigeminal-vestibulocochlear reflex increases the blood flow in the inner ear, releases active substances, and extravasates plasma protein, which could produce neurogenic inflammation to sensitize the first/second/third-order trigeminovascular neurons causing allodynia, followed by the manifestation of the VM symptoms (28).

TABLE 1 Characteristics of patients with VMC.

Characteristics	$N = 22$
Age (years)	10.7 ± 2.9
Sex	
Male	14 (63.6%)
Female	8 (36.4%)
Aura	5 (22.7%)
Headache aggravated by daily physical activity or stress	3 (13.6%)
Photophobia and/or phonophobia	8 (36.4%)
Motion sickness	7 (31.8%)
Family history	7 (31.8%)

VEMPs and the underlying pathway

Marcelli et al. (10) speculated that both central vestibular and peripheral pathways participate in the etiopathology in children with migraine without the involvement of the auditory pathway. Although the diagnosis of dizziness in children like VMC mainly depends on their medical history, the results of the vestibular test battery provide information about various underlying vestibular pathways. These tests could help in the differential diagnosis of dizziness in children (4, 6), although many studies presented almost normal results. For example, abnormal vestibular test results suggested a vestibular disorder rather than psychological problems, developmental disorders, torticollis, and ataxia (13).

According to the conduction path, ACS-cVEMP could be used to assess the pathway including the saccular and the inferior vestibular nerve; ACS-oVEMP could be used to assess the pathway including the utricle and the superior vestibular nerve (13). Some studies reported reduced amplitude or delayed latency of VEMP responses, while others found asymmetric ACS-VEMP responses with normal latency and amplitude (29). Similarly, O'Reilly et al. (3) and Brodsky et al. (4) reported

TABLE 2 Response rates of ACS-cVEMP and ACS-oVEMP.

ACS-cVEMP		Left		ACS-oVEMP		Left	
		Elicited	Not elicited			Elicited	Not elicited
Right	Elicited	20	0	Right	Elicited	19	1
	Not elicited	0	0		Not elicited	0	1

TABLE 3 Response rates of GVS-cVEMP and GVS-oVEMP.

GVS-cVEMP		Left		GVS-oVEMP		Left	
		Elicited	Not elicited			Elicited	Not elicited
Right	Elicited	18	0	Right	Elicited	16	2
	Not elicited	0	0		Not elicited	0	0

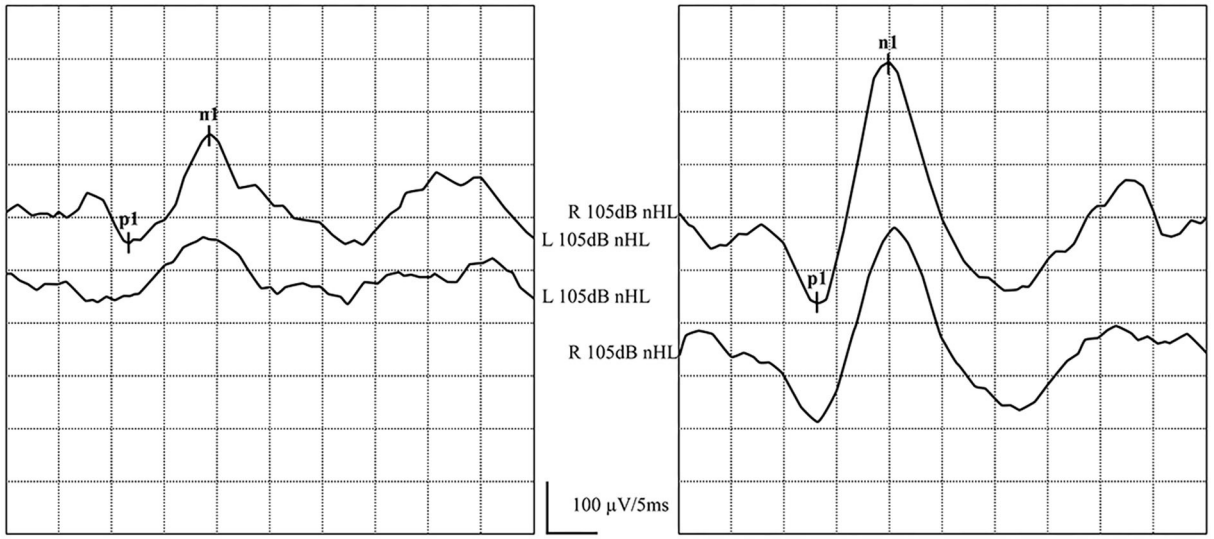

FIGURE 4
Normal ACS-cVEMP waveforms: Elicited bilaterally and AR = 38%. **(left)** ACS-cVEMP waveforms were elicited on the left side. **(right)** ACS-cVEMP waveforms were elicited on the right side.

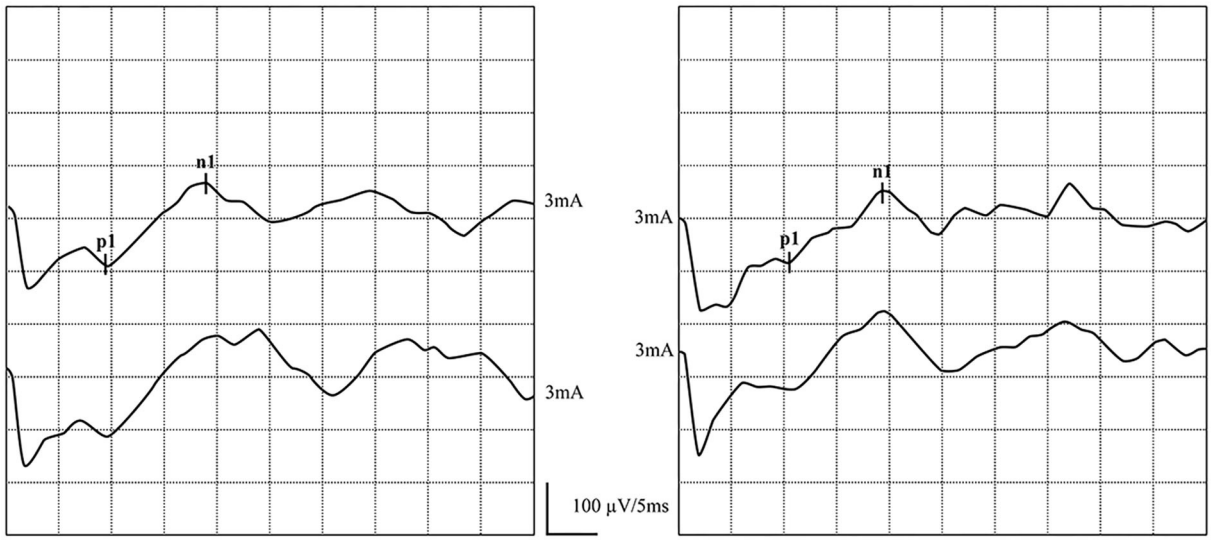

FIGURE 5
Normal GVS-cVEMP waveforms: Elicited bilaterally. **(left)** GVS-cVEMP waveforms were elicited on the left side. **(right)** GVS-cVEMP waveforms were elicited on the right side.

normal cVEMP results in all 25 and 16 pediatric patients with VM, respectively, while Langhagen et al. (5) demonstrated abnormal cVEMP results in 33% of children diagnosed with VM. Notably, oVEMP testing has rarely been reported previously because it is challenging to implement in the evaluation of patients with VMC. In the present study, the response rates of ACS-cVEMP and ACS-oVEMP were 100% (20/20) and 90.5% (19/21), respectively. The normal cVEMP results indicated that the pathway from the saccule, inferior vestibular nerve, vestibular nucleus, accessory nucleus, and accessory nerve to sternocleidomastoid muscle was intact. The higher abnormal rate of oVEMPs suggested that the utricle and the superior vestibular conduction pathways might be involved and impaired in VMC.

Opposite to ACS, GVS directly stimulates the vestibular afferent nerve. Compared to ACS-cVEMP, GVS-cVEMP

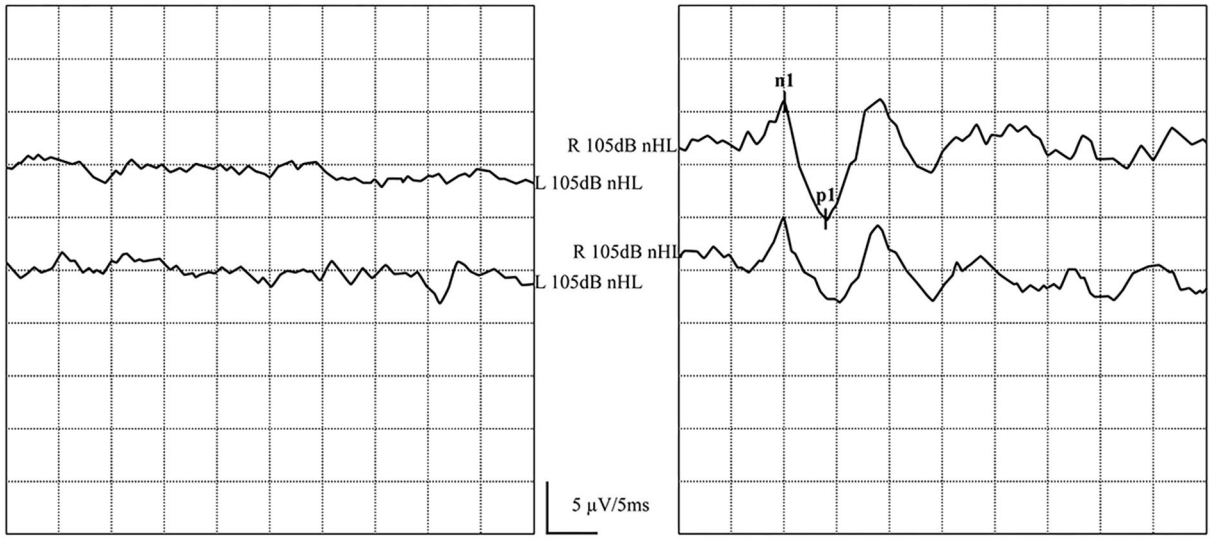

FIGURE 6
Normal and abnormal ACS-oVEMP waveforms: Not elicited on the left side and elicited on the right side. **(left)** Abnormal ACS-oVEMP waveforms: Not elicited on the left side. **(right)** Normal ACS-oVEMP waveforms: Elicited on the right side.

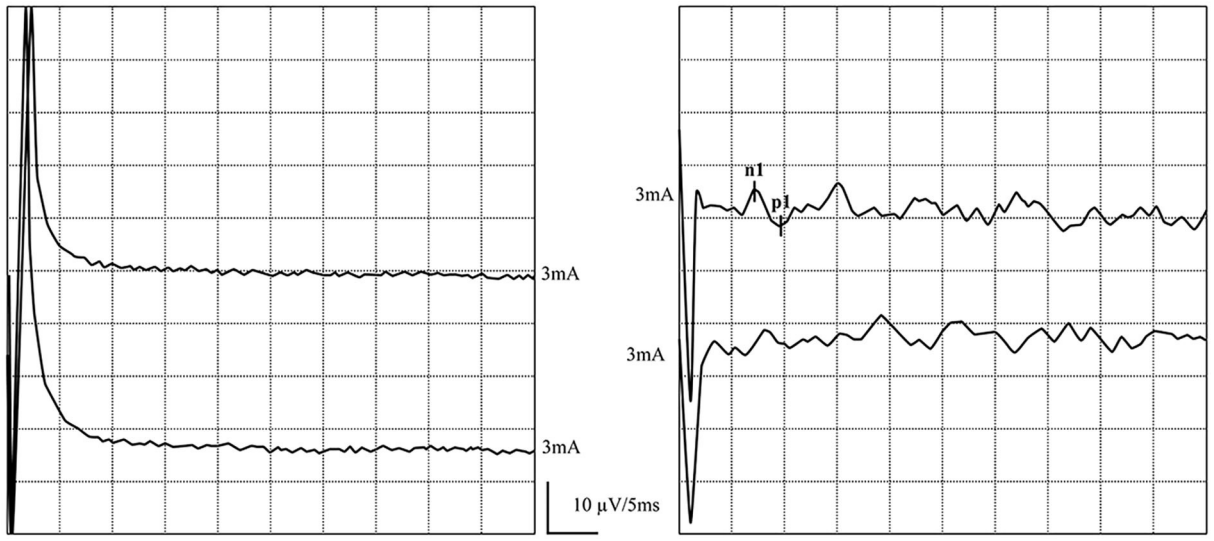

FIGURE 7
Normal and abnormal GVS-oVEMP waveforms: Not elicited on the left and elicited on the right side. **(left)** Abnormal GVS-oVEMP waveforms: Not elicited on the left side. **(right)** Normal GVS-oVEMP waveforms: Elicited on the right side.

provides locational information about whether a lesion is located in the labyrinth or retrolabyrinth (23, 30, 31). Hitherto, no studies have reported the use of GVS-VEMP in evaluating vestibular function in children. Herein, we obtained a reproducible GVS-VEMP waveform successfully. The response rate of GVS-cVEMP was 100% (18/18), consistent with ACS-cVEMP, and that of GVS-oVEMP was 88.9% (16/18), partially different from the results of ACS-oVEMP. Based on the current results, the deficit of the vestibular nerve or the receptor organs could not be determined. Moreover, in one 17-year-old patient, ACS-oVEMP was elicited bilaterally, but GVS-oVEMP was not elicited on the left at 3.0 mA. This could be attributed to insufficient electrical stimulation. Zhang et al. (24) demonstrated that with increasing age, the response rate decreased and the threshold increased.

TABLE 4 Comparison of the abnormal rates or the response rates of vestibular testing according to the course duration.

Group	Caloric test		ACS-oVEMP		GCS-oVEMP	
	Normal	Abnormal	Elicited	Not elicited	Elicited	Not elicited
Course duration <3 months	6	2	8	2	8	1
Course duration >3 months	10	1	11	0	8	1
P	0.55		0.21		1	

TABLE 5 Comparison of children with or without aura.

Group	Caloric test		ACS-oVEMP		GCS-oVEMP	
	Normal	Abnormal	Elicited	Not elicited	Elicited	Not elicited
Aura	5	0	5	0	5	0
No aura	11	3	14	2	11	2
P	0.53		1		1	

Caloric test, vHIT, and the underlying pathway

The caloric test provides ear-specific, low-frequency information about the horizontal semicircular canal and the superior branch of the vestibular nerve. vHIT testing shows the function of the semicircular canals at high frequency and both branches of the vestibular nerve (13, 32). The results of the previous studies on the caloric test and vHIT in patients with VMC were interpreted as normal, hyperreflexia, or weak, and the abnormality of vHIT was always low. Conversely, O'Reilly et al. (3) found normal results on the caloric test. Duarte et al. (33) demonstrated mostly normal or bilateral hyperreflexia in the caloric test. Another study on migraine sufferers with vestibular symptoms also showed bilateral weakness in 25% of children and unilateral weakness in 19% of children in the caloric tests, wherein the high abnormality could be due to a larger study population than in studies about VMC (10). Furthermore, Langhagen et al. (5) found that the abnormal rate of the caloric test and vHIT was 21% and 8%, respectively. In the current study, we observed partially reduced caloric response but no vHIT abnormality. The abnormal rate of the caloric test and vHIT was 15.8% (3/19) and 0% (0/22), indicating that the lateral semicircular canal (low-frequency function component) may be involved in VMC. Halmagyi et al. (34) speculated that isolated DP reflects a gain asymmetry between the neurons in the medial vestibular nucleus on either side, suggesting a status of vestibular decompensation.

Course duration, aura, and vestibular testing

While vestibular abnormalities are often found in patients with VM (35–37), high normal rates of vestibular function tests are observed in patients with VMC. This phenomenon could be explained based on the fact that abnormalities in vestibular function testing in patients with VM might result from ischemic damage due to long-term disease, whereas VMC children may have less time to develop such changes (4). Some studies used MRI-based voxel-based morphometry to evaluate patients with VM and found brain structural changes. The increased or decreased gray matter volume was related to self-adaptation of the nervous system or transmission circuitry impairment in the central vestibular cortex, respectively (38, 39). Obermann et al. (8) established a negative correlation between disease duration and gray matter volume in areas associated with headache and vestibular processing, indicating a pathophysiological change affected by the disease duration in patients with VM. However, in the two groups of patients with a duration of < or >3 months in this study, we did not find any statistical difference in the abnormal rate of vestibular testing. Also, vestibular function status did not aggravate disease duration in children with VMC.

Dizziness and vertigo are frequently associated with migraine. A study in 2010 on 22 migraine-suffering children with vestibular symptoms demonstrated that the vestibular test, including bithermal caloric test and VEMPs, was abnormal in 100% of children (10/10) with aura, indicating a significant involvement of vestibular pathways compared to 50% (6/12)

positive children without aura (10). However, no difference was observed in the vestibular testing outcomes in children with or without aura. In the current study, the dVMC population was included according to the diagnostic criteria of the Barany Society in 2021, which might vary from the grouping criteria described above.

