Peer Review File

Article information: https://dx.doi.org/10.21037/tp-24-23

Reviewer A

Comment 1: This is the story of a young boy that immediately was treated as an adult. I haven't' read about a rhinofibroscopy, an endocrinological evaluation.
Reply 1: We would like to thank you for the time and effort spent in reviewing this manuscript. During his three hospitalizations, we found his nasal mucosa was pale red, and there was no hypertrophy of the inferior nasal turbinate. We found the patient's nasopharyngeal mucosa to be smooth, with no evidence of neoplasm by an indirect laryngoscopy. We apologize for not performing further rhinofibroscopy examination. Endocrine-related examinations included thyroid-related blood tests, which yielded results within normal range. A cranial MRI revealed no abnormalities. We added related test results as you suggested in our manuscript.
Changes in the text: Other tests, including complete blood count (CBC), thyroid-related blood tests, high resolution computed tomography (HRCT) of temporal bone, cranial MRI and chest X-ray reflected no abnormalities.(line 15,page 5)

Comment 2: In young patient Meniere disease should be an exclusion diagnosis, due to its rarity. In this case report, since the beginning that boy was diagnosed an inner ear disease
Reply 2： Thanks for your professional advice. The author's institution is a tertiary vertigo and dizziness medical center prevention and treatment center. About 200-300 cases of definite MD are diagnosed and hospitalized each year in our center. Young cases of MD (under the age of 18) are very rare, with only 20 cases of young MD diagnosed in the past 10 years, accounting for 2.1% (20/942) of all cases with pediatric vestibular disorders. The boy was admitted to the hospital three times for examination and treatment, and after ruling out other similar diseases, he was finally diagnosed with MD.

Comment 3:*He denied any family history.* His parents denied…
Reply 3: Thanks for your correction.
Changes in the text: His parents denied any family history. (line 29,page 4)

Comment 4:*Although he had been administered with drugs to improve cerebral circulation at his local hospital previously,* Which drugs? Did you exclude, due to young age, endocrinological dysfunction?
Reply 4: Thanks for your careful advice. We felt sorry about this. Because the history of treatment in his local hospital was orally provided by his father, unfortunately his father didn't remember the exact names of the drugs. As for exclusion of endocrinological dysfunction, his parents declared no history and related symptoms of endocrinological dysfunction. During his hospitalization, we conducted thyroid-related blood tests and cranial MRI with this boy, and the results were within normal range.

Comment 5:*Pure tone audiometry (PTA) reflected a* *29 normal hearing threshold in low and medium frequencies (**Figure 1**).* What about tympanometry?
Reply 5: Thanks for your kind replenishment. This boy had A type of tympanometry in both sides.
Changes in the text: The tympanic membranes were normal. Tympanometry showed A type in both sides.(line 8,page 5)

Comment 6:*Caloric tests showed weakness of his left semicircular canal.* Please specify which semicircular …...
Reply 6: Thanks for your accurate correction. It is his left horizontal semicircular canal that performed weakness in the Caloric tests.
Changes in the text: Caloric tests showed weakness of his left horizontal semicircular canal.(line 13,page 5)

Comment 7:*high resolution computed tomography (HRCT)* Do you mean a cerebral HRCT? Or a middle-inner ear one
Reply 7: Sorry for our inaccuracy, we have specified it as high-resolution computed tomography of temporal bone.
Changes in the text: Other tests, including complete blood count (CBC), high resolution computed tomography (HRCT) of temporal bone…(line 16, page 5)

Comment 8: *including Ginaton,* please use active principle
Reply 8: We have corrected the error as you suggested.
Changes in the text: During 1 week of treatment with Ginaton, sodium aescinate, and mecobalamin, the boy was discharged without any further attacks of vertigo.(line 19,page 5)

