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ORIGINAL ARTICLE

Cochlear and vestibular involvement in children with IgA vasculitis

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Abstract

In this study, our purpose is to evaluate cochlear and vestibular function in juveniles with IgA vasculitis using audiometry, distortion product otoacoustic emissions, and cervical vestibular evoked myogenic potential (cVEMP) tests. Forty children diagnosed with IgA vasculitis from the pediatry clinic and 40 age- and sex-matched healthy children were evaluated with distortion product otoacoustic emissions, audiometry, and cVEMP test in a tertiary hospital. The audiometry average values for both ears of the IgA vasculitis group and the control subjects were compared, and as a result, median 4.7-dB sensorineural hearing loss (SHL) was found for the IgA vasculitis group compared to the control group at 250 Hz and it was statistically significant ($p < 0.001$). An average of 6.4-dB SHL was detected at 8000 Hz ($p < 0.001$). There was a statistically significant difference among IgA vasculitis and control groups regarding measurement results of average p1-n1 latency time of both ears (0.9 ms (ms) increase, $p = 0.035$). In IgA vasculitis patients, the median amplitude difference of both ears' average p1 n1 was found to be 5.6 mV, statistically significantly decreased compared to the control group ($p = 0.003$).
Conclusion: This study, firstly in literature, demonstrated that IgA vasculitis may have association with hearing loss and vestibular dysfunction in children. We think this might be due to autoimmune mechanisms.

What is Known:
- *Ig A vasculitis is a leukocytoclastic vasculitis with unknown etiology, involving the skin, joints, gastrointestinal system, kidneys, and rarely other organs.*
- *No study has been reported for the cochlear and vestibular association of Ig A vasculitis in current literature.*

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What is New:
- *This study demonstrated that Ig A vasculitis may have association with hearing loss in children.*
- *This study also demonstrated that Ig A vasculitis may have association with vestibular dysfunction in children.*

Keywords Ig A · Vasculitis · Hearing · DPOAE · Childhood · cVEMP

Abbreviations

cVEMP	Cervical vestibular evoked myogenic potential
dB	Decibel
dBnHL	Decibels in hearing level
DPOAEs	Distortion product otoacoustic emissions
HSV	Henoch-Schönlein vasculitis
ms	Millisecond
PTA	Pure-tone average
SCM	Sternocleidomastoid muscle
SHL	Sensorineural hearing loss
SNR	Signal to noise ratio

Introduction

Henoch-Schönlein vasculitis is a leukocytoclastic vasculitis with unknown etiology. The yearly rate of the disease is estimated to be between 13 and 20/100,000. IgA vasculitis is generally well progressed, does not leave sequelae, and lasts approximately 4–6 weeks, yet relapse may occur. Many systemic findings of IgA vasculitis such as gastrointestinal system, joints, skin, and kidney involvements have been reported before. The International Chapel Hill Consensus Conference (CHCC 2012) revised the nomenclature for vasculitis to include the pathophysiology of vasculitis in its name. Henoch-Schönlein purpura (HSP) is associated with IgA1-dominant immune deposits in small blood vessels (predominantly capillaries, venules, or arterioles). Therefore, the CHCC 2012 replaced the eponym "Henoch-Schönlein purpura" with IgA vasculitis to better define the pathophysiological features observed in this condition [1–6].

The possibility of cochlear and vestibular involvement in IgA vasculitis is an interesting and intriguing idea in the pediatric otologic field. As far as we know, there is no study reported before about children with IgA vasculitis. So, reasonable questions remain on this topic. Many studies showed auditory problems can be seen in some vasculitic and inflammatory diseases like Cogan syndrome and familial Mediterranean fever [7, 8].

Distortion product otoacoustic emissions (DPOAEs), audiometry testing, and cervical vestibular evoked myogenic potential (cVEMP) test can help to establish cochlear and vestibular involvement at an early period of auditory problems and balance disorders. In this study, our purpose is to evaluate cochlear and vestibular function in juveniles with IgA vasculitis using audiometry, DPOAEs, and cVEMP tests.