Limitations

The main limitations of this study are as follows: (1) a control group of healthy children was not recruited, thus lacking normal values of vestibular testing in children with matched age, which affected the determination of abnormal rates. (2) The number of study subjects was small and needs to be expanded for reliable statistical results. (3) Side differences in cVEMPs might be due to different muscle tones on the two sides as no corrected amplitudes were used.

Conclusion

Vestibular function status could be comprehensively reported by the vestibular test battery. The high abnormal rates of the caloric test and oVEMPs (ACS-oVEMP and GVS-oVEMP) suggested that the lateral semicircular canal (low-frequency function component), the utricle, and the superior vestibular conduction pathway might be involved in VMC. The vestibular function was neither aggravated with disease duration nor was affected by aura in children with VMC.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of the Xinhua Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

JY, MD, and JC contributed to the study design and reviewed and approved the final manuscript. FZ and JS contributed to the detailed study design, statistical analysis, and manuscript draft and revision. LW, XM, and WW performed the vestibular function tests. BH and YY contributed to data acquisition. QZha, XC, QZhu, and YJ critically reviewed the manuscript. All authors agree to be accountable for the content of this study and the integrity and accuracy of the data. 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.

Publisher's note

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EDITED BY
Jun Yang,
Shanghai Jiaotong University School of Medicine, China

REVIEWED BY
Silvia Colnaghi,
Neuroscience Department, Italy
Birgül Balci,
Dokuz Eylul University, Turkey
Sulin Zhang,
Huazhong University of Science and Technology, China

*CORRESPONDENCE
Haibo Wang
whboto11@163.com
Daogong Zhang
zhangdaogong1978@163.com

†These authors share first authorship

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Sensory organization of balance control in children with vestibular migraine and recurrent vertigo of childhood

Xiaofei Li†, Yalan Liu†, Yafeng Lyu, Yawei Li, Huirong Jian, Xiaoyi Li, Zhaomin Fan, Haibo Wang* and Daogong Zhang*

Department of Otorhinolaryngology-Head and Neck Surgery, Shandong Provincial ENT Hospital, Shandong University, Jinan, China

Background: Migraine plays an important role in some subgroups of children with recurrent vertigo. Moreover, the migraine component varies from definite to possibly absent as defined in this spectrum of three disorders—vestibular migraine of childhood (VMC), probable VMC (pVMC), and recurrent vertigo of childhood (RVC). However, studies on the sensory organization of balance control in these three disorders are rare.

Objective: To explore the balance control of children with RVC, VMC, and pVMC, when the three sensory systems are challenged.

Method: A retrospective analysis was performed on 125 children with VMC (18 female and 15 male; aged 11.64 ± 2.74), pVMC (10 female and eight male; aged 11.78 ± 2.51), and RVC (32 female and 42 male; aged 11.10 ± 2.60). All children in each subtype were divided into groups of children aged $\leq$12 years old and 13–17 years old. Vestibular examination screening and assessment for postural control using the six conditions of the sensory organization test (SOT) were performed. The three primary outcome measures were: equilibrium score (ES), strategy score (SS), and sensory analysis score of the SOT.

Results: Equilibrium score under six different conditions and composite score increased with age (all P-values < 0.05). The somatosensory and visual scores also improved with growing (P-values < 0.05). However, vestibular scores did not increase significantly with age as the other senses did ($P > 0.05$). In the children $\leq$12 year-old group, children with VMC had a significantly higher visual preference score than those with pVMC and RVC ($P < 0.05$). There was an effect of age on the horizontal HIT. Ocular vestibular evoked myogenic potential (oVEMP), cervical vestibular evoked myogenic potential (cVEMP), and unilateral weakness (UW) values showed no significant difference among three diseases.

Conclusion: Compared with patients at the age of 13–17 years old and with RVC and pVMC (both $\leq$12 years old), children with VMC had a higher degree of reliance on visual signals to maintain their balance and a poorer

central integration of peripheral information before reaching 12 years of age. In addition, vision may predominate by weakening vestibular function based on visuo-vestibular interactions. It must be noted that peripheral vestibular examinations could not distinguish the three disease subtypes.

KEYWORDS

sensory organization test, children, balance, vestibular migraine of childhood, recurrent vertigo of childhood

Introduction

Vertigo or dizziness is not infrequent in pediatric patients. A survey performed among school children revealed that 15% of them have experienced disequilibrium at least once (1). However, specific data on the prevalence of this condition is limited and could be influenced by various factors since children are often incapable of expressing their complaints or describing their symptoms. A retrospective review of 561,151 patients identified a 0.45% prevalence of diagnoses related to balance in children, while another study reported a 5.6% prevalence of dizziness and imbalance in the pediatric population (2, 3), which varied a lot.

Most causes of vertigo and dizziness that occur during childhood and adolescence are benign and treatable. In the past, the most frequent conditions believed to cause vertigo and dizziness during childhood were classified as benign paroxysmal vertigo of childhood (BPVC) and vestibular migraine (VM). However, it is likely that a substantial proportion of pediatric patients with episodic vertigo fit both BPVC and VM criteria. Moreover, published research has shown the likelihood of children with BPVC developing VM later in life (4, 5). Therefore, diagnostic criteria for vestibular migraine of childhood (VMC), probable Vestibular migraine of childhood (pVMC), and recurrent vertigo of childhood (RVC) were established by the Committee for the Classification of Vestibular Disorders of the Barany Society and the Migraine Classification subgroup of the International Headache Society to define subgroups frame more clearly. However, the underlying pathogenesis of these three subgroups, as well as their role in migraine is unclear.

It has been reported that migraine and vertigo in childhood and adolescence has been associated with the presence of behavioral and emotional difficulties (6). However, younger children, especially, are often unable to verbalize "vertigo" in a concrete manner. Therefore, vestibular and balance control assessments are essential for the early identification of vestibular and balance dysfunctions in children. Unlike adults, children's central nervous integration and peripheral sensory systems (vestibular, visual, and somatosensory) undergo changes as they develop. Somatosensory function is nearly mature by the age of 5 years, visual contribution reaches adult levels around ages 11–12 years, and vestibular function continues to mature at least through the age of 15–17 years (7). Strategies for weighing sensory information change as maturation occurs. Meanwhile, age, gender, height, and body mass index (BMI) all need to be accounted for in child vertigo assessment.

In this study, sensory organization test (SOT), postural control, and vestibular tests were explored in children with RVC, VMC, and pVMC to compare the clinical characteristic of these three subgroups.

Methods

Participants

The medical documents of 142 children who visited our vertigo clinic, from July 2018 to March 2022, with complaints of vertigo/dizziness were retrospectively analyzed (Figure 1). They were diagnosed according to the diagnostic criteria consensus document of the Classification Committee of Vestibular Disorders of the Barany Society and the International Headache Society in 2021 (8). Over-all, 33 cases with vestibular migraine of childhood (aged 11.64 $\pm$ 2.74), 18 cases with probable vestibular migraine of childhood (aged 11.78 $\pm$ 2.51), and 74 cases with recurrent vertigo of childhood (aged 11.10 $\pm$ 2.60) were included. According to the age division of Chinese children, the patients were divided into preschoolers (3–6 years old), early school age (7–12 years old), and adolescents (13–17 years old). The small group of 3–6-year-olds were merged with the group of 7–12-year-olds because they were often uncooperative in some of our tests (mainly SOT and caloric test). Thus, cases in each subtype were divided into groups of $\leq$12 years old and 13–17 years old. Meanwhile, 17 patients who were diagnosed with sensorineural hearing loss, benign paroxysmal positional vertigo, Meniere's disease, tumors and other lesions in the posterior fossa, hemodynamic orthostatic dizziness/vertigo, and recurrent episodes of serous otitis media were excluded.

Medical documents were used with written consent from all patients' guardians. The study was approved by the Shandong Provincial ENT Hospital Ethical Committee.

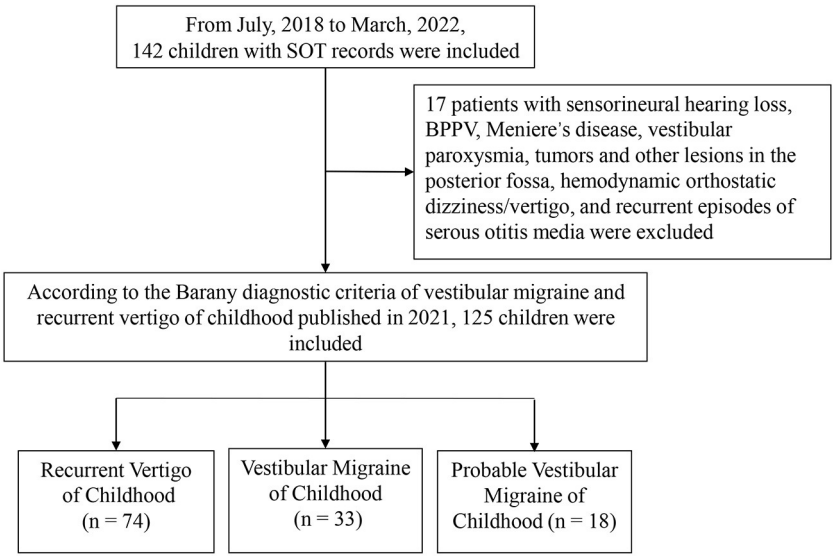

FIGURE 1
Flow chart.

Procedures and measures

All the included patients completed vestibular examination screening, including video head impulse test (vHIT), ocular vestibular evoked myogenic potential (oVEMP), cervical vestibular evoked myogenic potential (cVEMP), and caloric tests. They also underwent an assessment for postural control *via* the SOT. The SOT protocol consists of trials under six different sensory conditions: (1) eyes open, surround stable, and platform stable, (2) eyes closed, surround stable, and platform stable, (3) eyes open, sway-referenced surround, platform stable, (4) eyes open, surround stable, sway-referenced platform, (5) eyes closed, surround stable, sway-referenced platform, and (6) eyes open, sway-referenced surround, and sway-referenced platform. By limiting the conditions of the sensory input, SOT forces the individual to reweight another sensory input to maintain postural control. The details of the testing conditions and parameters are summarized in Supplementary Tables 1, 2 (9).

The three primary outcome measures of SOT were: equilibrium score (ES), strategy score (SS), and sensory analysis score of the SOT. Equilibrium score (ES1–ES6) means the stability of center of gravity in the six different challenges. The more stable, the higher the score is. Strategy score reflects that a person chooses to a hip strategy or ankle strategy when facing six different challenges. An ankle strategy means a higher score and a hip strategy means a lower score. The score is calculated mainly depend on the horizontal shear force in anterior-posterior axis. Sensory ratio analysis reflects the ability to use the ratio of visual/vestibular/ somatosensory signal to maintain balance facing six different challenges. The calculation formula can be found in the Supplementary Table 2.

Data analysis

The mean of the three trials of the six SOT conditions was determined for further analysis. Data are shown as mean and standard deviation. Multivariate analysis of variance were performed to compare the significant difference of variables at different ages ($\leq$12 years old and 13–17 years old) and diseases (RVC, VMC, and pVMC). Multiple comparisons were performed followed by the Bonterroni test. A significance level of 0.05 was adopted.

Results

First, detailed basic characteristics of the study group are shown in Table 1, including the ages, gender, height, weight, and body mass index.

Equilibrium score

The data showed a significant effect of age on each variable, with greater scores in the >12 years group. No effect of disease was observed. The equilibrium score under six different

TABLE 1 Demographic details of the patients.

	≤12 years			>12 years		
	RVC $n = 48$	VMC $n = 19$	pVMC $n = 10$	RVC $n = 26$	VMC $n = 14$	pVMC $n = 8$
Age	9.60 (1.81)	9.79 (2.00)	10.00 (1.83)	13.88 (1.11)	14.14 (1.01)	14.00 (0.93)
Gender (F:M)	14:34	8:11	6:4	18:8	10:4	4:4
Height (cm)	143.96 (14.14)	145.00 (14.76)	141.29 (19.80)	163.45 (9.44)	162.20 (7.17)	169.55 (9.09)
Weight (kg)	42.17 (19.64)	37.42 (12.87)	37.15 (13.24)	58.62 (17.12)	58.14 (11.82)	66.25 (16.85)
Body mass index (kg/m^2)	20.27 (9.68)	17.46 (4.50)	18.08 (3.26)	21.88 (5.54)	22.03 (3.85)	22.84 (4.33)

Data are shown as mean (SD).
F, female; M, male.

conditions and composite score increased with age growing (all P-values < 0.05, Tables 2, 3).

Somatosensory, visual and vestibular score

A significant effect of age on somatosensory and visual score, with greater scores in the >12 years group; no effect of disease, indicating that somatosensory and visual scores improved with growing ($P = 0.001$, $P = 0.019$). However, vestibular scores did not increase significantly with age as the other senses did ($P > 0.05$; Table 3, Figures 2A,B).

Visual preference

Visual preference score means the degree to the subject who relies on visual signal to maintain balance (correct/incorrect information). The visual preferece score analysis indicated no effect of age ($F = 1.643$, $P = 0.202$), no effect of disease ($F = 1.297$, $P = 0.277$), a significant effect of age*disease interaction, with a significant greater score in the VMC disease group, compared with either tje RVC or the pVMC group ($P = 0.013$, $P = 0.027$, respectively), only in the ≤12 years group. There are significant differences between the two age groups in RVC ($P = 0.015$). No significant difference was found between different ages in children with VMC or pVMC ($P > 0.05$; Tables 3, 4, Figures 2C,D).

Strategy score

There was no significant effect of age on each variable; no effect of disease with the exception of condition 3, whose score was significantly lower in the pVMC group compared with VMC group ($P = 0.030$) in both age groups.

Peripheral vestibular tests

Video head impulse test reflect the high frequency function of each semicircular canal. The main outcome parameter was vHIT VOR gain by evaluating the relation between eye and head velocity. The data revealed an effect of age on the horizontal HIT, with a greater VOR gain of right horizantal semecircular canal in the ≤12 years group ($F = 8.370$, $P = 0.005$); No effect of disease and age*disease ($P > 0.05$; Table 3, Figures 2E,F). The other peripheral vestibular test results, including, unilateral weakness (UW) of caloric test, and asymmetry rate of VMEP were compared and had no significant differences (all P-value > 0.05). Note that not all the patients compete the peripheral vestibular tests as indicated in Table 2.

Last, some symptomatological data were complemented on when the test were done, age of onset age, attack duration and number of attack in the last 3 months. Almost all the patients have had attacks within about 1 week before visit, suggesting that the examination data comes from an active phase (Table 5).

Discussion

This study aimed to explore the postural control of children with RVC, VMC, and pVMC, when the three sensory systems are challenged, using computerized dynamic posturography testing. Since differences in postural control and sensory weighting may be attributed to not only neural integration but also anthropometric characteristics (height, weight, BMI etc.) (7), the included patients were divided into different groups depending on their ages. Thus, the current study explore the postural control of children from two point of view, ages and diseases.

As the sensory system and central system develop, the equilibrium ability and pattern of children gradually mature. Significant age-associated increases in overall performance on the SOT were found in healthy children (7). In the current study, the equilibrium score revealed that the ability to use the vestibular input does not increase significantly with age unlike

TABLE 2 Mean values of variables in different ages and diseases.