Comment 9: Fig.2 is too small. What do you mean for *profound endolymphatic hydrops?*
Reply 9: We felt sorry for uploading the figure with compressed quality.We have reuploaded figure 2 with a higher quality. Gadolinium-enhanced MRI showed gadolinium signal in both cochlear and vestibule, indicating that gadolinium entered into the perilymph. the signal was not clear in vestibule and cochlea of the left side, showing significant endolymphatic hydrolysis according to grading of endolymphatic hydrops in MRI[1].
Changes in the text: Revised Figure 2.
Gd-MRI indicated significant endolymphatic hydrops (EH) of the left ear.(line 8,page 6)
Red arrow shows significant endolymphatic hydrops in the left ear. MRI, magnetic resonance imaging.(legend of Figure 2)

Comment 10:Discussion
The discussion, in my opinion should include other similar cases published in the literature to clarify better the peculiarity of the case that you present.
Reply 10: We thank the reviewer for this helpful suggestion.We have added some comparison between this case and other published cases of pediatric MD.
Changes in the text: **S**ince the first report of pediatric MD in 1940, there have been relatively few cases reported in the literature. Meyerhoff documented nine cases of pediatric Meniere's disease (MD) treated with endolymphatic sac drainage procedure to assess its safety and efficacy (25). Nevertheless, the efficacy of this surgery in pediatric patients remains contentious due to developmental and pathophysiological differences compared to adults. Akaji described three pediatric MD cases that achieved prompt recovery with medication (26). Abouzari reported a pediatric MD patient who exhibited complete responsiveness to dietary and lifestyle modifications for migraine, along with magnesium and riboflavin supplementation (27). Another study reported favorable outcomes in a pediatric MD case associated with allergy and dysautonomia following an allergen-restricted diet (28). These studies primarily focus on treatment rather than the progression of MD in children and lack certain modern technical tests to evaluate vestibular function. Although this paper is constrained by a single case report and necessitates further follow-up, it presents a pediatric MD case with dissociated symptoms alongside comprehensive vestibular examinations over a timeline.(line 18,page 8)

Comment 11:*Thus, the roles that vestibular maturation and rehabilitation16 play in pediatric patients with MD remain to be seen，15-16.* What are 15-16?

Reply 11: Sorry for our careless mistake, 15-16 here should be deleted**.**
Changes in the text:
However, the specific effects need to be further studied in more children cases.(line 12, Page 7)

Reviewer B

Comment 1: In the paper is reported a case of Menière's disease in a pediatric patient with a non-synchronous onset of cochlear and vestibular symptoms. Pediatric MD and progression of symptoms has already been reported in case series and my opinion is that this single case report does not add anything.
Moreover the whole manuscript is characterized by a poor accuracy.
Reply 1: We would like to thank you for the time and effort spent in reviewing this manuscript. MD rarely occurred in children. Previous pediatric MD case series might have lacked some of the modern audiovestibular evaluation methods. In this report, we conducted thorough modern audiovestibular testing of the boy in temporal order to follow how vertigo and hearing loss progress in children with MD. And this boy had disassociated symptoms. We have studied comments carefully and we felt very sorry for some inaccuracy in our expression, we would like to rectify them according to your professional review.

Comment 2: Beginning from line 8 of introduction "children have inferior balance score", which tests do you consider?
Reply 2: Thanks for your correction. Previous researches reported that children might have inferior balance score in sensory organization test(SOT) and computerized dynamic posturography(CDP)[2–4]. We have specified it in the text.
Changes in the text: children have inferior balance scores in tests such as sensory organization test(SOT) and computerized dynamic posturography(CDP) due to their insufficient vestibular system and central nervous system integration.(line 8,page 4)

Comment 3: Reading the case presentation I have more questions and doubts
- There is a lack of informations about possible comorbidities (migraine, motion sickness) and familial history (migraine above all). No audiometric exam is shown
Reply 3: Thanks for your advice. The boy had no history of symptoms related to migraine or motion sickness, as well as no autoimmune diseases/allergy. His parents denied any familial history of dizziness and vertigo. PTA results were shown in Figure 1. We have added the results of ABR in the text as suggested.
Changes in the text: The boy had no history of symptoms related to migraine or motion sickness. (line 29, page 4)
His parents denied any family history of vertigo disease.(line 1,page 5)
Auditory brain stem response (ABR) reflected differentiated I,III,Vwave within normal latencies in both ears.(line 9,page 5)

