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Vestibular Involvement in Patients With Otitis Media With Antineutrophil Cytoplasmic Antibody-associated Vasculitis

Yuka Morita, Kuniyuki Takahashi, Shuji Izumi, Yamato Kubota, Shinsuke Ohshima, and Arata Horii

Department of Otolaryngology Head and Neck Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Objective: Otitis media (OM) with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMAAV) is a novel concept of ear disease that is characterized by progressive mixed or sensorineural hearing loss with occasional systemic involvement. Considering the accumulating knowledge about the characteristics of and treatment for auditory dysfunction in OMAAV, the objective of this study was to investigate the vestibular function and symptoms of patients with OMAAV.
Study Design: Retrospective chart review.
Setting: University hospital.
Patients: Thirty-one OMAAV patients met criteria proposed by the OMAAV study group in Japan.
Main Outcome Measures: Clinical characteristics and vestibular tests.
Results: Eleven of 31 OMAAV patients had vestibular symptoms; 3 patients had acute vertigo attack with sudden hearing loss and 8 patients had chronic dizziness. Episodic vertigo was not seen in any of the patients. Three patients who received a less intensive therapy without immunosuppressive agents developed intractable persistent dizziness. All symptomatic patients and six of the nine OMAAV patients without vestibular symptoms showed unilateral or bilateral caloric weakness; therefore, vestibular involvement was present in 84% of OMAAV patients. Gain of vestibulo-ocular reflex was reduced in symptomatic patients. The eye-tracking test and optokinetic nystagmus revealed no evidence of central dysfunction.
Conclusion: Vestibular dysfunction was seen in 84% of OMAAV patients. One-third of OMAAV patients showed vestibular symptoms such as acute vertigo attack or chronic dizziness, which are of peripheral origin. One-third of the symptomatic patients developed intractable dizziness. Initial intensive treatment by combination therapy with steroid and immunosuppressive agents may be essential for preventing the development of intractable dizziness. **Key Words:** ANCA-associated vasculitis—Antineutrophil cytoplasmic antibody—Immunosuppressant—Otitis media—Steroid—Vestibular.

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The antineutrophil cytoplasmic antibody (ANCA) against neutrophil lysosomal enzymes such as myeloperoxidase (MPO) and proteinase 3 (PR3) releases lytic enzymes that cause vascular inflammation; this leads to systemic vasculitis known as ANCA-associated vasculitis (AAV) (1–3). On the basis of histological findings and the vessel size affected, AAV is classified into three categories: granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis polyangiitis (EGPA, formerly known as Churg–Strauss syndrome) (4–7). These ANCA-associated diseases may involve organs throughout the body, such as the eye, nose, ear, lung, and kidney (4–7). It has been reported that 19 to 61% of systemic AAV patients show otologic symptoms such as otalgia, hearing loss, aural fullness, tinnitus, and vertigo during their clinical courses, and in turn, otologic symptoms are sometimes the initial manifestation of systemic AAV (8,9). As it is very difficult to diagnose AAV based only on otologic symptoms, the resulting delay in diagnosis may lead to unfavorable outcomes such as profound bilateral hearing loss that may require a cochlear implant (10). Recently, the concept of otitis media with AAV (OMAAV) has been proposed OMAAV is, in fact, not a recent ear disease but a historically well-known intractable ear disease associated with AAV. However, it is important to note that AAV localized to the ear (OMAAV) can be an initial manifestation of systemic AAV, and that prompt diagnosis and treatment may prevent its progression to systemic disease (AAV) (10). Table 1 shows the diagnostic criteria of OMAAV, which was proposed by the OMAAV study group of the

Address correspondence and reprint requests to Yuka Morita, M.D., Ph.D., Department of Otolaryngology Head and Neck Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan;
E-mail: yukam@med.niigata-u.ac.jp
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TABLE 1. *Diagnostic criteria of OMAAV*

Experience of suffering from intractable otitis media with effusion or granulation, which was resistant to antibiotics and insertion of tympanic ventilation tube, accompanied by progressive hearing loss over less than 2 months.
At least one of the following four findings:
positivity for serum MPO- or PR3-ANCA
histopathology consistent with AAV
diagnosis of AAV (GPA, MPA, EGPA) by the presence of other involvements before occurrence of ear symptoms
at least one sign/symptoms of AAV-related involvements other than ear (eye, nose, pharynx/larynx, lung, kidney, facial palsy, hypertrophic pachymeningitis, and the others).
Exclusion of the other intractable otitis media such as bacterial otitis media, cholesterol granuloma, cholesteatoma, malignant osteomyelitis, tuberculosis, neoplasms and eosinophilic otitis media, as well as exclusion of the other autoimmune and vasculitis diseases other than AAV such as Cogan's disease and PN.