	≤12 years			>12 years		
	RVC $n = 48$	VMC $n = 19$	pVMC $n = 10$	RVC $n = 26$	VMC $n = 14$	pVMC $n = 8$
Equilibrium score						
Condition 1	90.54 (3.65)	91.10 (4.47)	91.67 (2.60)	92.93 (5.23)	93.56 (1.43)	93.73 (2.77)
Condition 2	87.42 (4.77)	86.28 (6.80)	86.48 (4.91)	91.19 (4.02)	91.06 (2.48)	92.73 (2.05)
Condition 3	85.12 (6.37)	87.25 (4.67)	85.07 (4.83)	89.72 (6.14)	89.68 (3.53)	88.98 (4.80)
Condition 4	68.98 (14.69)	65.22 (14.70)	65.70 (19.35)	75.96 (18.66)	81.65 (8.86)	73.10 (31.97)
Condition 5	54.72 (15.77)	45.64 (20.03)	48.25 (19.03)	57.62 (26.70)	66.61 (12.80)	54.17 (29.55)
Condition 6	44.07 (20.92)	45.55 (20.68)	32.70 (23.43)	58.03 (24.56)	61.29 (24.56)	61.29 (20.83)
Composite	66.92 (10.68)	64.84 (11.47)	62.40 (12.19)	73.54 (14.94)	77.50 (7.50)	70.75 (19.97)
Sensory ratio analysis						
Somatosensory	96.67 (4.20)	94.89 (4.41)	94.20 (5.61)	98.35 (5.01)	97.50 (2.88)	99.00 (1.93)
Visual	75.67 (14.76)	72.37 (16.05)	71.80 (21.58)	81.15 (18.44)	87.50 (10.07)	77.75 (33.26)
Vestibular	60.19 (16.64)	49.79 (21.61)	53.00 (21.70)	61.04 (28.33)	71.50 (14.06)	57.25 (31.14)
Visual preference	91.02 (14.43)	103.37 (20.99)	87.10 (12.71)	100.38 (17.46)	95.93 (12.52)	98.00 (6.89)
Strategy score						
Condition 1	95.73 (1.73)	95.90 (1.35)	96.07 (1.14)	95.22 (3.93)	95.71 (1.21)	95.35 (1.36)
Condition 2	94.57 (2.02)	94.90 (1.93)	94.45 (3.27)	94.54 (2.68)	95.32 (1.18)	94.46 (1.61)
Condition 3	93.98 (3.09)	95.14 (1.41)	93.12 (3.68)	94.15 (3.47)	94.86 (1.96)	92.21 (3.41)
Condition 4	85.06 (5.77)	86.71 (5.49)	85.98 (5.70)	84.28 (9.37)	86.43 (4.97)	87.35 (3.62)
Condition 5	78.62 (9.93)	82.43 (7.67)	79.70 (8.09)	78.02 (9.43)	79.05 (7.49)	77.33 (9.85)
Condition 6	80.91 (7.61)	84.41 (6.33)	80.62 (9.33)	82.19 (5.80)	80.67 (7.40)	75.54 (9.66)
Peripheral vestibular tests						
HIT RA	1.01 (0.13), $n = 41$	1.03 (0.07), $n = 17$	1.05 (0.07), $n = 10$	0.99 (0.10), $n = 25$	1.07 (0.08), $n = 14$	1.01 (0.11), $n = 7$
HIT RH	0.99 (0.08), $n = 41$	1.02 (0.07), $n = 17$	1.02 (0.03), $n = 10$	0.98 (0.09), $n = 25$	0.96 (0.11), $n = 14$	0.93 (0.13), $n = 7$
HIT RP	1.00 (0.07), $n = 41$	0.97 (0.07), $n = 17$	0.99 (0.10), $n = 10$	0.95 (0.08), $n = 25$	0.97 (0.10), $n = 14$	0.96 (0.10), $n = 7$
HIT LA	1.02 (0.13), $n = 41$	1.04 (0.08), $n = 17$	1.00 (0.09), $n = 10$	0.97 (0.14), $n = 25$	1.06 (0.09), $n = 14$	0.98 (0.05), $n = 7$
HIT LH	0.98 (0.11), $n = 41$	0.91 (0.25), $n = 17$	1.02 (0.06), $n = 10$	0.99 (0.07), $n = 25$	0.95 (0.11), $n = 14$	0.92 (0.18), $n = 7$
HIT LP	0.98 (0.06), $n = 41$	0.96 (0.12), $n = 17$	1.00 (0.09), $n = 10$	0.97 (0.08), $n = 25$	0.98 (0.09), $n = 14$	0.91 (0.11), $n = 7$
UW (%)	25.47 (21.47), $n = 41$	26.16 (16.57), $n = 15$	$n = 0$	23.82 (21.37), $n = 23$	17.90 (19.14), $n = 14$	14.38 (17.94), $n = 8$
cVEMP asymmetry ratio of amplitude (%)	29.69 (31.98), $n = 42$	31.19 (31.54), $n = 18$	$n = 0$	34.21 (37.65), $n = 24$	33.00 (37.58), $n = 14$	27.41 (33.71), $n = 7$
oVEMP asymmetry ratio of amplitude (%)	30.50 (34.50), $n = 42$	38.42 (33.48), $n = 17$	$n = 0$	47.25 (43.79), $n = 21$	40.15 (40.38), $n = 14$	41.21 (45.66), $n = 6$

Data are shown as mean (SD).

HIT, video head impulse test; L, left; R, right; A, anterior; H, horizontal; P, posterior; UW, unilateral weakness; cVEMP, cervical vestibular evoked myogenic potential; oVEMP, ocular vestibular evoked myogenic potential.

Note, not all the children completed all the peripheral vestibular tests.

TABLE 3 Tests of between-subject effects of variables.

	Age				Disease					Age* disease	
	≤12 years	>12 years	*F*	*P*-values	RVC	VMC	pVMC	*F*	*P*-values	*F*	*P*-values
Equilibrium score											
Condition 1	91.10 (0.54)	93.41 (0.64)	7.719	0.006	91.73 (0.48)	92.32 (0.69)	92.70 (0.93)	0.546	0.581	0.017	0.983
Condition 2	86.73 (0.65)	91.66 (0.76)	24.231	0.000	89.31 (0.57)	88.67 (0.83)	89.61 (1.12)	0.286	0.751	0.524	0.594
Condition 3	85.81 (0.78)	89.46 (0.91)	9.246	0.003	87.42 (0.69)	88.46 (0.99)	87.02 (1.34)	0.502	0.606	0.404	0.669
Condition 4	66.63 (2.36)	76.91 (2.74)	8.077	0.005	72.47 (2.07)	73.44 (2.99)	69.40 (4.03)	0.335	0.716	0.892	0.413
Condition 5	49.54 (2.79)	59.47 (3.25)	5.365	0.022	56.17 (2.45)	56.12 (3.54)	51.21 (4.77)	0.456	0.635	2.233	0.112
Condition 6	40.77 (3.07)	57.89 (3.57)	13.189	0.000	51.05 (2.69)	53.42 (3.90)	43.53 (5.25)	1.184	0.310	0.213	0.808
Composite	64.72 (1.72)	73.93 (2.00)	12.245	0.001	70.22 (1.50)	71.17 (2.18)	66.58 (2.93)	0.838	0.435	0.651	0.523
Sensory ratio analysis											
Somatosensory	95.25 (0.60)	98.28 (0.70)	10.817	0.001	97.51 (0.53)	96.20 (0.76)	96.60 (1.03)	1.095	0.338	0.928	0.398
Visual	73.28 (0.44)	82.14 (2.83)	5.617	0.019	78.41 (2.14)	79.93 (3.09)	74.78 (4.16)	0.500	0.608	0.867	0.423
Vestibular	54.33 (2.99)	63.26 (3.48)	3.803	0.054	60.61 (2.62)	60.65 (3.79)	55.13 (5.10)	0.493	0.612	2.609	0.078
Visual preference	93.83 (2.17)	98.10 (2.53)	1.643	0.202	95.70 (1.91)	99.65 (2.76)	92.55 (3.71)	1.297	0.277	3.516	0.033
Strategy score											
Condition 1	95.90 (0.31)	95.43 (0.36)	0.969	0.327	95.48 (0.27)	95.81 (0.40)	95.71 (0.53)	0.264	0.769	0.091	0.913
Condition 2	94.64 (0.30)	94.77 (0.35)	0.078	0.780	94.56 (0.27)	95.11 (0.39)	94.45 (0.52)	0.829	0.439	0.120	0.887
Condition 3	94.08 (0.41)	93.74 (0.48)	0.290	0.591	94.07 (0.36)	95.00 (0.52)	92.66 (0.70)	3.596	0.030	0.254	0.776
Condition 4	85.92 (0.90)	86.02 (1.05)	0.006	0.940	84.67 (0.79)	86.57 (1.14)	86.67 (1.54)	1.278	0.282	0.193	0.825
Condition 5	80.25 (1.27)	78.13 (1.47)	1.185	0.279	78.32 (1.11)	80.74 (1.61)	78.52 (2.16)	0.798	0.453	0.271	0.763
Condition 6	81.98 (1.02)	79.47 (1.19)	2.579	0.111	81.55 (0.90)	82.54 (1.30)	78.08 (1.74)	2.201	0.115	2.048	0.134
Peripheral vestibular tests											
HIT RA	1.03 (0.02)	1.02 (0.02)	0.241	0.625	1.00 (0.01)	1.05 (0.02)	1.03 (0.03)	2.285	0.107	0.955	0.388
HIT RH	1.01 (0.01)	0.95 (0.02)	8.370	0.005	0.99 (0.01)	0.99 (0.02)	0.97 (0.02)	0.193	0.825	1.506	0.227
HIT RP	0.99 (0.01)	0.96 (0.01)	2.093	0.151	0.97 (0.01)	0.97 (0.01)	0.97 (0.02)	0.000	1.000	1.051	0.353
HIT LA	1.03 (0.02)	1.01 (0.02)	0.596	0.442	1.00 (0.01)	1.05 (0.02)	1.00 (0.03)	2.522	0.085	0.986	0.376
HIT LH	0.97 (0.02)	0.95 (0.02)	0.422	0.517	0.98 (0.02)	0.93 (0.02)	0.97 (0.03)	1.759	0.177	1.536	0.220
HIT LP	0.98 (0.01)	0.95 (0.02)	2.419	0.123	0.97 (0.01)	0.97 (0.02)	0.95 (0.02)	0.390	0.678	2.235	0.112
UW (%)	25.82 (3.06)	18.70 (3.31)	1.164	0.283	24.65 (2.64)	22.03 (3.76)	14.74 (7.16)	0.536	0.587	0.518	0.473
cVEMP asymmetry ratio of amplitude (%)	30.44 (4.81)	31.54 (5.76)	0.178	0.674	31.95 (4.37)	32.09 (6.09)	27.42 (12.91)	0.096	0.909	0.033	0.857
oVEMP asymmetry ratio of amplitude (%)	34.46 (5.45)	42.87 (6.76)	1.177	0.281	38.88 (5.07)	39.28 (6.85)	41.22 (15.49)	0.012	0.988	0.777	0.380

Data are shown as mean (SD).
HIT, video head impulse test; L, left; R, right; A, anterior; H, horizontal; P, posterior; UW, unilateral weakness; cVEMP, cervical vestibular evoked myogenic potential; oVEMP, ocular vestibular evoked myogenic potential.
Note, not all the children completed all the peripheral vestibular tests.

vision and somatosensory, which may be one of the causes of vertigo in children.

The ability to utilize specific sensory inputs effectively develops at different ages. Somatosensory function is nearly mature by the age of 5 years, visual contribution reaches adult levels around ages 11–12 years, and vestibular function continues to mature at least through the age of 15–17 years (7). In the current study, vision dependence difference among three subtype groups was only observed in children aged ≤12 years rather than in older children, which might be because visual signals are dominant before 12 years of age. Moreover, young children are more dependent on visual cues, although the visual system is less mature than other sensory inputs for postural control (10). No differences in the visual preference ratio were observed among three subtype groups in older children (13–17 years old), indicating that the factors of age and

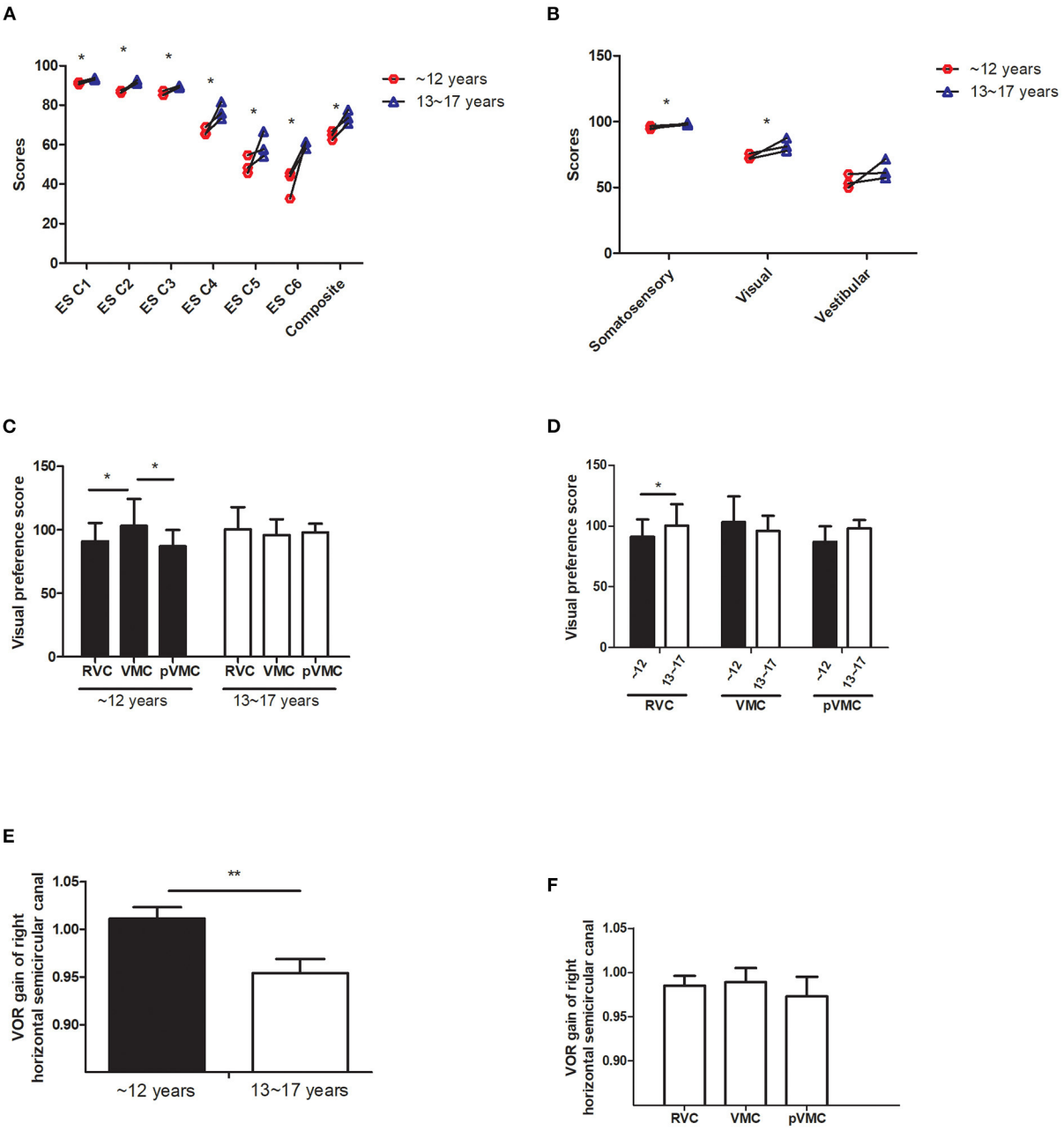

FIGURE 2
Sensory organization test analysis. **(A)** Equilibrium score. **(B)** Sensory ratio analysis. **(C,D)** Visual preference score in different age groups and diseases. **(E,F)** VOR gain value of horizontal semicircular canal in different age groups and disease.ES C, Equilibrium score condition; SS C, strategy score condition; VMC, vestibular Migraine of Childhood; pVMC, probable Vestibular Migraine of Childhood; RVC, Recurrent Vertigo of Childhood; VOR, vestibular ocular reflex. *$P < 0.05$, **$P < 0.05$.

development should be taken into consideration in the diagnosis and intervention of the three subtypes.

Furthermore, children with VMC showed a higher visual preference score, suggesting that those with VMC were more dependent on visual signals (correct/incorrect information) to maintain balance than those with pVMC and RVC at the same age (≤12 years old). Previous study reported that the cerebellum nodulus and uvula (integration centers for canal and otolith signals) have been found to have increased sensitivity in vestibular migraine patients (11). This increased sensitivity could cause increased inhibition of the vestibular nuclei, as well as inhibition of the velocity storage of vestibular signals, which would lead to increased dependence on visual signals. It is postulate that VM patients have impaired visuo-vestibular

cortical interactions, which in turn disrupts normal vestibular function (12). Therefore, it can be inferred that the peripheral vestibular signals of those with VMC are impaired induced by increased inhibition of the vestibular nuclei. In addition, a visual preference suggests that vision may predominate by weakening vestibular function based on visuo-vestibular interactions. We speculated that both mechanisms are involved in the different performances of the three disease subtypes. However, further research is needed to confirm this.

In addition, our data found there is a meaningful difference of visual preference between the two age groups in RVC; there is no significant difference between the two age groups in VMC and pVMC. It is speculated that vertigo disorders in children with or without migraine may be substantially different. Morever, in the case of RVC, the implication is that the timing of the intervention may affect the patient's sensory processing pattern.

Other studies have reported clinical implication of peripheral vestibular impairment in vestibular migraine patients. Woo Seok Kang et al. revealed that abnormal video head impulse and caloric tests in VM patients predicted prolonged preventive medication requirement, suggesting that peripheral vestibular abnormalities are closely related to the development of vertigo in VM patients (13). In our study, vHIT of right horizontal canal had significant difference in ages but not in diseases. It has been reported that healthy population have a higher VOR gain in right side than that of left. Meanwhile, VOR gain value of vHIT decreases with age increasing (14). Therefore, in current study, it is believed that the significant difference of vHIT is mainly attributed to ages and sides, not due to diseases. Alternatively, peripheral vestibular function was not different among these diseases, implying that the difference mainly comes from the central integration and processing of peripheral information rather than the peripheral sensory input. A previous study utilized the functional head impulse test (fHIT) with and without an optokinetic stimulus to unveil a functional vestibular impairment in adult patients with VM, mainly impairing the capability to integrate different vestibular stimuli (15). A similar impairment was also reported for the integration of rotational and gravitational cues (16), as well as visual motion stimulation that disturbed the postural stability of adult patients with VM (17). Some additional studies on pediatric VM revealed that abnormalities are more common on balance tests than on vestibular tests in pediatric VM (18, 19). These studies are consistent with our findings. Therefore, we speculate that for children with vertigo disease, more attention should be paid to the overall balance ability rather than just examining the peripheral vestibular function.