Comment 4:- Was an autoimmune disorder ruled out?
Reply 4: We appreciate your pointing out this important aspect. The boy had no history of autoimmune-related symptoms and did not exhibit physical signs related to autoimmune diseases (such as joint pain, rubella, fever, etc.), and there was no relevant personal or family history of autoimmune diseases. Blood and urine tests (such as C-reactive protein, coagulation-related tests, immunoglobulin, etc.) were within normal ranges.
We supplemented this important section in the text.
Changes in the text: The boy had no history of autoimmune-related symptoms and did not exhibit physical signs related to autoimmune diseases (such as joint pain, rubella, fever, etc.).(line 3,page5)

Other tests, including complete blood count (CBC), C-reactive protein, coagulation-related tests, immunoglobulin, thyroid-related blood tests , high resolution computed tomography (HRCT) of temporal bone, cranial MRI and chest X-ray reflected no abnormalities.(line 15,page5)

Comment 5:- It's strange that cochlear symptoms follow vertigo
Reply 5: We appreciated your professional opinion. The onset of cochlear symptoms(aural fullness, tinnitus) was contaminant with vertigo attack in this child. However, it was many years after experiencing vertigo attacks that hearing loss descent appeared. And hearing loss can attack even without vertigo in this case. What suggests to us is that the typical symptoms of MD may not appear at the same time initially, so the diagnosis of MD needs to capture evidence over a period of time rather than being limited to a single time point.
Changes in the text: One possible explanation is there might be an early-onset hearing loss, although it is not persistent and there was no evidence of it detected initially. Another possibility is that the boy's hearing loss did occur in a time gap, independent of vestibular symptoms. What suggests to us is that the typical symptoms of MD may not appear at the same time initially, so the diagnosis of MD needs to capture evidence over a period of time rather than being limited to a single time point. What suggests to us is that the typical symptoms of MD may not appear at the same time initially, so the diagnosis of MD needs to capture evidence over a period of time rather than being limited to a single time point. (line 26, page 6)

Comment 6: Did you see any nystagmus during hospitalisation?
Reply 6: We thank you for your professional remind. The boy had no acute vertigo attack during his hospitalizations and we did not notice any spontaneous nystagmus.
Changes in the text: We did not observe spontaneous nystagmus during his hospitalization.(line 7,page 6)

Comment 7:- Line 18: Dehidratation medication are diuretics?
Reply 6: Thanks.we have specified *dehydration medication* into *Sodium aescinate* in the text.
Changes in the text: He was advised to take dehydration medication(Sodium aescinate) orally and undergo vestibular rehabilitation exercise; he remained free of vertigo during the 1 year of follow-up.(line 1,page 6)

Comment 8:- Line 22: which vestibular exams were performed?
Reply 8: We apologize for not specifying the physical examination in our text. Physical examination showed negative signs of spontaneous nystagmus, smooth pursuit, gaze nystagmus, Romberg, Mann, Fukuda, Dix-hallpike and Roll-test. A battery of vestibular tests included caloric tests, vHIT and c/oVEMP (results were shown in Table 1).
Changes in the text: Physical examination showed negative signs of spontaneous nystagmus, smooth pursuit, gaze nystagmus, Romberg, Mann, Fukuda, Dix-hallpike and Roll-test (line 5,page 5)

Comment 9:- In discussion, line 13: you tried to explain that "the reasons of dissociated symptoms..", but I didn't understand your explanation.
Reply 9: Thank you for your suggestion, and we apologize for any lack of clarity in our explanation. We speculate that in this boy, hearing loss and vertigo attack appear separately during the progression of MD. . It is reported that 25% patients with MD have disassociated symptoms[5]. We speculated the reasons might be as follows. On the one hand, vestibule and cochlea might be differential sensitivity of cochlear and vestibular sensory cells[6]. On the other hand, vestibular system is not fully developed in children until about 17 years of age, in this case, the development of the vestibular system itself, the interaction of vision and proprioception would superimpose the MD induced impairment of vestibular function. However, the specific effects need to be further studied in more children cases.