Materials and methods

This research was sequenced in the otorhinolaryngology and pediatry clinics of a tertiary hospital between October 2017 and February 2021. Forty consecutive patients diagnosed with IgA vasculitis from the pediatry clinic and 40 age- and sex-matched healthy children that were admitted to the otorhinolaryngology and pediatry clinics were included (30 females, 41% and 50 males, 59%). There were 24 males and 16 females in the IgA vasculitis group. The control group included 21 females and 19 males. The median age was 8 (5–16.5) for the IgA vasculitis group. The median age was 7 (4–16) for the control group. Patients with IgA vasculitis were diagnosed according to EULAR/PReS criteria (Table 1). Study permission was acquired from the hospital's Ethics Committee Commission (ethical approval registration number: 2017/11–284). "Informed Volunteer Consent Form" was taken from families of children. It was showed by examinations and tests that the control subjects had no chronic ear disease before and was not suffering from active ear disease. Also, all IgA vasculitis patients had no ear abnormality in their history.

Audiometry, tympanometry, DPOAE, and cVEMP results showed that auditory and vestibular responses were normal for the control subjects. All subjects with a history of hearing loss, ear surgery, ototoxic drug use, tinnitus, vertigo, and recurrent otitis media; subjects with abnormal findings in the otoscopic examination; and subjects who could not adapt to audiometry were excluded.

The audiometric assessment was applied in a noise-proof cabinet. Pure-tone average (PTA) was applied to determine the hearing thresholds. A hearing level of < 25 dB was considered normal. Measurements of distortion product otoacoustic emissions (DPOAEs) were carried out for all subjects while the subjects were seated in a noise-proof cabinet.

Table 1 Classification criteria for IgA vasculitis

Palpable purpura (mandatory criterion) in the presence of at least one of the following four features:
• Diffuse abdominal pain
• Any biopsy showing predominant IgA deposition
• Arthritis (acute, any joint) or arthralgia
• Renal involvement (any hematuria and/or proteinuria)

cVEMP evaluation

Electromyographic activity of the sternocleidomastoid muscle (SCM) surface was measured with the Interacoustic Eclipse (Middlefart, Denmark) device for the cVEMP test. The positive electrode was stabilized on the upper part of the SCM, and the ground electrode was stabilized to the forehead. Then, the reference electrode was stabilized to the point where SCM joints to the sternum. The patient was asked to sit in a vertical position and to make head rotation towards the contralateral side of the tested ear and to hold it in this position. Thus, it was aimed to provide tonic activation of SCM. To check the precision of the results obtained from the patients, two records were made and the values obtained via an average of these two records were taken. Measurements were made at 95 dBnHL. The presence of the first positive wave (p13) accompanied by a negative wave (n23) was described as a cVEMP response. For each individual, p13 latency (msn), n23 latency (msn), and p13–n23 amplitude values (lV) were analyzed in both right and left ears.

Statistical analysis

SPSS version 15.0 program was used in the statistical analysis of the study data. All analyses were performed within the 95% confidence interval. While presenting descriptive analyses, mean, standard deviation, and median values were used. While the variables with a normal distribution (parametric) were evaluated between the groups, in the cases where the *T*-test did not show a normal distribution in independent groups, groups of 2 were evaluated with the Mann–Whitney *U* test. The Spearman correlation test was performed to analyze the measurement data with each other. A p value under <0.05 was assessed as statistically significant outcomes.

Table 2 Features of the IgA vasculitis group

Age at disease onset (years)	8 (5–16.5)
Organ ınvolvement	
Joint	40
Skin	40
Gastrointestinal	10
Kidney	12
Pediatric vasculitis activity score	38 (24–48)
Treatment	
Rest + NSAID (acetylsalicylic acid)	40
Steroid	14
Disease course	
Full recovery	40
Relaps	0
Chronic-persistent	0
Follow-up period (months)	22 (7–48)

Table 3 Comparison of average pure-tone audiometry losses for both ears in IgA vasculitis and control groups

	IgA vasculitis group		Control group		p
	Mean ± SD	Median	Mean ± SD	Median	
250 Hz	19.5 ± 9.3	15.0	12.8 ± 3.1	11.3	< 0.001
500 Hz	18.2 ± 11.1	14.0	10.8 ± 3.7	9.0	0.002
1000 Hz	17.2 ± 12.2	10.0	11.8 ± 3.6	10.0	0.014
2000 Hz	17.8 ± 14.8	10.0	13.1 ± 4.5	10.0	0.025
4000 Hz	19.2 ± 15.6	18.0	15.7 ± 9.0	14.0	0.003
8000 Hz	24.5 ± 18.8	22.6	17.4 ± 14.5	14.2	< 0.0012