TABLE 4 Pairwise comparison of visual preference score.

Comparison	Visual preference score	*P*-values
≤12 years: RVC vs. VMC	91.02 (14.43) vs. 103.37 (20.99)	0.013
≤12 years: RVC vs. pVMC	91.02 (14.43) vs. 87.10 (12.71)	1.000
≤12 years: VMC vs. pVMC	103.37 (20.99) vs. 87.10 (12.71)	0.027
>12 years: RVC vs. VMC	100.38 (17.46) vs. 95.93 (12.52)	1.000
>12 years: RVC vs. pVMC	100.38 (17.46) vs. 98.00 (6.89)	1.000
>12 years: VMC vs. pVMC	95.93 (12.52) vs. 98.00 (6.89)	1.000
RVC: ≤12 years vs. >12 years	91.02 (14.43) vs. 100.38 (17.46)	0.015
VMC: ≤12 years vs. >12 years	103.37 (20.99) vs. 95.93 (12.52)	0.180
pVMC: ≤12 years vs. >12 years	87.10 (12.71) vs. 98.00 (6.89)	0.145

Data were shown as mean (SD). Bonterroni test was performed for pairwise comparison. P value here are shown as N* 0.05. N means the number of tests.
VMC, vestibular Migraine of Childhood; pVMC, probable Vestibular Migraine of Childhood; RVC, Recurrent Vertigo of Childhood.

Limitations

First, this was a cross-sectional study that cannot observe the longitudinal outcomes of the three disease subtypes in the same cases. The current comparison between the two groups of younger and older children also provides some useful information. Second, there was no healthy patients included as control. Thus, the results (no difference) observed in some parameters can only be applied for those with the three disease subtypes, and not for normal patients.

Conclusion

Compared with patients at the age of 13–17 years old and with RVC and pVMC (both ≤12 years old), children with VMC had a higher degree of reliance on visual signals to maintain their balance and a poorer central integration of peripheral information before reaching 12 years of age.

TABLE 5 Symptomatological information.

Age of onset (years)		Interval since the last attack (days)		Number of attack in the last 3 months		Attack duration (hours)	
RVC	VMC + pVMC	RVC	VMC + pVMC	RVC	VMC + pVMC	RVC	VMC + pVMC
9.92 (2.82)	9.84 (3.47)	7.10 (10.23)	6.49 (9.90)	14.48 (23.23)	24.61 (53.74)	8.62 (15.19)	7.54 (21.82)

Data are shown as mean (SD).
VMC, vestibular migraine of childhood; pVMC, probable vestibular migraine of childhood; RVC, recurrent vertigo of childhood.

In addition, vision may predominate by weakening vestibular function based on visuo-vestibular interactions. It must be noted that peripheral vestibular examinations could not distinguish the three disease subtypes.

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 Shandong Provincial ENT Hospital Ethical Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

HW and DZ contributed to the conception of the work. DZ, ZF, and YLyu contributed to the experimental design. YLi, HJ, and XL collected data. XL performed the analysis. XL and YLiu wrote the manuscript. DZ revised the manuscript. 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.970610/full#supplementary-material

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Shinichiro Oka,
International University of Health and Welfare (IUHW), Japan
Jinsei Jung,
Yonsei University, South Korea

*CORRESPONDENCE
Xin Ni
✉ nixin@bch.com.cn
Jie Zhang
✉ stzhangj@263.net

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Effectiveness and acceptance of Vestibulo-Ocular Reflex adaptation training in children with recurrent vertigo with unilateral vestibular dysfunction and normal balance function

Ning Ma[1,2], Handi Liu[1,2], Bing Liu[1,2], Li Zhang[1,2], Bei Li[1,2], Yang Yang[1,2], Wei Liu[1,2], Min Chen[1,2], Jianbo Shao[1,2], Xiao Zhang[1,2], Xin Ni[1,2]* and Jie Zhang[1,2]*

[1]Department of Otorhinolaryngology Head and Neck Surgery, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China, [2]Beijing Key Laboratory for Pediatric Diseases of Otolaryngology Head and Neck Surgery, Beijing, China

Objective: This was a block randomized controlled study to evaluate the effectiveness and acceptance of Vestibulo-Ocular Reflex (VOR) adaptation training in children with recurrent vertigo with unilateral vestibular dysfunction (UVD) and normal balance function.

Methods: Thirty children, aged 4–13 years, diagnosed with recurrent vertigo of childhood (RVC) with UVD (according to a caloric test) and normal balance function were analyzed. These 30 children were divided into 10 blocks based on similar age and severity of vertigo. Three children in each block were randomly assigned to one of three groups to receive 1 month of treatment. Group A received vestibular-ocular reflex (VOR) adaptation training, Group B received Cawthorne-Cooksey training, and a control group received no training. All children were administered pharmacotherapy [Ginkgo biloba leaf extract (drops)]. The Dizziness Handicap Inventory (DHI), Visual Analog Scale of Quality of Life with Vertigo (VAS-QLV), and canal paralysis (CP) on the caloric test were recorded before and after treatment, and the effectiveness of treatment was evaluated. The Visual Analog Scale of Acceptance (VAS-A) was used to evaluate the acceptance of the training in the two groups that received training.

Results: There were 10 children each in Group A, Group B, and the control group; the male to female ratio was 1, and the average age in each group was 9.0 ± 3.2, 8.4 ± 3.0, and 8.3 ± 2.6 years, respectively. The effective rate was 100% in Group A, 65% in Group B, and 60% in Group C. The recovery rate on caloric testing after treatment was 100, 70, and 50%, respectively. DHI scores before and after training were 56.8 ± 12.4 and 8.8 ± 6.1 in Group A, 57.8 ± 12.6 and 18.8 ± 9.7 in Group B, and 56.8 ± 12.4 and 24.0 ± 15.3 in Group C (all $P = 0.000$). VAS-QLV scores before and after training were 7.5 ± 1.0 and 0.9 ± 0.9 in Group A, 6.4 ± 2.2 and 2.7 ± 1.1 in Group B, and 6.6 ± 1.6 and 2.6 ± 1.4 in Group C (all $P < 0.05$). The CP values before and after training were

35.7 ± 15.1 and 12.9 ± 8.7 in Group A, 33.6 ± 20.1 and 23.6 ± 19.3 in Group B, and 38.6 ± 21.1 and 24.8 ± 17.9 in Group C ($P = 0.001$, $P = 0.015$, and $P = 0.050$, respectively). Between-group comparisons showed that the decreases in DHI and VAS-QLV scores after training were significantly different ($P = 0.015$, $P = 0.02$), while CP values were not ($P = 0.139$). After training, the DHI value had decreased significantly more in Group A compared with Group C ($P < 0.05$), but there were no other differences. After training, VAS-QLV scores in Group A had decreased significantly more compared with Group B and C ($P < 0.05$). In terms of acceptance, the VAS-A score was 7.6 ± 2.2 in Group A and 3.1 ± 2.8 in Group B (P =0.004), The acceptance rate was 70% in group A and 10% in group B. there was no significant correlation between age and VAS-A in either group A or group B ($P > 0.05$).

Conclusion: This study strongly suggests that vestibular rehabilitation training should be performed in children with vertigo to improve symptoms. For children with RVC with UVD but normal balance function, a single VOR adaptation program can effectively improve vertigo symptoms, and given its simplicity, time-effectiveness, and excellent outcomes, it is associated with better acceptance in children compared to classic Cawthorne-Cooksey training.

KEYWORDS

vestibular rehabilitation, recurrent vertigo of childhood, unilateral vestibular dysfunction, children, Vestibulo-Ocular Reflex

1. Introduction

Recurrent vertigo of childhood (RVC) is clearly defined in the clinical guidelines of the Bárány Society and the Vestibular Disorders Classification Committee of the International Headache Society in 2021 (1). Diagnostic criteria of Recurrent Vertigo of Childhood (RVC) include: A: At least three episodes with vestibular symptoms of moderate or severe intensity, lasting between 1 min and 72 h. B. None of the criteria for Vestibular Migraine of Childhood or Probable Vestibular Migraine of Childhood. C. Age < 18 years D. Not better accounted for by another headache disorder, vestibular disorder, or other condition. As this type of vertigo is moderate to severe and occurs repeatedly, it can affect daily life and learning behavior (2), produce anxiety (3), and even affect the child's family. The targeted treatment is vestibular rehabilitation (VR) (4), but VR is not widely used in the clinic. One key issue is the uncertainty of the effectiveness, applicability, and acceptance of VR in children with vertigo. Moreover, there is a lack of corresponding research data on how to improve the effectiveness of treatment in children with RVC, enhance acceptance, and achieve stable short-and long-term effects.

VR includes gaze stability exercises, balance and gait training, and walking for endurance. Gaze stability exercises include adaptation training, alternative training, and habitual training (4). Different exercise approaches have been proposed to address these different problems. Vestibulo-Ocular Reflex (VOR) adaptation training are based on inducing changes in the neuronal response of the vestibular system to a specific error signal retinal slip. The goals of these exercises are to decrease visual blurring during head movement, improve postural stability, and decrease symptoms (5). Most vestibular rehabilitation programs include balance training, gait exercises and endurance training (5). The classic VR is the Cawthorne-Cooksey training (6), which is complex and time taking. Although it can be used in children, persistence, understanding, and compliance are poor, and therefore, training often stops early and/or does not play much of a therapeutic role (7, 8). In our clinical work, we found that for children, increased training time will reduce the children's training compliance and adherence. It leads to the premature termination of training and has a negative impact on the therapeutic effect. A considerable number of children with RVC have unilateral vestibular dysfunction (UVD), but have not shown a balance disorder. For these children, we adopted a targeted and single intensive Vestibulo-Ocular Reflex (VOR) adaptation training only. Reduce the training time and complexity, so as to improve the compliance and completion of vestibular rehabilitation training. In this study, by comparing with the classical Cawthorne-Cooksey training, we investigated the effectiveness and suitability of this simplified VR in children with RVC with a view to improving the therapeutic effect in this patient group.

2. Materials and methods

Children aged 4–13 years who visited the outpatient clinic of the Department of Otorhinolaryngology Head and Neck Surgery of Beijing Children's Hospital affiliated to Capital Medical University between 2021 and 2022 with recurrent dizziness as the main complaint were studied. A total of 30 children who met the diagnostic criteria (1) for RVC proposed by the Bárány Society International Classification of Vestibular Disorders (ICVD) and the Vestibular Disorders Classification Committee of the International Headache Society with unilateral peripheral vestibular dysfunction and normal balance function were recruited.

Peripheral vestibular dysfunction was determined by a saccade test, smooth pursuit test, optokinetic test, gaze test, spontaneous nystagmus, caloric test, and positioning nystagmus (Dix-Hallpike test and supine roll test). Saccade tests and gaze tests were normal in all the children. Smooth pursuit tests response type I or type II. Optokinetic tests response: 20 and 40°/s symmetry. There were no spontaneous nystagmus or irrigation nystagmus. Dix-Hallpike tests and supine roll tests were negative. The caloric tests indicate that unilateral horizontal semicircular canal function were hypofunction (9, 10). Head MRI indicated unilateral external semicircular canal dysfunction (11) in one patient. The evaluation of balance function includes the collection of history and the examination of balance function. During the consultation, children said that he could stand and walk normally during the attack of vertigo, without unstable feelings such as stepping on cotton and floating, falling history, and having physical or motor coordination problems. Balance function was examined using the Tandem Romberg test (Mann test), Fukuda stepping test, and past pointing test. Tandem Romberg test (Mann test): Maintain a stable position for more than 10 s. Fukuda stepping test: *in-situ* offset angle $< 30°$, self-rotation angle $< 90°$, moving distance <50 cm. Past pointing test: no finger crossing. Children who meet the above conditions are considered to have normal balance function (12).

The vestibular rehabilitation training programs implemented were the VOR adaptation training and the Cawthorne-Cooksey training, and a control group was set up. All children were administered drugs (Ginkgo biloba extract drops agent) for symptomatic treatment. According to a block random design, children were divided into 10 blocks according to age and vertigo severity. Three children in each block were randomly assigned to each of the three groups (A: the VOR adaptation training group; B: Cawthorne-Cooksey training group C: the control group no training) by lottery, and the course of treatment in each group was 1 month. Informed consent was signed by the guardian of all children. This study was approved by the Hospital's Ethics Committee.

Inclusion criteria included: (1) diagnosis of RVC (at least three episodes with vestibular symptoms of moderate or severe intensity, lasting between 1 min and 72 h).All the children enrolled had recurrent vertigo episodes in the past 1–2 months at that time, ranging from once a day to several times a day; (2) unilateral peripheral vestibular dysfunction; (3) normal balance function; (4) bilateral ear canal patency and tympanic membrane integrity examined by otoscopy; (5) normal hearing thresholds (children 6 years and under) underwent pediatric behavioral audiometry using Interacoustics AD229b (Interacoustics; Middelfart, Denmark) and children over 6 years underwent pure tone audiometry using Conera (GN Otometrics; Copenhagen, Denmark); (6) type A tympanogram.

Exclusion criteria included: (1) ophthalmologic and central vertigo confirmed by ophthalmology and neurology; (2) benign paroxysmal positional vertigo; (3) vestibular migraine (1); and (4) possible vestibular migraine (1).

2.1. Evaluation methods

2.1.1. Vestibular caloric test

The canal paralysis (CP) value was calculated and recorded. CP was considered abnormal if the CP value was more than 25% (9, 10, 13).

2.1.2. Dizziness Handicap Inventory (DHI)

A total of 25 questions were asked, and the answer options were: four points for yes, two points for sometimes, and 0 points for no. A score of 0–30 indicated a mild disorder, 31–60 indicated a moderate disorder, and 61–100 indicated a severe disorder (14). Reduction of the DHI was evaluated.

In order to control the quality of the questionnaire, all the questions were given to the children after they were interpreted by the vestibular studio technician and parents.

2.1.3. Visual Analog Scale-Quality of Life with Vertigo (VAS-QLV)

A total of two questions were asked: (1) the impact of vertigo on daily life and (2) the impact of vertigo on learning behavior. Possible ratings were 0–10 points, with 0 points indicating no effect and 10 points indicating complete inability to partake in normal activity and learning behavior. The two questions were scored separately, and the average score was taken. A score of 0–3 indicated a mild effect, 4–6 indicated a moderate effect, and 7–10 indicated a severe effect.

2.1.4. Acceptance

The Visual Analog Scale-Acceptance (VAS-A) score was calculated from a total of two questions that covered: (1)

understanding of the vestibular rehabilitation training program and (2) completion of the vestibular training program. Possible ratings were 0–10 points, with 0 points indicating no understanding or no training and 10 points indicating full understanding or complete training according to the plan and frequency. The two questions were scored separately, and the average score was taken. A score of 0–3 points indicated poor acceptance, 4–6 points indicated general acceptance, and 7–10 points indicated good acceptance. The acceptance rate and the completion rate were assessed after treatment in both groups. The acceptance rate was the number of good acceptability results measured by VAS-A/10.

2.2. Training method

2.2.1. Group A (VOR adaptation training group)

Training included shaking head fixation, alternate fixation, separation fixation, and reverse fixation for a total of 5 min (15). The specific methods were as follows: (1) shaking head fixation: fix the eyes on the target in front and turn the head from left to right and up and down; (2) alternate fixation: the eyes look at the target objects up, down, left, and right, and the head moves with the eyes at the same time; (3) separation fixation: the eyes look at the target objects up, down, left, and right, and the eyes move first, the head moves later; and (4) reverse fixation: the eyes look at the target objects up, down, left, and right, and the head moves in the opposite direction as the eyes. Five repetitions of each movement were completed in every training session.

2.2.2. Group B (Cawthorne-Cooksey training group)

Cawthorne-Cooksey exercises (6) represent a general approach to vestibular rehabilitation and include a standardized series of exercises that involve a progression of eye movements only, head movements with eyes open or closed, bending over, sitting-standing, tossing a ball, and walking.

2.2.3. Group C (control group)

This group received no training.

We made videos to guide children to follow the training programs, including the explanation of movements and suggestions on the angle and speed of turning the head. Group A received 5 min of video training 3 times a day for 1 month. Group B received 17 min of video training 3 times a day for 1 month. The children were supervised by their parents to watch the video and train at home, and the training was recorded daily. The patients were followed up by telephone every week, followed up by a follow-up visit at the end of the 1-month course of treatment.

2.3. Efficacy evaluation

The caloric test was conducted before and after treatment to compare the recovery of vestibular function and evaluate the decline of CP value. The DHI and the VAS-QLV were completed with the assistance of the child's guardian. The evaluation method was as follows: the efficacy was evaluated according to the difference of DHI score and VAS-QLV before and after training. The improvement of moderate and severe disorder to mild disorder was considered effective. The VAS-A score was used to evaluate the acceptance of the training programs in Group A and Group B. The acceptance rate and the completion rate were assessed after treatment in both groups.