Changes in the text: It's reported that vestibule and cochlea might be differential sensitivity of cochlear and vestibular sensory cells (24). What's more, the reasons of dissociated symptoms might be different between children and adults. Age-associated changes in balance function can occur during infancy and childhood (6). Vestibular system is not fully developed in children until about 17 years of age(7), in this case, the development of the vestibular system itself, the interaction of vision and proprioception would superimpose the MD induced impairment of vestibular function. However, the specific effects need to be further studied in more children cases. Importantly, it reminds us of the necessity to prolong the follow-up period of pediatric MD and monitor aural symptoms sensitively even though vertigo did not recur.(line 5,page 7)

Comment 10: As a final consideration, I'm doubtful about the possibility that case report may add something to what is known on the topic.

Reply 10: Thanks for your comment. MD rarely occurs in children. The author's institution is a tertiary vertigo and dizziness medical center prevention and treatment center. About 200-300 cases of definite MD are diagnosed and hospitalized each year in our center. Young cases of MD (under the age of 18) are very rare, with only 20 cases of young MD diagnosed in the past 10 years, accounting for 2.1% (20/942) of all cases with pediatric vestibular disorders. The boy was admitted to the hospital three times for examination and treatment, and after ruling out other similar diseases, he was finally diagnosed with MD.This study may provide some insights for future considerations regarding pediatric patients with MD, such as whether isolated symptoms are common in children, the progression of MD during the maturation of vestibular function, and the necessity of extending follow-up time for pediatric patients. Your opinion is very insightful and professional. We appreciate your thorough suggestions. We have supplemented and revised the content of the article according to your suggestions, and we hope you could give us an opportunity to present this case.

Reviewer C

Firstly, I would like to congratulate you on the written article. I find the topic very interesting, and I believe it is clearly described. I appreciate the contribution and the detailed explanation of all the diagnostic tests conducted. However, I have noted some corrections that I believe could enhance the text.

In this article, the authors aim to emphasize the independent progression of symptoms in pediatric Ménière's disease through a comprehensive evaluation using diagnostic tests. The presented case is of interest for enhancing the understanding of this pathology. However, I suggest some minor corrections that could improve the clarity and comprehension of the case.

Strengths:

- The article presents a clear and organized methodology, providing detailed descriptions of the patient's case and the conducted tests.
- Detailed results of diagnostic tests are provided, facilitating a thorough understanding of the case.

Limitations:

- The sample size, being a single case, prevents the generalization of findings.
- The mentioned 6-month follow-up, may not be sufficient to reveal the long- term evolution of symptoms.
- Considering the constant development in pediatric patients, the characteristics of this Ménière's disease case may vary across different age groups. To extrapolate data to

the entire pediatric population, broader studies analyzing the disease characteristics by age groups should be conducted.

We appreciate for your warm review work earnestly, and hope that the correction will meet with approval.

Minor Corrections:

Comment 1:

1) *Key Findings. Page 2, line 16:* When referring to "postauricular administration," are you alluding to intratympanic corticosteroid therapy? Please clarify. Thank you.

Reply 1: Thanks for your professional correction. postauricular administration here refers to subcutaneous administration of corticosteroid, we have clarified it in the manuscript.

Changes in the text: Apart from systemic administration of corticosteroids, postauricular subcutaneous administration might also be effective in pediatric MD during acute attacks.(line16 ,page 2)

Comment 2:

2) *Abstract. Page 2, line 27:* In the case description, considering the evaluation of a pediatric pathology, the patient's age should be included at this point.

Reply 2: Thanks a lot for your suggestion. We have added the age information in the abstract.

Changes in the text: A 14-year-old pediatric patient with disassociated episodes between vertigo and hearing loss was finally diagnosed with MD. (line 27,page 2)

Comment 3:

3) *Introduction. Page 4, lines 7 and 8: "Compared to adults, children have inferior balance scores due to their insufficient vestibular system and central nervous system integration".* It might be an error to assume uniform characteristics for all children. Consider mentioning the age at which the vestibular system matures and the age limit beyond which problems are attributed to its lack of maturity.