Results

As we examined the patients according to organ involvement, all patients had skin findings and joint pain, while 10 patients had additional gastrointestinal involvement and 12 patients had kidney involvement. Pediatric vasculitis activity score was 38 (24–48) on average. All patients were started on acetylsalicylic acid as a non-steroidal anti-inflammatory drug, and additional steroid therapy was given to 14 patients. All patients fully recovered. The mean follow-up period was 22 (7–48) months (Table 2).

The audiometry average values for both ears of the IgA vasculitis group and the control subjects were compared, and as a result, a median 4.7-dB sensorineural hearing loss (SHL) was found for the IgA vasculitis group compared to the control group at 250 Hz and it was statistically significant ($p < 0.001$). An average of 6.4-dB SHL was detected at 8000 Hz ($p < 0.001$) (Table 3).

There was no statistically significant difference among the 2 groups regarding tympanometry measurement outcomes (Table 4).

In the IgA vasculitis group, otoacoustic emission SNR average values were found to be decreased as the median of 3.4 SNR at 4000 Hz and were statistically significant (p

Table 4 Comparison of the tympanometry test results of the groups

		IgA vasculitis group		Control group	
		Right	Left	Right	Left
Tympanometry %	Tip A	88	92	100	100
	Tip B	0	0	0	0
	Tip C	12	8	0	0

Table 5 Comparison of average otoacoustic emission frequencies for both ears for IgA vasculitis and the control groups

	IgA vasculitis group		Control group		*p*
	Mean ± SD	Median	Mean ± SD	Median	
OAE 1000 Hz	3.6 ± 14.9	1.4	5.7 ± 6.4	4.2	0.216
OAE 1500 Hz	11.4 ± 12.0	10.0	10.3 ± 8.6	9.3	0.475
OAE 2000 Hz	10.1 ± 14.6	11.0	12.8 ± 7.4	11.1	0.530
OAE 3000 Hz	9.9 ± 11.0	9.3	13.6 ± 9.5	12.6	0.376
OAE 4000 Hz	5.7 ± 13.7	10.0	14.7 ± 9.4	13.4	0.005
OAE 6000 Hz	4.3 ± 11.2	2.9	9.2 ± 10.3	8.1	0.034

0.005). In the IgA vasculitis group, a decrease of 5.2 SNR was found OAE 6000-Hz frequency compared to the control group and it was statistically significant (*p* 0.034) (Table 5).

There was a statistically significant difference among IgA vasculitis and control group regarding measurement results of average p1-n1 latency time of both ears (0.9 ms (ms) increase, $p = 0.035$). In IgA vasculitis patients, the median amplitude difference of both ears' average p1 n1 was found to be 5.6 mV, statistically significantly decreased compared to the control group ($p = 0.003$) (Table 6).

Discussion

Several hypotheses have been introduced for the pathogenesis of IgA vasculitis [9, 10]. Widespread accumulation of IgA in vessels suggests that the autoimmunity response related to IgA may play a role in the pathogenesis of the disease. IgA vasculitis is usually a self-limiting disease that does not require special treatment other than support. Skin rashes usually go away on their own. During the rash, excessive exercise and prolonged standing may increase the rash. Therefore, rest is recommended. Joint symptoms are usually controlled with non-steroidal anti-inflammatory drugs. Steroid therapy is used according to clinical findings and the severity of organ involvement. Other immunosuppressive drugs can be used in patients with progressive organ damage [11–14]. In our study, all patients were given acetylsalicylic acid as a non-steroidal anti-inflammatory drug and no immunosuppresive drug was nedeed.