2.4. Statistical analysis

SPSS Statistics 21 software was used for statistical analysis according to a block randomized controlled design. For CP values, DHI scores, and VAS-QLV scores, two-way ANOVA was used between the overall groups, different time points and the interaction between time and group. ANOVA was used for the overall comparison between the three groups at the same time point, LSD method was used for the comparison between the two groups, and paired t-test was used for the before and after comparison of the same group. Pearson correlation analysis was used between age and VAS-A correlation analysis. Statistical significance was set at $P < 0.05$.

3. Results

There were 10 children in group A, group B and group C, the male to female ratio was 1:1:1, the minimum age was 4 years, the maximum age was 13 years, the average age of each group was 9.0 ± 3.2, 8.4 ± 3.0, 8.3 ± 2.6, respectively.

The frequency of attacks in all patients ranged from 2 to 3 times per week to 7 to 8 times per day in the month before their visit. The duration of the chief complaint of all the children was counted. The duration of the chief complaint was defined as the duration from the first onset of vertigo to the time of diagnosis. Patients can be classified as having a visit within 2 weeks, 3 months, or more than 3 months. The results are shown in the Table 1. The number of DHI and VAS-QLV severity of each group before and after treatment are shown in Table 2. Group A showed 100% efficiency, group B showed 65% efficiency, and group C showed 60% efficiency. The recovery rate on the caloric tests after treatment was 100, 70, and 50% ($P = 0.350$), respectively.

The results of CP are shown in Tables 3, 4.

The results of two-way ANOVA showed that there was no statistically significant difference between the overall groups ($P > 0.05$), there was a statistically significant difference between

different time points ($P < 0.05$), and the interaction between time and group was not statistically significant ($P > 0.05$).

The comparison of treatment effect showed that CP values did not have a statistically significant difference ($P = 0.498$). The before and after CP values were 35.7 ± 15.1 and 12.9 ± 8.1 in Group A, 33.6 ± 20.1 and 23.6 ± 19.3 in Group B, and 38.6 ± 21.1 and 24.8 ± 17.9 in Group C ($P = 0.001$, $P = 0.015$, and $P = 0.050$, respectively).

The results of DHI are shown in Tables 5, 6.

TABLE 1 Duration of chief complaint.

	N1	N2	N3
Group A	3	4	3
Group B	4	3	3
Group C	4	3	3

The duration of the chief complaint: the duration from the first onset of vertigo to the time of diagnosis. N1, the number of children who complained within 2 weeks; N2, the number of children who complained within 3 months; N3, the number of children who complained over 3 months.

The results of two-way ANOVA showed that there was no statistically significant difference between the overall groups ($P > 0.05$), there was a statistically significant difference between different time points ($P < 0.05$), and the interaction between time and group was not statistically significant ($P > 0.05$).

The before and after treatment scores on the DHI were 56.8 ± 12.4 and 8.8 ± 6.1 in Group A, 57.8 ± 12.6 and 18.8 ± 9.7 in Group B, and 56.8 ± 12.4 and 24.0 ± 15.3 in Group C, demonstrating a significant improvement in all groups (all $P < 0.001$). The comparison of treatment effect showed that DHI scores differed significantly between groups ($P = 0.017$). After training, the DHI in Group A decreased significantly compared with Group C ($P < 0.05$).

The results of VAS-QLV are shown in Tables 7, 8.

The above results of two-way ANOVA showed that there was no statistically significant difference between the overall groups ($P > 0.05$), there was a statistically significant difference between different time points ($P < 0.05$), and the interaction between time and group was a statistically significant difference ($P < 0.05$).

TABLE 2 The scores of DHI and VAS-QLV severity before and after treatment.

		Group A (*n*)		Group B (*n*)		Group C (*n*)	
		Pre-treatment	After-treatment	Pre-treatment	After-treatment	Pre-treatment	After-treatment
DHI	Mild	0	10	0	7	0	6
	Moderate	7	0	7	3	7	4
	Severe	3	0	3	0	3	0
VAS-QLV	Mild	0	10	0	6	0	6
	Moderate	2	0	2	4	2	4
	Severe	8	0	8	0	8	0

TABLE 3 Results of two-way ANOVA of CP.

Source	Type III sum of squares	df	Mean square	*F*	*P*	η
Group	552.400	2.000	276.200	1.044	0.359	0.037
time	6,000.001	1.000	6,000.001	22.683	<0.001	0.296
Group*time	289.200	2.000	144.600	0.547	0.582	0.020

TABLE 4 Comparison of CP between and within groups before and after treatment.

Group	CP-pre	CP-post	CP-difference	Paired *t*-test	*P*
A	35.7 ± 15.1	12.9 ± 8.1	22.8 ± 15.2	4.752	0.001
B	40.3 ± 19.9	16.9 ± 11.4	23.4 ± 24.7	2.995	0.015
C	38.6 ± 21.1	24.8 ± 17.9	13.8 ± 19.3	2.264	0.050
F	0.152	2.129	0.716		
P	0.860	0.139	0.498		

TABLE 5 Results of two-way ANOVA of DHI.

Source	Type III sum of squares	df	Mean square	*F*	*P*	η
Group	616.133	2.000	308.067	2.221	0.118	0.076
time	23,920.067	1.000	23,920.067	172.454	<0.001	0.762
Group*time	584.133	2.000	292.067	2.106	0.132	0.072

TABLE 6 Comparison of DHI between and within groups before and after treatment.

Group	DHI-pre	DHI-post	DHI-difference	Paired *t*-test	*P*
A	56.8 ± 12.4	8.8 ± 6.1*	48.0 ± 9.3*	16.347	<0.001
B	57.8 ± 12.6	18.8 ± 9.7	39.0 ± 10.4	11.831	<0.001
C	56.8 ± 12.4	24.0 ± 15.3	32.8 ± 13.3	7.814	<0.001
F	0.021	4.896	4.723		
P	0.979	0.015	0.017		

*Indicates a statistically significant difference from group C ($P < 0.05$).

TABLE 7 Results of two-way ANOVA of VAS-QLV.

Source	Type III sum of squares	df	Mean square	*F*	*P*	η
Group	1.900	2.000	0.950	0.481	0.621	0.017
time	340.817	1.000	340.817	172.485	<0.001	0.762
Group*time	25.433	2.000	12.717	6.436	0.003	0.192

TABLE 8 Comparison of VAS-QLV between and within groups before and after treatment.

Group	VAS-QLV-pre	VAS-QLV-post	VAS-QLV-difference	Paired *t*-test	*P*
A	7.5 ± 1.0	0.9 ± 0.9*&	6.6 ± 1.4*&	15.461	<0.001
B	6.4 ± 2.2	2.7 ± 1.1	3.7 ± 2.4	4.959	0.001
C	6.6 ± 1.6	2.6 ± 1.4	4.0 ± 2.3	5.477	<0.001
F	1.265	8.272	5.997		
P	0.299	0.002	0.007		

*Indicates a statistically significant difference from group C ($P < 0.05$).
&Indicates a statistically significant difference from group B ($P < 0.05$).

The before and after treatment scores on the VAS-QLV were 7.5 ± 1.0 and 0.9 ± 0.9 in Group A, 6.4 ± 2.2 and 2.7 ± 1.1 in Group B, and 6.6 ± 1.6 and 2.6 ± 1.4 in Group C, demonstrating a significant improvement in all groups ($P < 0.001$, $P = 0.001$, and $P < 0.001$, respectively). The comparison of treatment effect showed that VAS-QLV scores differed significantly between groups ($P = 0.007$). After training, the VAS-QLV in Group A decreased significantly compared with Group B and C ($P < 0.05$).

The results of VAS-A are shown in Tables 9, 10.

In terms of acceptance, the VAS-A score was 7.6 ± 2.2 in Group A and 3.1 ± 2.8 in Group B ($P = 0.004$), The acceptance rate was 70% in group A and 10% in group B.

The relationship between the age and acceptance is shown in Figure 1. The results of Pearson correlation analysis showed that there was no significant correlation between age and VAS-A in either group A or group B ($P > 0.05$).

4. Discussion

Treatment measures are gradually improving with an increased focus on vertigo in children and improvements in diagnosis. The American physical therapy association neurology section published an Evidence-Based Clinical Practice Guideline of Vestibular Rehabilitation for Peripheral Vestibular Hypofunction. Clinicians should offer vestibular rehabilitation to patients with chronic unilateral vestibular hypofunction (Evidence quality: I; recommendation strength: strong) (4).

TABLE 9 The correlation between acceptance ratio and VAS-A severity.

	VAS-A severity (*n*)			Acceptance
	Poor	General	Good	Ratio (%)
Group A	0	3	7	70%
Group B	8	1	1	10%

VAS-A severity, scores of VAS-A severity.

TABLE 10 The analysis of correlation between age and VAS-A.

Index	Statistic	A_Age	B_Age
A_VAS-A	*R*	−0.356	–
	P	0.312	–
B_VAS-A	*r*	–	0.362
	P	–	0.304

In addition to treating the symptoms, vestibular rehabilitation training is increasingly recommended as a treatment for children (16). However, its clinical application has limitations; the adopted training scheme and effect of training need to be further explored. The Cawthorne-Cooksey approach is one of several exercise programs that can be used in the treatment of unilateral vestibular hypofunction (7). However, many patients do not follow an exercise program for chronic dizziness. Many factors underlie this situation, such as the discomfort of emerging dizziness while exercising, an inability to devote time to exercise in one's daily life, a lack of enjoyment of exercise, and a lack of understanding regarding how exercises can correct dizziness (8). Because children's compliance and endurance are worse than adults, its applicability is worse in pediatric patients. therefore, the therapeutic purpose is not reached.

In this study, children aged 4–13 with RVC with unilateral peripheral vestibular dysfunction and normal balance function were treated with vestibular rehabilitation. According to the characteristics of moderate to severe impairment and repeated attacks of recurrent vertigo in children, we focus on the core of vestibular rehabilitation; adaptation training, especially VOR training (17), simplified the original training program, increased the frequency of reinforcement for a single training method, significantly improved applicability and completion, and enhanced the treatment efficiency. In order to enable children to better complete the training, Rine et al. (18) and Braswell and Rine (19) increased the difficulty level by 80% according to age. Nevertheless, for fixation stability training, children often fail to understand the meaning of shaking

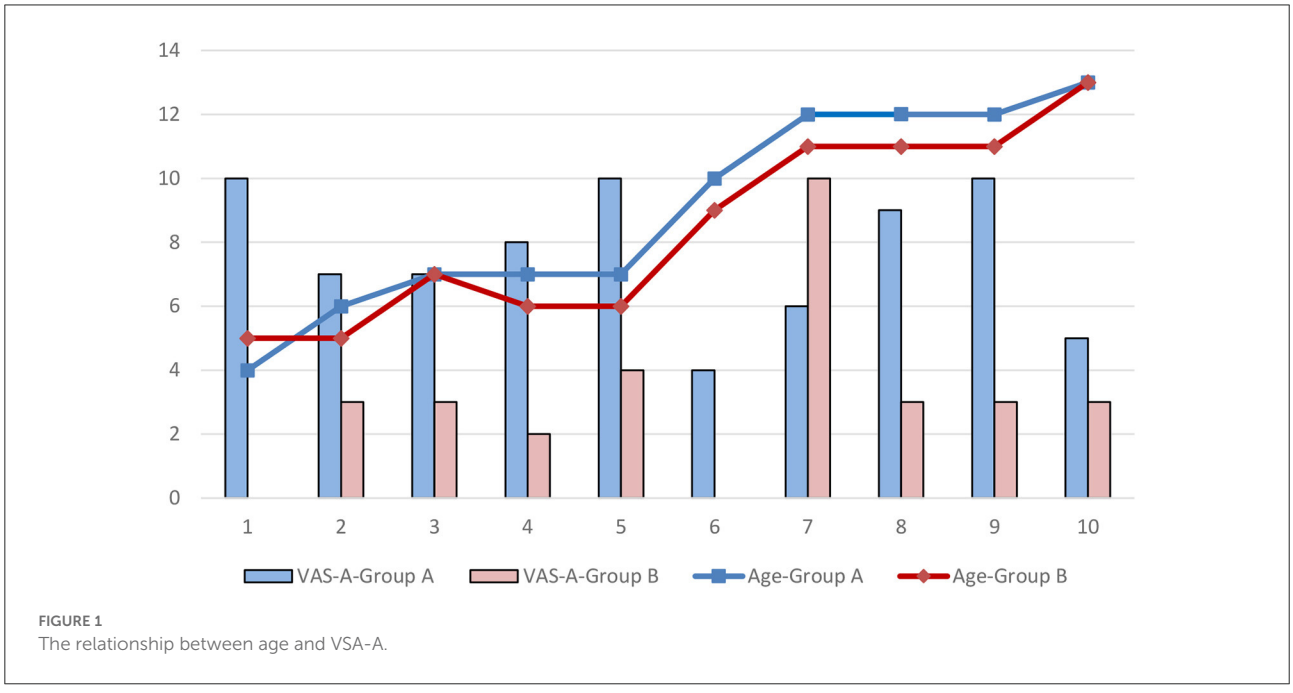

FIGURE 1
The relationship between age and VSA-A.

their heads quickly while keeping the target clear (16). The training procedure was filmed into a video that could guide the movements of the children. The video suggested the angle and speed of head turning and eye rotation, which was completed under the supervision of a guardian. The results of the study showed that Group A, the single-item intensive VOR adaptation training group, took 5 min each time to watch the guidance video, and the acceptance rate was 70%, which was significantly better than the 10% acceptance rate of Group B, the Cawthorne-Cooksey training group. The completion rate of Group A was 100% for a single training session per day and 30% for three training sessions per day, which was slightly insufficient, but the recovery rate of the caloric test and the marked effective rate were both 100%. This also suggests that we need to study the frequency and duration of training further to attain the best training routine. The training time of Group B was 20 min each time, the completion rate of a single session per day was 60%, the completion rate of three sessions per day was 10%, and the marked effective rate was 70%. During the return visit, it was found that the reason for not being able to complete the training well was the psychological resistance of children or parents caused by the long training time, thinking that training is a very complicated thing. This single-strength training is not only highly targeted but suitable for children and the coordination of short training is greatly improved.

In order to eliminate the influence of age and vertigo severity on the therapeutic effect, a block randomized controlled design was used for this study. The CP value in the caloric test represents the decreased value of the unilateral semicircular canal function, which is a quantitative assessment of the VOR function of the external semicircular canal (20, 21). The caloric test was conducted on all children, the results and CP values were recorded, and the training effect was objectively and quantitatively evaluated. For unilateral and bilateral vestibular dysfunction, DHI can sensitively reflect the effect of vestibular rehabilitation training (22). The DHI questionnaire was used to evaluate the subjective perception of vertigo symptoms in children (23, 24), and the VAS-QLV score was used to evaluate the impact of vertigo attacks on children's daily life and learning behavior. This confirmed the effectiveness of the training program from another dimension. In our study, the results showed that for such children, the VOR adaptation training, the Cawthorne-Cooksey training, and oral medication alone could improve the children's symptoms. The CP values decreased obviously after treatment of 1 month, which established statistically significant differences before and after treatment. Therefore, CP is significant from the perspective of treatment time. However, there are no significant differences between the interaction and post-intervention groups. Therefore, it can be assumed that spontaneous recovery after the onset of vertigo has occurred. Several different mechanisms are involved in the recovery of function following unilateral vestibular loss. These mechanisms include cellular recovery, spontaneous re-establishment of the tonic firing rate centrally, adaptation of residual vestibular function, the substitution of alternative strategies for the loss of vestibular function, and habituation of unpleasant sensations. Vestibular rehabilitation treatment should begin as early as possible, since there is evidence that early intervention with vestibular exercises facilitates a decrease in symptoms and improves gait stability compared with no exercises in patients with unilateral vestibular loss (25). In our study, intervention in 70% of cases occurred within 3 months. The spontaneous recovery may be due to vestibular compensation during the acute phase after the onset of vertigo. This may be related with the fact that the main outcome of DHI showed no interaction. Moreover, the suboutcome of VAS-QLV shows an interaction and a simple main effect after the intervention. Regarding this result, we believe that the intervention in this study is effective in improving subjective symptoms of vertigo. After training, the VAS-QLV in Group A decreased significantly compared with Group B and C. Compared with the classical Cawthorne-Cooksey program, the simple and targeted VOR adaptation training has the highest symptom alleviation efficiency, and the impact on life and learning behavior is improved more significantly, thus highlighting the advantages of the VOR adaptation training. Certainly, we will continue to follow up the patients to study the effect of each group's training regimen on the long-term vertigo alleviation efficacy in children.

The age applicability of this VOR adaptation training design is also high. The minimum age of the children in this study was 4 years, and the maximum was 13 years. Not only has it been confirmed that rehabilitation training for children with recurrent vertigo can provide a good effect, but also that rehabilitation training for young children has been conducted. Among them, the youngest was a 4-year-old child who completed the training in full accordance with the training approach, frequency, and sessions. Our study showed that the acceptance of rehabilitation training was not significantly related to age. It should be noted that pediatric patients still need to be trained under the guidance of the guardian, which also means that the guardian's compliance with treatment needs to be improved to complete the training and achieve its purpose.

5. Conclusions

For children with recurrent vertigo with unilateral vestibular dysfunction but normal balance function, single strengthening of VOR adaptation training can effectively improve vertigo symptoms, which is feasible and highly acceptable. However, the training frequency, duration, and long-term efficacy should be further discussed.