Reply 3： Thanks for your professional correction. It is reported that the capacity to effectively employ particular balance sensory inputs undergoes development at varying stages of life. Results from different studies suggested that by the age of 5, somatosensory function might be nearly mature, while visual contribution might reach adult levels around 11 to 12 years old. Additionally, vestibular function might continue to mature at least until the ages of 15 to 17 years[2,7,8]. We have specified it in the text as you adviced.

Changes in the text: It is reported that vestibular function might continue to mature at least until the ages of 15 to 17 years (7).(line 10, page 4)

Comment 4:

4) *Case Presentation. Page 4, line 26:* Specify the drug used when referring to "drugs to improve cerebral circulation"

Reply 4: We appreciate your careful specification and we regret the oversight. The treatment history from his local hospital was verbally relayed by his father, who unfortunately couldn't recall the specific names of the medications.

Comment 5:

5) *Case Presentation. Page 5, line 28:* Specify the drug when mentioning "diuretic medication".

Reply 5: Thanks for your advice. We have specified it in the text.

Changes in the text: During our 6-month telephone follow up, the patient had taken dehydration medication (Sodium aescinate) and undergone vestibular rehabilitation exercise regularly.(line 13,page 6)

Comment 6:

6) *Discussion:* I recommend adding the previously mentioned study limitations to the discussion.

Reply 6: Thanks for your kind suggestion. we have supplemented this part in discussion.

Changes in the text: Since the first report of pediatric MD in 1940, there have been relatively few cases reported in the literature. Meyerhoff documented nine cases of pediatric Meniere's disease (MD) treated with endolymphatic sac drainage procedure to assess its safety and efficacy (25). Nevertheless, the efficacy of this surgery in pediatric patients remains contentious due to developmental and pathophysiological differences compared to adults. Akaji described three pediatric MD cases that achieved prompt recovery with medication (26). Abouzari reported a pediatric MD patient who exhibited complete responsiveness to dietary and lifestyle modifications for migraine, along with magnesium and riboflavin supplementation (27). Another study reported favorable outcomes in a pediatric MD case associated with allergy and dysautonomia following an allergen-restricted diet (28). These studies primarily focus on treatment rather than the progression of MD in children and lack certain modern technical tests to evaluate vestibular function. Although this paper is constrained by a single case report and necessitates further follow-up, it presents a pediatric MD case with dissociated symptoms alongside comprehensive vestibular examinations over a timeline.(line 18,page 8)

Reference:

1. Nakashima T, Naganawa S, Pyykkö I, Gibson WPR, Sone M, Nakata S, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Oto-Laryngologica. 2009;129:5–8.

2. Ferber-Viart C, Ionescu E, Morlet T, Froehlich P, Dubreuil C. Balance in healthy individuals assessed with Equitest: maturation and normative data for children and young adults. Int J Pediatr Otorhinolaryngol. 2007;71:1041–6.

3. Foudriat BA, Di Fabio RP, Anderson JH. Sensory organization of balance responses in children 3-6 years of age: a normative study with diagnostic implications. Int J Pediatr Otorhinolaryngol. 1993;27:255–71.

4. Cherng RJ, Chen JJ, Su FC. Vestibular system in performance of standing balance of children and young adults under altered sensory conditions. Percept Mot Skills. 2001;92:1167–79.

5. Harcourt J, Barraclough K, Bronstein AM. Meniere's disease. BMJ. 2014;349:g6544.

6. Hara M, Kimura RS. Morphology of the Membrana Limitans. Ann Otol Rhinol Laryngol. 1993;102:625–30.

7. Sinno S, Dumas G, Mallinson A, Najem F, Abouchacra KS, Nashner L, et al. Changes in the Sensory Weighting Strategies in Balance Control Throughout Maturation in Children. J Am Acad Audiol. 2021;32:122–36.

8. Hirabayashi S, Iwasaki Y. Developmental perspective of sensory organization on postural control. Brain Dev. 1995;17:111–3.