Table 6 Comparison of IgA vasculitis group and control group cVEMP values

	IgA vasculitis group		Control group		*p*
	Mean ± SD	Median	Mean ± SD	Median	
p1 time, ms	15.1 ± 4	15.1	14.5 ± 2	14.9	0.375
n1 time, ms	23.1 ± 5	23.1	23.2 ± 5	23.3	0.077
p1-n1 inter-latency time, ms	8.5 ± 6	8.6	8.0 ± 4	7.7	0.035
p1-n1 inter-amplitude difference, mV	14.5 ± 14	13.5	30.8 ± 48	19.1	0.003

IgA vasculitis can be because of parenchyma damage by vasculitic pathways. Cochlear association might occur possibly in this way. It is known that the continuity of normal blood supply is vital for the normal cochlear function [15]. When an inflammatory condition occurs, IL-1β and TNF-α are secreted in the early period. These proinflammatory cytokines may lead to a pathway that produces various chemoattractants that could activate inflammatory cells and could break down neighboring vascular endothelial cells of the cochlea. This state is like a vicious circle that increases inflammatory cell trafficking from circulation to inflammatory sites [16].

As far as we know, there is no research for the cochlear and vestibular association of IgA vasculitis in current literature. When the literature was searched for vasculitis in terms of hearing-balance disorders, only Cogan syndrome and Behçet's disease were identified as related to this condition [7, 17].

DPOAEs are simply suitable and extra worthy for identifying the cochlear component of hearing impairment and show accurately little differences in the cochlea correlated to other audiological methods. An audiometry may show initial findings of cochlear injury and is beneficial for the evaluation of the subjects at risk of hearing impairment [8, 18].

For the evaluation of the vestibular system, the clinician provides important information from the combination of subjective and objective tests to establish an accurate diagnosis. Thus, the cVEMP test is one of the simplest, quick, non-invasive methods for evaluating the saccule function, inferior vestibular nerve, and vestibulocolic reflex arcs from otolithic organs [19].

In our study, by using audiometry, we proved hearing levels of IgA vasculitis patients in 250-Hz and 8000-Hz frequencies decreased compared to the control group as displayed in Table 2, proposing a cochlear association. Also, our study revealed that the amplitude difference between cVEMP p1 n1 in patients with IgA vasculitis in both ears decreased compared to the control group as displayed in Table 5, suggesting vestibular involvement. We assumed that autoimmune causes may be similar in pathogenesis for this condition like Cogan syndrome and Behçet's disease. This study showed no hearing loss according to the World Health Organization guideline regarding all patients who had lesser pure-tone avarage values of 20 dB and patients had no balance dysfunction clinically, but there was a correlation

between audiometry, OAE, and cVEMP as normal with statistically different values in some thresholds and wave patterns. As a result, our study is the first study to indicate a possible association of cochlear and vestibular involvement in children with IgA vasculitis.

Conclusion

Our study demonstrated that IgA vasculitis may have an association with hearing loss and vestibular dysfunction in children, but our data do not prove that IgAV causes hearing loss and vestibular dysfunction. We think this might be due to autoimmune mechanisms. These findings also suggest that regular follow-up of auditory and vestibular function in children with IgA vasculitis may help determine the early possible hearing loss and balance disorders. Also, this area of research is a novel field, and this study is the first in the literature to investigate the cochlear and vestibular involvement of IgA vasculitis. Therefore, prospective, multicentered, controlled studies with long-term follow-up and larger participation are needed to clarify this issue.

Authors' Contributions Conceptualization: SK, AB, ABü. Data curation: ÇG, AB, SK. Formal analysis: ÇG, EY, AK. Methodology: SK, AB, AK. Project administration: SK, ABü, EY. Visualization: ÇG, AB, EY. Writing—original draft: SK, AK, EY. Writing—review and editing: SK, ÇG, ABü.

Availability of data and material Available.

Code availability SPSS version 15.0 program.