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 Medical Ethics Committee, Beijing Children's Hospital, Capital Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

NM contributed to the conception of the study. NM, HL, BLiu, LZ, BLi, YY, WL, MC, JS, and XZ performed the experiment. NM and JZ contributed significantly to analysis and manuscript preparation. NM, HL, and JZ performed the data analyses and wrote the manuscript. NM, XN, and JZ helped perform the analysis with constructive discussions. 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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EDITED BY
Widdershoven Josine,
Maastricht University Medical Centre, Netherlands

REVIEWED BY
Ruben Hermann,
Hospices Civils de Lyon, France
Kristen Leigh Janky,
Boys Town, United States
Eugen Constant Ionescu,
Hospices Civils de Lyon, France

*CORRESPONDENCE
Emile Monin
✉ emile.monin@bluewin.ch

†These authors have contributed equally to this work and share last authorship

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Development of a new clinical tool to evaluate the balance abilities of children with bilateral vestibular loss: The Geneva Balance Test

Emile Monin*, Céline Bahim, Lou Baussand, Jean-François Cugnot, Maurizio Ranieri, Nils Guinand, Angélica Pérez Fornos† and Hélène Cao Van†

Division of Otorhinolaryngology (ORL) Head and Neck Surgery Institute, Clinical Neurosciences Department, University Hospital of Geneva (HUG), Geneva, Switzerland

Introduction: Vestibular deficits are considered rare in children, but the lack of systematic screening leads to underdiagnosis. It has been demonstrated that chronic vestibular dysfunction impacts the normal psychomotor development of children. Early identification is needed to allow for clinical management, ensuring better global development. For this purpose, our research group has developed the Geneva Balance Test (GBT), aiming to objectively quantify the balance capacity of children over a broad age range, to screen for bilateral vestibulopathy (BV), and to quantify the improvement of balance abilities in children.

Methods: To determine the capacity of the GBT to quantify the balance capacity of children with BV, we conducted an observational prospective study with three populations: 11 children with BV, and two age-matched control groups composed of (1) 15 healthy subjects without the vestibular or auditory disorder (HS) and (2) 11 pediatric cochlear implant recipients (CIs) without vestibular disorders. Results of the three populations have been compared in three different age sub- groups (3–5, 6–9, and ≥10 years), and with results of a short, modified version of the Bruininks-Oseretsky test of Motor proficiency Ed. 2 (mBOT-2).

Results: Statistical analyses demonstrated significant differences in the scores of the GBT between children aged 3–5, 6–9, and ≥10 years with BV and in both control populations (HS and CI). BV scores reflected poorer balance capacities at all ages. Children in the youngest CI sub-group (3–5 years) showed intermediate GBT scores but reached HS scores at 6–9 years, reflecting an improvement in their balance capacities. All the results of the GBT were significantly correlated with mBOT-2 results, although only a few BV completed the entire mBOT-2.

Discussion: In this study, the GBT allowed quantifying balance deficits in children with BV. The BOT-2 test is not validated for children <4.5 years of age, and the GBT seems to be better tolerated in all populations than the mBOT-2. Furthermore, mBOT-2 results saturated, reaching maximum values by 6–9 years whereas the GBT did not, suggesting that the GBT could be a useful tool for monitoring the development of balance capacities with age and could be used in the follow-up of children with severe vestibular disorders.

KEYWORDS

balance, children, vestibulopathy, cochlear implant, test, GBT

1. Introduction

Dizziness, vertigo, and imbalance are frequent complaints in the adult population, and it is estimated that up to 30% of adults will present these symptoms at least once (1). However, these symptoms appear less common in the pediatric population, where current estimates suggest that 8% of children have presented dizziness (2). Nevertheless, systematic screening, even in

the presence of symptoms, is rarely included in current clinical procedures. Consequently, the exact incidence of chronic vestibular disorders in the pediatric population and their impact on development remain unknown.

The few currently available studies show that in the pediatric population, transient dizziness is often benign, but chronic or progressive balance disorders of vestibular origin have a real impact on the psychomotor development of children (3). Moreover, mixed vestibulo-cochlear disorders are frequent, and more than a third of children with profound sensorineural deafness have vestibular disorders (4). This precise population endures a double sensory deficit, which means it is particularly at risk for developmental delays. To ensure better overall clinical management, potential vestibular disorders should be actively screened in children with hearing impairments, who are particularly at risk (5).

In the clinical field, semicircular canal and otolith function are evaluated using assessments of the vestibulo-ocular reflex and vestibular myogenic potentials. Although massively used, these tests only assess the function of single sub-units of the vestibular system independently. This does not completely represent the impact of vestibular impairments on the global balance function and/or the patient's ability to adapt to the vestibular deficit. Thus, no correlation has been established between the subjective symptoms of patients assessed with the Dizziness Handicap Inventory and their vestibular function tested by vHIT, caloric testing, o/cVEMP, or posturography (6). Interestingly, rotational testing seems to be most amenable in young children and best correlated with balance function. In addition, a moderate correlation has been found between the vestibulo-ocular reflex gain on the rotatory chair test and the results of the Bruininks-Oseretsky test of Motor proficiency Ed. 2 (BOT-2), which is the most widely used test for assessing balance in the pediatric population (4).

Although the above-mentioned diagnostic tests are easily performed in adults, they are restrictive and not always feasible in children. Consequently, children with balance disorders are often assessed using a global clinical evaluation, not always including objective measures of balance or vestibular function. In this context, the BOT-2 was demonstrated to be a sensitive and specific tool to screen for children with bilateral vestibulopathy (BV) (7). However, this test has only been validated for children aged between 4.5 and 12 years. A literature review found only a few other clinical tests evaluating the balance capacities of children. The Ghent Developmental Balance Test seems to be a useful tool for this purpose but is only validated until 5 years of age (8). A clinical tool, evaluating balance capacities over a broad age range, is lacking and could be useful in the identification of children with severe vestibular dysfunction and their follow-up.

In this context, our group has developed a new clinical test: the Geneva Balance Test (GBT) that integrated a playful dimension that can be easily accepted by young children, as soon as they can walk. Our main goal in designing the GBT was to create a test that could objectively measure balance capacities. This way, this test could be used as a screening test for severe vestibular dysfunction in children, such as BV, and could be used during follow-up to assess the evolution of balance abilities with age.

The hypotheses of this study are the following:

1. Children with BV should obtain significantly poorer scores at the GBT when compared to children in control groups.
2. The GBT and the mBOT-2 results should be in agreement in all tested subjects.
3. GBT scores should improve with age, providing useful information about the development of balance.

2. Method

2.1. Design and participants

The main objective of this study is to assess the ability of the GBT to quantify the balance capacity of children with BV compared and an age-matched population without vestibular dysfunction. To achieve this, an observational study was designed including a case and two control populations:

- Children with BV diagnosed following the Bárány consensus criteria (9) constituted the case population. They presented mixed vestibulo-cochlear disorders and were therefore cochlear implant or hearing aid users.
- A group of healthy subjects (HS) with no vestibular dysfunction and no hearing impairment constituted the first control group.
- A group of children with cochlear implant(s) (CI) without vestibular dysfunction constituted the second control group to exclude any involvement of hearing impairments and/or the cochlear implant in balance abilities.

A total of 37 children were included in the study: 15 HS, 11 BV, and 11 CI without vestibular disorders (see detailed demographic characteristics in Table 1). The children included were aged between 3 and 16 years and, due to the normal psychomotor development of children (11), we separated the three populations into three different age sub-groups. The youngest sub-group (for which the BOT-2 is not validated) was composed of 5 BV, 4 CI, and 5 HS who were 3–5 years of age. The second age sub-group included 3 BV, 2 CI, and 4 HS who were 6–9 years of age. The oldest sub-group included 3 BV, 5 CI, and 6 HS who were $\geq$10 years of age.

Comparing the results of the GBT gathered with the three above-mentioned populations should reveal the capacity of the test to quantify the balance abilities of children during walking. These results were then compared to their results on the mBOT-2. Additional analyses in which children were clustered in different age sub-groups further assessed the capacity of the test to evaluate the psychomotor development of balance abilities in children.

Note that in Switzerland, CI users are implanted following the guidelines of the workgroup for cochlear implantation of the Swiss ENT society (12). All subjects included in the study were "experienced" CI users, with a period of use of 1–14 years post-implantation. Children wearing external hearing aid(s) had been using the device(s) as soon as possible following the diagnosis of deafness.

2.2. Setting

Given the limited existing literature concerning children with BV, a prospective observational exploratory study was conducted to verify the hypotheses detailed earlier. This study was designed

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TABLE 1 Demographic characteristics of the participants included in the study.

Study group	Age [years] at data collection	Biological gender	Hearing status *R*	Hearing status *L*	Etiologies
BV 3–5 ans	5	Female	CI	CI	Waardenburg II
BV 3–5 ans	5	Male	CI	CI	Idiopathic
BV 3–5 ans	3	Male	CI	CI	CHARGE
BV 3–5 ans	4	Female	CI	CI	CMV
BV 3–5 ans	4	Male	Ext. hearing aid	Ext. hearing aid	CMV
BV 6–9 ans	7	Female	CI	CI	Idiopathic
BV 6–9 ans	6	Female	CI	CI	Usher
BV 6–9 ans	9	Female	Ext. hearing aid	Ext. hearing aid	CHARGE
BV ≥10 ans	10	Male	Ext. hearing aid	Ext. hearing aid	CHARGE
BV ≥10 ans	10	Male	CI	CI	Idiopathic
BV ≥10 ans	15	Male	CI	CI	Idiopathic
IC 3–5 ans	4	Female	CI	CI	Prematurity
IC 3–5 ans	3	Female	CI	CI	Usher
IC 3–5 ans	5	Male	CI	CI	CMV
IC 3–5 ans	4	Male	CI	CI	Idiopathic
IC 6–9 ans	8	Male	CI	CI	Idiopathic
IC 6–9 ans	8	Female	CI	CI	Idiopathic
IC ≥ 10 ans	10	Female	CI	CI	Prematurity
IC ≥ 10 ans	10	Male	CI	CI	Idiopathic
IC ≥ 10 ans	14	Male	CI	Ext. hearing aid	Congenital
IC ≥ 10 ans	17	Female	Ext. hearing aid	CI	Idiopathic
IC ≥ 10 ans	11	Male	CI	Ext. hearing aid	CMV
HS 3–5 ans	5	Male	-	-	-
HS 3–5 ans	5	Male	-	-	-
HS 3–5 ans	4	Male	-	-	-
HS 3–5 ans	4	Female	-	-	-
HS 3–5 ans	3	Male	-	-	-
HS 6–9 ans	7	Male	-	-	-
HS 6–9 ans	6	Female	-	-	-
HS 6–9 ans	9	Female	-	-	-
HS 6–9 ans	9	Male	-	-	-
HS ≥ 10 ans	12	Female	-	-	-
HS ≥ 10 ans	11	Female	-	-	-
HS ≥ 10 ans	16	Female	-	-	-
HS ≥ 10 ans	15	Female	-	-	-
HS ≥ 10 ans	10	Male	-	-	-

BV in blue, CI in orange, and HS in gray, from lightest to darkest 3–5, 6–9, and ≥10 years.

TABLE 2 Inclusion and exclusion criteria for the study participants.

General inclusion criteria: - Ability to walk independently [from 17 months on average (11)].
Inclusion criteria for children with BV: - BV diagnosed according to the diagnostic criteria of the Bárány Society (9).
Inclusion criteria for the CI control group: - Bilateral or unilateral CI user. - Normal vestibular function documented with the vHIT test (post-implantation; gain $\geq$ 0.7 for horizontal semi-circular canals). - Age-matched to BV group.
Inclusion criteria for healthy controls HS): - Voice acoumetry within the norm (whispered voice understood on both ears). - vHIT $\geq$ 0,8 gain for horizontal semi-circular canals, both sides. - Age-matched to BV group.
Exclusion criteria: - Physical or cognitive disability that prevents understanding or performing the tasks required. - Refusal of the participant or of one of his/her representatives to participate in the study. - Non-compliance with inclusion criteria.

in compliance with the guiding criteria for reporting observational studies (STROBE) (10).

The study took place at the Division of ORL and Head-and-Neck Surgery of the Geneva University Hospitals (HUG), from November 2020 to July 2021. Patient recruitment took place in May 2021. The data were collected from May 2021 to June 2021. Data analysis took place from June to July 2021.

2.3. Recruitment

The inclusion and exclusion criteria for the study are presented in Table 2. Children diagnosed with BV using the vHIT and/or the caloric test were identified using the clinical databases of the Division of ORL and Head-and-Neck Surgery of the Geneva University Hospitals. Confirmation of BV in these patients according to the diagnostic criteria of the Bárány Society (9) was done at the time of recruitment that took place during the clinical follow-up visits of patients. A total of 13 children were identified in the clinical databases, but two of them were not included since they could not come to the clinic during the study period (between May and July 2021). The pediatric CI users included in this study were selected to be age-matched with BV children. A total of 12 CI were identified as age-matched and meeting the inclusion criteria (see Table 2). One CI subject had to be excluded during the recruitment phase due to a pathological result on the vHIT for one lateral canal. The group of healthy control subjects (HS) was recruited from the outpatient clinic of the Division of ORL and Head-and-Neck Surgery of the Geneva University Hospitals. The HS group was selected to be age-matched to the included BV or CI group and was included in the study after excluding a vestibular disorder by vHIT and a hearing disorder by voice acoumetry.

One subject in the CI group was excluded because of a lack of compliance (the child did not want to perform the GBT or any of the mBOT-2 tasks). Figure 1 below summarizes the recruitment process.

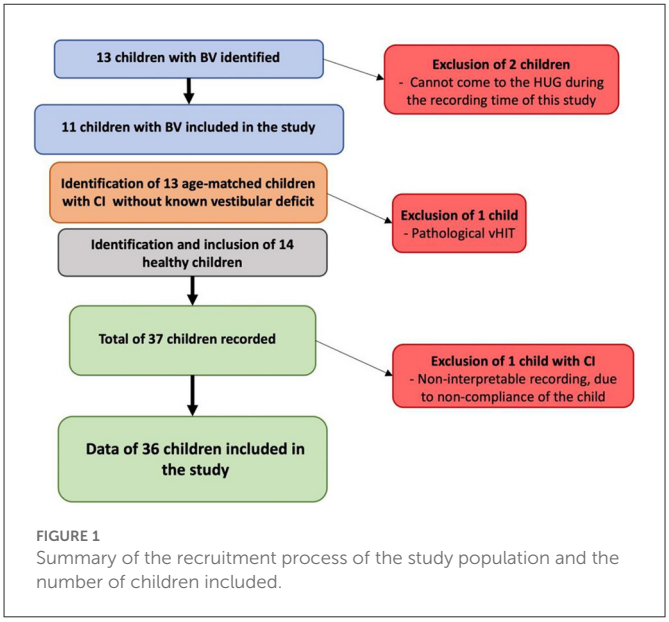


FIGURE 1
Summary of the recruitment process of the study population and the number of children included.

2.4. Study procedures

After giving oral information to the parents and collecting oral consent, the children underwent the GBT and the mBOT-2 for ~30 min (5 min for the oral consent, 10 min for the GBT, and 15 min for the mBOT-2). Written information and consent forms were provided and gathered from the parents after study completion for scientific purposes. The procedure, the information forms, and the consent forms have been approved by the Cantonal research ethics commission in Geneva (CCER 2022-00034). None of the participants have been rewarded for their participation, and consent was provided freely.

The GBT was designed to be adapted to children over a broad age range (ideally as soon as they can walk, up to any age), to be cost-effective, and rapidly performable in children. The aim was to isolate the vestibular function from other senses contributing to the balance function (proprioception and vision). To reduce the contribution of proprioception, the tested subject was asked to walk in the middle of a 6 m*1 m*2 cm foam mat, at a normal walking pace (always with one foot on the ground) in bright light conditions (BL; 45–70 lx), provided by ceiling lights. Then, to reduce the contribution of vision, the same test was performed again in dim light conditions (DL) provided by two punctual lights (KORNSNÖ® LED night light, IKEA, Älmhult, Sweden) on both walls. Red LED biking bracelets (STOKE®, Ochsner Sport, Dietikon, Switzerland) were worn by participants on both wrists and both ankles (maximum luminosity 3 lx) to permit visualization of the feet and hands of each participant in DL.

Each test condition was repeated three times and recorded. A camera placed 1 m in front of the mat recorded the entire evaluation. The recorded videos were then superimposed using the iMovie application version 10.2.2.7 (Apple Inc., Cupertino, United States of

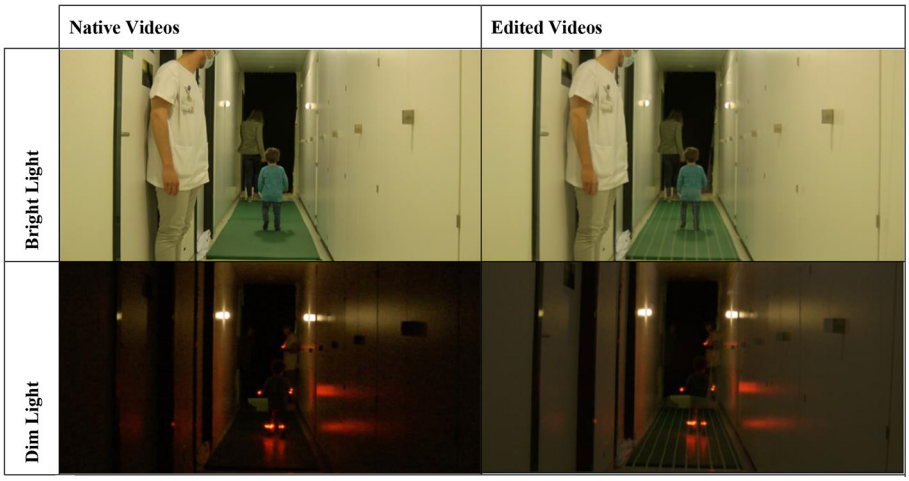


FIGURE 2
Illustration of the two conditions of the test: bright light—BL **(upper panels)** and dim light—DL **(lower panels)**, before video editing **(left panels)** and after video editing **(right panels)**.

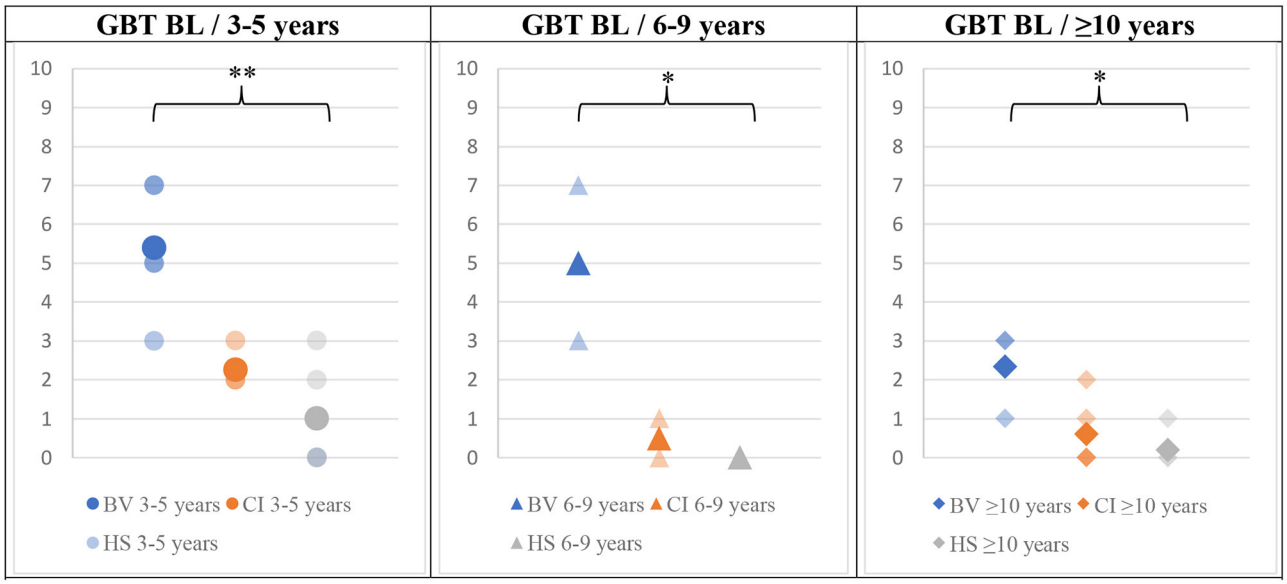


FIGURE 3
Means (solid symbols) and individual results (semi-transparent symbols) of the GBT in the BL condition, for the three age sub-groups, from left to the right; 3–5/6–9/≥10 years old. *$p < 0.017$/**$p < 0.004$ (with Bonferroni correction).

America) with a reference image showing the same mat with lines spaced 10 cm apart. Once the video and the reference image were superimposed, the transparency of the videos was adjusted to permit a better view of the lines and the subject. The alignment of the two videos could be controlled with the superposition of the two punctual night lights on both walls of the corridor. It was thus possible to measure the deviation to the midline during each walking trial frame by frame, for each subject (Figure 2). The scoring below was used to quantify the deviation in each condition.

0: The subject walks in a straight line, staying in the two central lanes.
1: The subject steps once into the 1st lateral lane.
2: The subject takes several steps in the 1st lateral lane.
3: The subject steps once into the 2nd lateral lane.
4: The subject takes several steps in the 2nd lateral lane.
5: The subject steps once into the 3rd lateral lane.
6: The subject takes several steps in the 3rd lateral lane.
7: The subject steps once into the 4th lateral lane.
8: The subject takes several steps in the 4th lateral lane.
9: The subject uses the walls for support.

The points scored in the right and left lateral lanes were cumulative, for a maximum score of 18 pts if the subject went from one wall to the other.

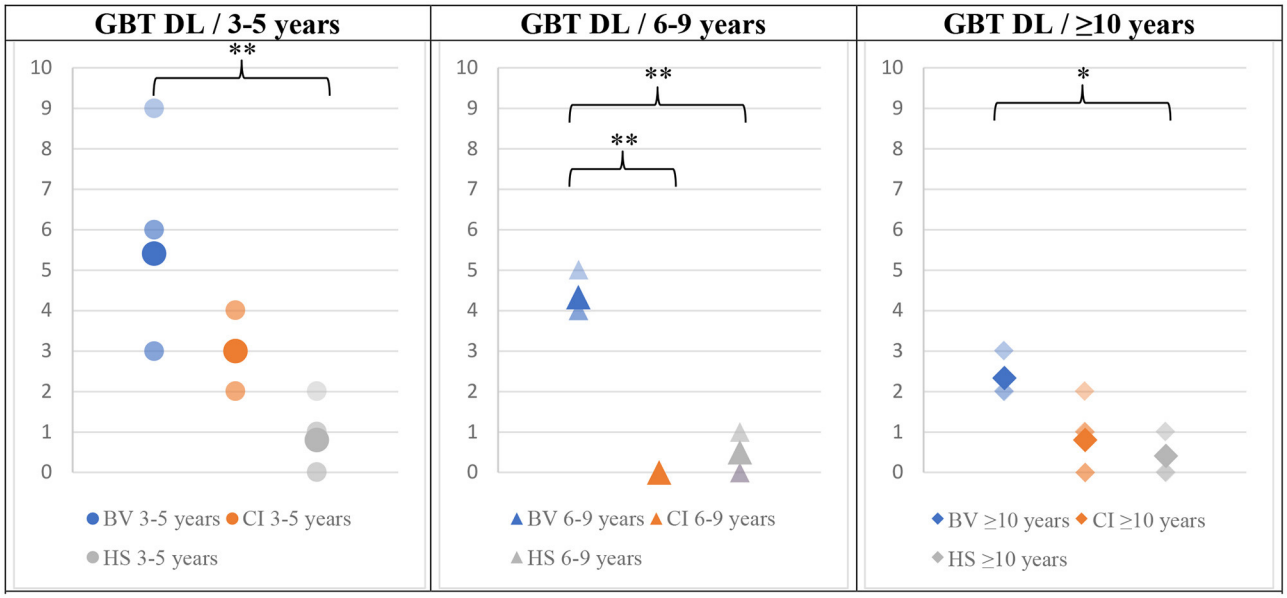
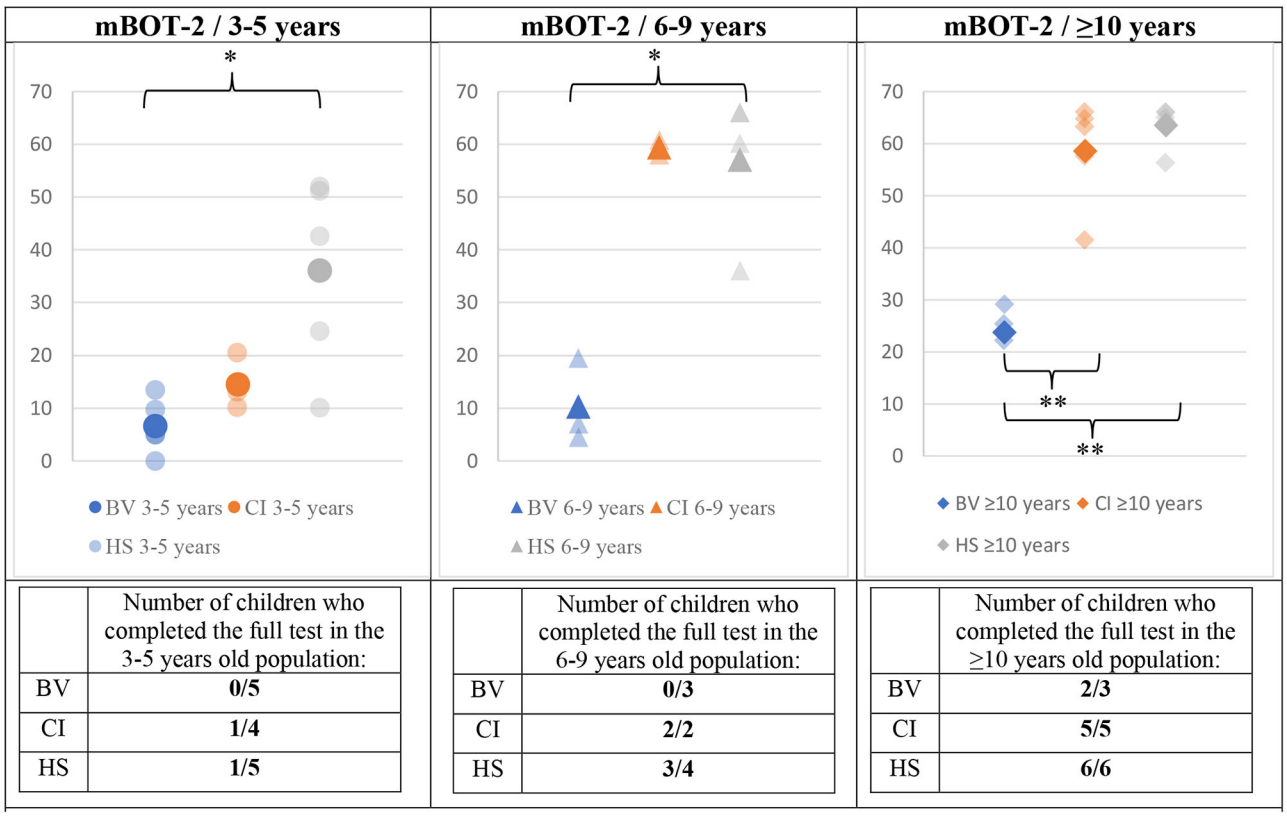


FIGURE 4
Means (solid symbols) and individual results (semi-transparent symbols) of the GBT in DL for the three age sub-groups, from left to right; 3–5/6–9/≥10 years old. *$p < 0.017$/**$p < 0.004$ (with Bonferroni correction).



	Number of children who completed the full test in the 3-5 years old population:
BV	**0/5**
CI	**1/4**
HS	**1/5**

	Number of children who completed the full test in the 6-9 years old population:
BV	**0/3**
CI	**2/2**
HS	**3/4**

	Number of children who completed the full test in the ≥10 years old population:
BV	**2/3**
CI	**5/5**
HS	**6/6**

FIGURE 5
Means (solid symbols) and individual results (semi-transparent symbols) of the BOT2 for the three age sub-groups, from left to right; 3–5/6–9/≥10 years old. The number of children who completed the test (if a task of the test is refused by the subject, a score of 0 is given for that task) is presented in a table below each panel. *$p < 0.017$/**$p < 0.004$ (with Bonferroni correction).

Note that, for this test, a score of 0 would be representative of perfect balance abilities in a given condition, while higher scores represent worse balance control. Only the run with the best score of the three (i.e., the lowest score) was considered for the BL and DL conditions. The scoring task took ∼15 min per subject.

2.5. Modified Bruininks-Oseretsky test of Motor proficiency Ed. 2 (mBOT-2)

Participants performed a short, modified version of the balance subtest of the BOT-2 after the GBT. We used a modified version of the BOT-2 as our objective was to perform a short test, bearable for the youngest children (max 30 min overall). The mBOT-2 consists of five out of the six tasks standardly done on the firm ground of the BOT-2, with the repetition on both sides of the one-leg stance [walking on a line feet apart has been excluded of the mBOT-2 as the least sensitive and specific task following Oyewumi (7)]. We did not perform the tasks on the balance beam, as tasks on the firm ground were already unachievable for most of our case subjects. We analyzed the raw results of the following different tasks:

1. Standing on a line with heel to toes (tandem stance), eyes open (9).
2. Standing on a line with heel to toes (tandem stance), eyes closed (9).
3. Standing on one leg, eyes open (9).
4. Standing on one leg, eyes closed (9).
5. Standing on the second leg, eyes open (9).
6. Standing on the second leg, eyes closed (9).
7. Walking forward on a line, heel to toes (tandem walking) (6).

The score for static tasks is calculated by timing the maximum hold time of the required positions. The dynamic test is scored according to the number of steps that the subject can take over the line without deviating. The maximum score for the static tasks is 10 s per task and the maximum score for the dynamic task is six steps, for a total maximal score of 66 points. Therefore, low mBOT-2 scores would be presented in the case of balance problems, and a high mBOT-2 score would be characteristic of good balance skills (i.e., the higher the score, the better the balance skills). All participants had up to two attempts to do the perfect score for each task. The mBOT-2 was filmed using the same parameters as the GBT. The exact timing and the counting of the steps were done frame by frame using the iMovie application, version 10.2.2.7 (Apple Inc., Cupertino, United States of America).

If a task was not completed by the participant, a score of 0 was given for this particular task. The examiner(s) tried to convince each child to perform the task, by miming the asked position or asking several times to do so. All the tests were done in the presence of a parent to ensure a trusting environment.

2.6. Statistics

Tests of normality according to Kolmogorov–Smirnov, linearity by point clouds, search for outliers by Mahalanobis distances, and multicollinearity analysis by correlation according to Spearman's Rho were carried out first to verify the suitability of parametric statistical analyses. Since these tests were passed, the scores of the GBT and mBOT-2 were compared among the BV, HS, and CI populations grouped per age ranges of 3–5, 6–9, and ≥10 years using one-way multivariate analysis of variance (MANOVA). If a significant difference was found by the MANOVA, an ANOVA with Bonferroni *post-hoc* tests was used only between significant values, to identify the significant differences.

3. Results

The mean GBT scores obtained in BL and DL are presented in Figures 3, 4, respectively. BV presented the highest scores (i.e., worse balance abilities) for all age sub-groups (blue symbols). CI (orange symbols) showed higher scores in the youngest 3–5 years sub-group (left panels in the figures), but their scores became similar to HS's results for the two older age sub-groups (6–9 and ≥10 years; middle and right panels in the figures). The HS (gray symbols) showed low scores of 0–1 (close to perfect balance abilities) across all age sub-groups.

The results of the mBOT-2 tests for all age sub-groups are presented in Figure 5. The BV obtained the worst scores across all age sub-groups. CI obtained intermediate scores for the youngest age. For older age sub-groups, CI obtained close-to-perfect scores that even reached the maximum of 66 points for the majority of subjects. The best scores across age sub-groups were obtained by HS, which also saturated the maximum score for the test for the 6–9 and ≥10 years of age sub-groups. The total number of children being able to complete the test in each group is also an interesting outcome (tables below each panel of Figure 5). The reliability of the results and comparisons of the mBOT-2 scores for the youngest age sub-group of 3–5 years is limited since only two out of the total 14 participants (all groups taken together) were able to complete the test. One of the successful participants was in the CI group and the other one was in the HS group. Thus, most children in the CI and HS groups of 6–9 years of age were able to complete the mBOT-2, obtaining scores near the maximum allowed by the test, while all BV were unable to achieve the requested tasks. Finally, for the ≥10 years of age sub-group, all CI and HS were successful in performing the entire mBOT-2, also obtaining close-to-perfect scores. Two out of three BV subjects could also complete the test but scored much poorer than the other two groups.

The Bonferroni-corrected ($p < 0.017$) MANOVA analysis (validated by preliminary statistical analyses, see Methods section) revealed a statistically significant intergroup difference (Pillai's Trace = 1,56 and $p = 0.03$) for the results of the GBT in both BL and DL conditions and for the mBOT-2. When considering the dependent variables separately, the significant between-subjects effects in the younger age sub-group (3–5 years old) were GBT BL ($p = <0.001$), GBT DL ($p = 0.005$), and mBOT-2 ($p = 0.005$). An ANOVA with a Bonferroni *post-hoc* test was then conducted on these three variables that showed significant intergroup differences to identify exactly between which populations the significance exists. The difference was significant only between BV and HS groups, for all tests (GBT BL $p < 0.001$; GBT DL $p = 0.004$; mBOT-2 $p = 0.006$).