Declarations

Ethics approval All procedures performed in this study were following the ethical standards of the University Ethical Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (ethical approval registration number: 2017/11–284).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

References

1. Maritati F, Canzian A, Fenaroli P, Vaglio A (2020) Adult-onset IgA vasculitis (Henoch-Schönlein): update on therapy. Presse medicale (Paris, France : 1983) 49(3)104035. Advance online publication. https://doi.org/10.1016/j.lpm.2020.104035
2. Piram M, Mahr A (2013) Epidemiology of immunoglobulin A vasculitis (Henoch-Schönlein): current state of knowledge. Curr Opin Rheumatol 25(2):171–178. https://doi.org/10.1097/BOR.0b013e32835d8e2a
3. Iannetti L, Zito R, Bruschi S, Papetti L, Ulgiati F, Nicita F, Del Balzo F, Spalice A (2012) Recent understanding on diagnosis and management of central nervous system vasculitis in children. Clin Dev Immunol 2012:698327. https://doi.org/10.1155/2012/698327
4. Bagga A, Dillon MJ (2001) Leukocytoclastic vasculitis. In: Cassidy JT, Petty RE, eds. Textbook of pediatric rheumatology, W.B. Saunders, Philadelphia: pp 569–579
5. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F et al (2013) 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitis. Arthritis Rheum 65:1–11
6. Yang YH, Hung CF, Hsu CR, Wang LC, Chuang YH, Lin YT, Chiang BL (2005) A nationwide survey on epidemiological characteristics of childhood Henoch-Schönlein purpura in Taiwan. Rheumatology (Oxford) 44(5):618–622
7. Grasland A, Pouchot J, Hachulla E, Blétry O, Papo T, Vinceneux P, & Study Group for Cogan's Syndrome (2004) Typical and atypical Cogan's syndrome: 32 cases and review of the literature. Rheumatology (Oxford) 43(8):1007–1015. https://doi.org/10.1093/rheumatology/keh228
8. Bucak A, Ulu S, Bukulmez A et al (2014) Inner ear ınvolvement in children with familial mediterranean fever. J Int Adv Otol 10:124–127. https://doi.org/10.5152/iao.2014.34
9. Sundel R, Szer I (2002) Vasculitis in childhood. Rheum Dis Clin North Am 28(3):625–654. https://doi.org/10.1016/s0889-857x(02)00008-x
10. O'Donoghue DJ, Jewkes F, Postlethwaite RJ, Ballardie FW (1992) Autoimmunity to glomerular antigens in Henoch-Schoenlein nephritis. Clinical science (London, England : 1979) 83(3)281–287. https://doi.org/10.1042/cs0830281
11. Miller ML (2004) Vasculitis syndromes. Nelson textbook of pediatrics 826-828
12. Dedeoglu F, Sundel RP (2005) Vasculitis in children. Pediatr Clin North Am 52(2):547–vii. https://doi.org/10.1016/j.pcl.2005.01.006
13. Leung A, Barankin B, Leong KF (2020) Henoch-Schönlein purpura in children: an updated review. Curr Pediatr Rev 16(4):265–276. https://doi.org/10.2174/1573396316666200508104708
14. Kim GB, Yu JJ, Yoon KL, Jeong SI, Song YH, Han JW, Hong YM, Joo CU (2017) Medium- or higher-dose acetylsalicylic acid for acute Kawasaki disease and patient outcomes. J Pediatr 184:125-129.e1. https://doi.org/10.1016/j.jpeds.2016.12.019
15. Scherer EQ, Yang J, Canis M et al (2010) Tumor necrosis factor-α enhances microvascular tone and reduces blood flow in the cochlea via enhanced sphingosine-1-phosphate signaling. Stroke 41(11):2618–2624. https://doi.org/10.1161/STROKEAHA.110.593327
16. Ichimiya I, Yoshida K, Hirano T, Suzuki M, Mogi G (2000) Significance of spiral ligament fibrocytes with cochlear inflammation. Int J Pediatr Otorhinolaryngol 56(1):45–51. https://doi.org/10.1016/s0165-5876(00)00408-0
17. Ak E, Harputluoglu U, Oghan F, Baykal B (2004) Behçet's disease and hearing loss. Auris Nasus Larynx 31(1):29–33. https://doi.org/10.1016/j.anl.2003.07.006
18. Polat K, Uysal IO, Senel S, Güler C, Durmuş K, Müderris S (2013) Evaluation of hearing in patients with familial Mediterranean fever. European archives of oto-rhino-laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 270(11)2871–2874. https://doi.org/10.1007/s00405-013-2347-x
19. Rosengren SM, Welgampola MS, Colebatch JG (2010) Vestibular evoked myogenic potentials: past, present and future. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 121(5):636–651. https://doi.org/10.1016/j.clinph.2009.10.01