In the 6–9 years sub-groups, a statistically significant intergroup difference was also present for the three tests (Pillai's Trace = 1.817 and $p = 0.0129$). When considering the dependent variables

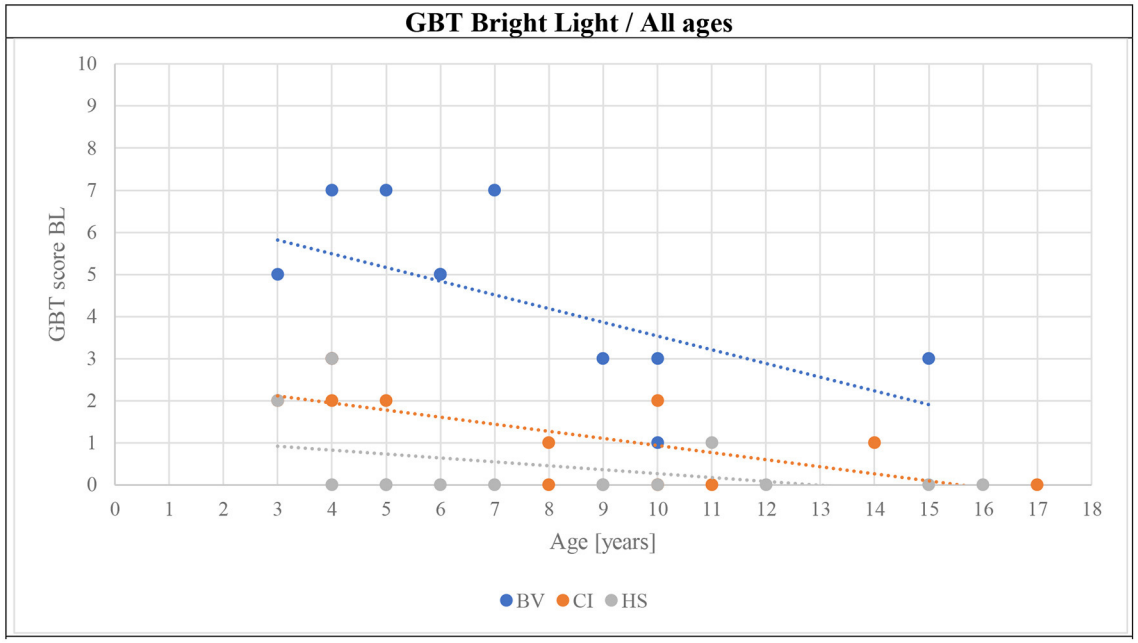


FIGURE 6
Evolution of the GBT scores of all subjects in BL conditions as a function of age (BV, blue symbols; CI, orange symbols; HS, gray symbols).

separately, the significant between-subjects effects in the 6–9 years sub-group were GBT BL ($p = 0.004$), GBT DL ($p = <0.001$), and mBOT-2 ($p = 0.003$). An ANOVA with a Bonferroni *post-hoc* test was then conducted which revealed a significant difference between BV and HS for all conditions (GBT BL $p = 0.005$; GBT DL $p < 0.001$; mBOT-2 $p = 0.005$) and also for the GBT in DL between BV and CI ($p < 0.001$).

The analysis of the results of the ≥10 years of age sub-groups also revealed a statistically significant intergroup difference (Pillai's Trace = 0.876 and $p < 0.001$). When considering the dependent variables separately, the significant between-subjects effects in this age sub-group were GBT BL ($p = 0.007$); GBT DL ($p = 0.004$), and mBOT-2 ($p < 0.001$). An ANOVA with a Bonferroni *post-hoc* test was then conducted which revealed a significant difference between BV and HS in both BL and DL conditions of the GBT test (BL $p = 0.015$; DL $p = 0.009$). The mBOT-2 results were significant between BV and CI ($p < 0.001$) and between BV and HS ($p < 0.001$).

The final hypothesis of this article required the investigation of the evolution of GBT and mBOT-2 scores with age. Figures 6–8 present this comparison. Several observations can be made from these results. First, the scores for the GBT, both in BL and DL, are always higher in BV than in CI and HS groups, at all ages. An improvement in scores with age can be also observed for the three participant groups (BV, CI, and HS), but BV never reaches the performance levels for the other two populations. Interestingly, CI seems to have intermediate scores at young ages, but their scores improve and become comparable to the scores of HS from 7 years old. On the other hand, HS has good scores from the earliest age. Similar observations can be made for mBOT-2 scores: the scores of the BV are poorer than the CI and HS groups, and they remain low even at the oldest ages tested. The youngest CI and HS have low scores that saturate from 5 years. It should be reminded that the BOT-2 is only validated from 4.5 years of age and that only a few children completed the mBOT-2 in the youngest sub-groups.

Finally, a comparison of the GBT in BL and DL and the mBOT-2 results showed a strong correlation between tests [Spearman's Rhô correlation analysis; BL-DL $r_s = 0.891$ ($p < 0.001$); BL-mBOT-2 $r_s = -0.787$ ($p = 0.001$); DL-mBOT-2 $r_s = -0.732$ ($p < 0.001$)].

4. Discussion

In the present study, the results suggested that the GBT could be a useful tool for the evaluation of balance capacities in children over a broad age range and for their follow-up. HS obtained high scores on the test from the earliest age. GBT scores for BV were consistently and significantly poorer than for the two control populations included in this study, for all age sub-groups. A small improvement is visible in the BV as a function of age, but they never reached the scores of the control populations. CI presented poorer GBT scores in the 3–5 years age sub-group than their HS counterparts, but this difference seemed to improve with age since the results of older populations were comparable to those of the HS.

The results obtained with the GBT seemed to be in accordance with those obtained with the mBOT-2. BV consistently obtained lower scores. However, our results show that the mBOT-2 is not well-accepted by the youngest children included in this study. Only a few subjects aged 3–5 years completed the test, the interpretation of their results is thus biased. However, these results are concordant with the fact that the BOT-2 is not validated for children <4.5 years of age. The mBOT-2 was performed after the GBT for each child. This could constitute a bias, as children could not achieve it because of tiredness. This bias is limited, as we aimed to perform tests as short as possible.

HS obtained low GBT scores from the 3–5 years age sub-group, presumably reflecting good balance skills starting at an early age. We also observed slight improvements with age. BV presented high scores on this test from the age of 3–5 years, presumably confirming their balance disorder. These children improve their scores with

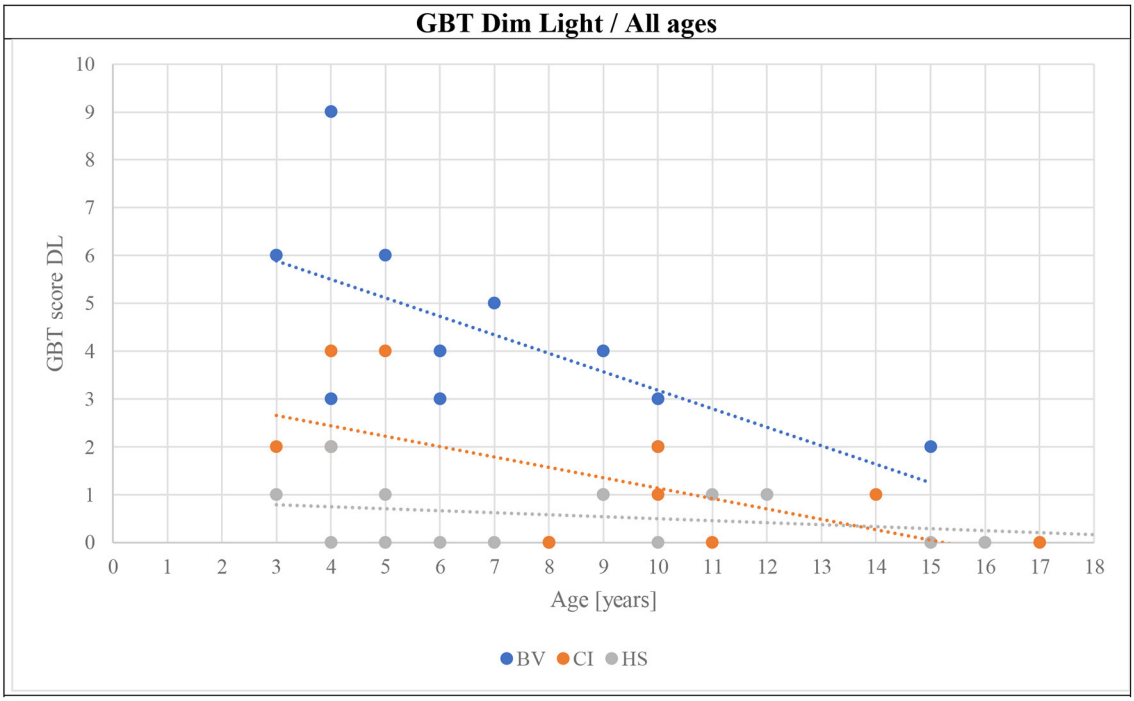


FIGURE 7
Evolution of the GBT scores of all subjects in DL conditions as a function of age (BV, blue symbols; CI, orange symbols; HS, gray symbols).

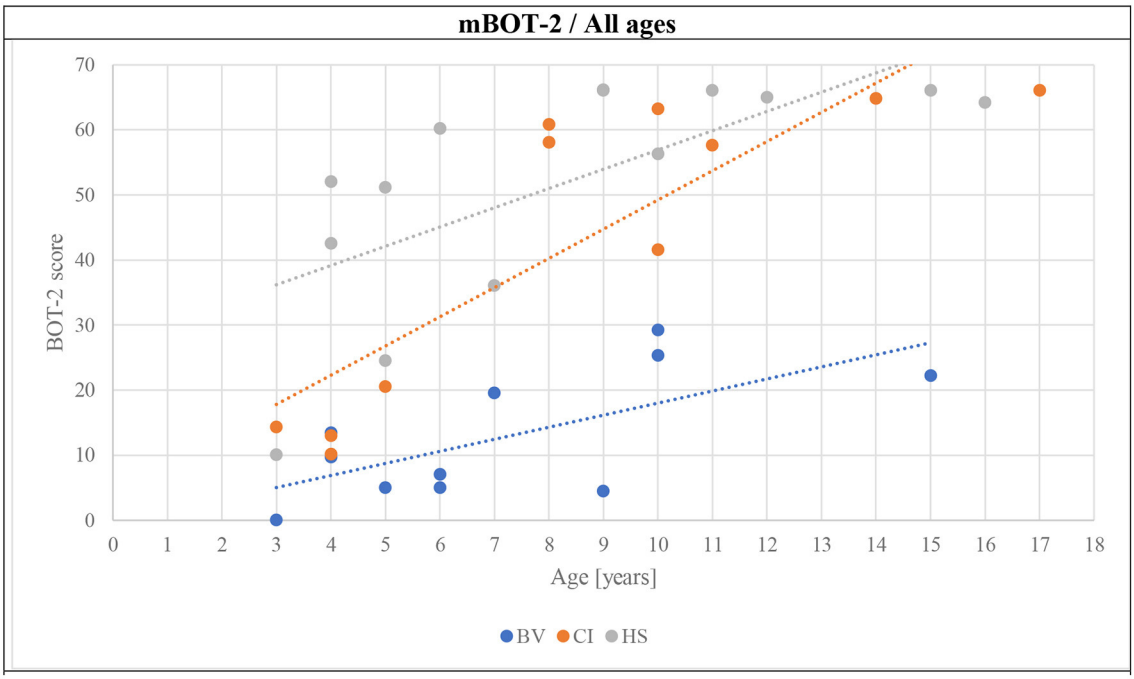


FIGURE 8
Evolution of the mBOT-2 scores of all subjects as a function of age (BV, blue symbols; CI, orange symbols; HS, gray symbols).

increasing age but maintain poorer scores for ≥10 years old than young 3–5 years old HS. The possibility of observing clear and consistent improvements with age demonstrates the potential of the GBT to monitor the evolution of children's balance abilities with age, which would represent a useful tool that is currently lacking in the clinic for patients over a broad age range. Furthermore, the GBT is shorter to perform than BOT-2 or even the mBOT-2. The mBOT-2 showed saturation of the maximal scores by subjects who

are 6–9 years old for HS and CI, which was not the case for the GBT. Moreover, in the specific BV population, the mBOT-2 shows improvement, but the test is poorly accepted and rarely completed. The interpretation of these results in our target population is therefore questionable, with the results of a test that was not completely achieved by the vast majority of BV children.

We also observed that young CI recipients aged 3–5 years had intermediate scores on the GBT, between HS and BV. From the age sub-group of 6–9 years, the scores of the GBT in the CI population reached close-to-perfect scores, which were comparable with the scores of the HS of the same age. This interesting observation tends to the same conclusion as De Kegel et al. (13), who examined the impact of CI on motor development prospectively. It could suggest that deafness or CI might impact the development of balance abilities even in the absence of vestibular deficits. In the small cohort included in this study, it seems that the CI was an effective means to normalize the development of balance abilities with age. The hearing has been indeed shown to play an important role in balance in a healthy population (14). Further studies in a larger cohort are needed to validate this hypothesis and to identify more precisely the influence of CI and/or auditory rehabilitation in the development of balance abilities.

The main limitation of this study is its small sample size. All the BV known in our clinic were included in the study, it was therefore impossible to increase the number of included case patients. A larger scale study would improve the statistical power of the results and would be useful to validate these preliminary findings. In addition, the inclusion of additional pathological populations would also contribute to our understanding of the development of balance abilities in children and help identify potential obstacles and useful tools to improve clinical outcomes at a larger scale.

The age of the children of course influenced the results in terms of normal psychomotor development. It is therefore an effect modifier of our results, which has been diminished by separating the populations into three age sub-groups. The narrower the sub-group of age, the more precise the analysis. A larger scale study would permit to lower this effect. The future use of this test in larger populations could furthermore allow normative results for each age. It could thus define a precise cutoff for each age, reinforcing the screening ability of the GBT.

This project was a preliminary study on the effectiveness of this new clinical tool. The GBT showed some promising results, and the actual setting is perfect in many ways. To allow a more precise definition of the GBT score and an increase in the rapidity of the scoring, an automatic computer-based analysis would be needed. A further study should confirm the transposition of the GBT actual settings with motion capture technology.

5. Conclusion

The Geneva Balance Test seems to be a useful tool to contribute to the screening for BV, as they perform significantly lower than the two control groups. The improvement of its scores with age indicates that it could be used in the follow-up of children with BV as well and even to evaluate the effectiveness of therapeutic interventions (e.g., vestibular rehabilitation). The test showed comparable results to the mBOT-2, consisting of most tasks of the balance subunit of the BOT-2 which is validated in the literature. Yet, the GBT seems to be better accepted by young children and allowed to quantify an improvement according to age, which is not easily assessable with the mBOT-2. Finally, an interesting result concerns the improvement in balance abilities of CI users between the two age categories: 3–5 and 6–9 years old. This result could emphasize the influence of CI on balance capacities, even in children without vestibular disorders, but a study with a bigger cohort would be needed to confirm this interesting finding.

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 Commission Cantonale d'Ethique de la Recherche sur l'être Humain de Genève. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

EM, CB, and LB carried out the tests. The inclusion/exclusion criteria were confirmed by CB and EM. CB carried out the vHIT when needed. EM was responsible to confirm the diagnostic of BV following the Bárány criteria, searching for the important information in the patients' database, and wrote the first version of the manuscript. HC, LB, and EM were in charge of the recruitment and communication with the parents and the patients. AP and EM carried out the statistical analysis. CB, MR, J-FC, LB, and EM were in charge of the materials needed for the test. AP and MR were in charge of the engineering needed in this study. All authors contributed to the development of the GBT, planned the experiments, contributed and were proofreaders, and approved the final version of the manuscript.

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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.2023.1085926/full#supplementary-material

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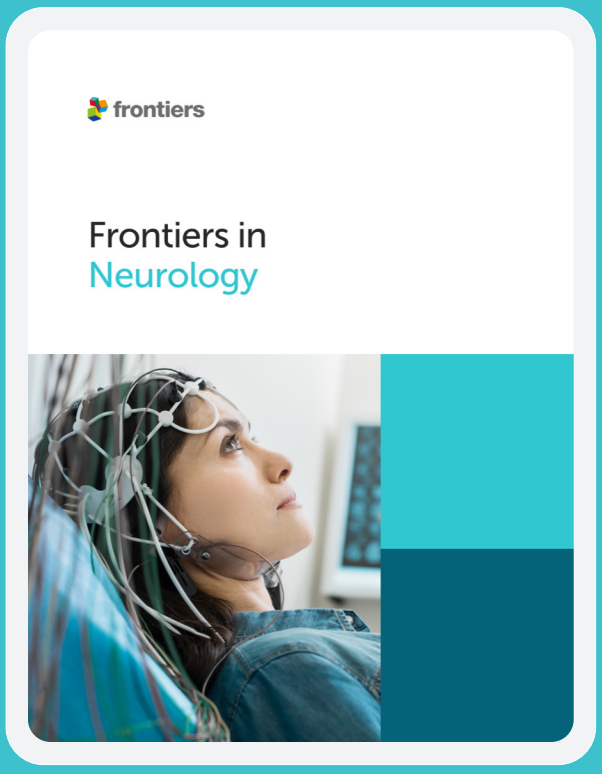

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