ANCA indicates antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

Japan Otological Society (11). According to these criteria, the characteristic symptoms and clinical findings of OMAAV are: 1) intractable otitis media against antibiotics and tube insertion, 2) otitis media with sudden or progressive hearing loss (mixed or sensorineural hearing loss), 3) MPO- and/or PR3-ANCA positive, and 4) effectiveness of a combination therapy comprising steroids and immunosuppressive agents such as cyclophosphamide or methotrexate (10,11). As members of the OMAAV study group in Japan, we have treated 31 patients with OMAAV. Although there is no description of vestibular symptoms in the diagnostic criteria of OMAAV, we encountered OMAAV patients who exhibited not only auditory symptoms but also intractable vestibular symptoms even after treatment. In the present study, we focused on vestibular symptoms and vestibular function of OMAAV patients.

METHODS

This study was approved by the IRB of Niigata University Medical and Dental Hospital (No. 2440). From 2004 to 2014, we treated 31 OMAAV patients who met the diagnostic criteria of OMAAV as proposed by the OMAAV study group of the Japan Otological Society (11) (Table 1). The following audiovestibular tests were performed at the acute or subacute stage of the disease before treatment: 1) otological examination including endoscopic examination of tympanic membrane and pure-tone audiometry were performed for all 31 patients; the affected side (unilateral or bilateral) was determined by the hearing level, which is a mean of 0.5, 1, and 2 kHz. 2) For 19 of the randomly selected patients, the following vestibular tests were performed: eye tracking test (ETT), bithermal caloric test, vestibulo-ocular reflex (VOR) test on rotatory chair, and optokinetic nystagmus (OKN) test, all of which were recorded by electronystagmography. For the bithermal caloric test, each ear was irrigated with 50 mL of water alternately at 30°C and 44°C for 40 seconds. For patients who had tympanic membrane perforation, air caloric stimulation at 26°C and 45°C was substituted for the bithermal caloric test. The maximum slow-phase eye velocity (SPEV) of caloric nystagmus was measured. Canal paresis (CP) of more than 20% (as calculated by Jongkee's formula) was considered unilateral caloric weakness. In most of OMAAV patients, inner ear function (auditory or vestibular) was damaged bilaterally; consequently, conventional evaluation using CP% as a marker of vestibular dysfunction might not be adequate. Therefore, we used a maximum SPEV of less than 6°/s as a cut-off value to determine the reduced caloric response. For example, if the maximum SPEV of all caloric nystagmus was less than 6°/s, it was defined as bilateral caloric weakness. For the VOR test, the subject was seated in a chair that was rotated sinusoidally around on earth vertical axis by a servo-controlled DC motor, with a maximum angular velocity of 40°/s and a frequency of 0.1 Hz. The test was performed in total darkness with eyes closed, and the VOR gain was calculated. The optokinetic drum was rotated at the maximum angular velocity of 100°/s, and the maximum SPEV of optokinetic nystagmus under 40°/s was considered a poor response. The EET was classified into normal, ataxic, or saccadic patterns, as judged by the waveforms. MPO-ANCA and PR3-ANCA titers were measured by antigen-specific enzyme-linked immunosorbent assay.

With respect to treatment strategies, oral prednisolone (20–60 mg/day) was administered with or without cyclophosphamide as an induction therapy. Patients with severe pulmonary and renal diseases were treated with intravenous administration of methylprednisolone (1,000 mg/day) for 3 days and/or intravenous cyclophosphamide (500 mg) once a week. We did not offer vestibular rehabilitation.

Patients were divided into two groups according to the presence or absence of subjective vestibular symptoms. Group I consisted of 11 patients who had subjective vestibular symptoms, whereas Group II consisted of 20 patients without vestibular symptoms (Table 2). Differences in each parameter between any two groups were analyzed by Mann–Whitney U test or χ^2 test using SPSS version 21.0 computer software for Windows. $p < 0.05$ was considered significant.

RESULTS

Table 2 shows background data for the symptomatic Group I and asymptomatic Group II patients. There were no significant differences in age, sex, affected side (bilateral or unilateral), ANCA-status (positivity of MPO and PR3), hearing level of affected ear before treatment, involvement of other organs throughout the clinical course, including during treatment and follow-up periods. With respect to the tympanic membrane findings, we confirmed the existence of granulation tissue in the tympanic cavity in only one patient, in whom it was visible through the tympanic membrane perforation. Because exploratory tympanostomy or random biopsy was not routinely performed, it was uncertain what percentage of patients had granulation in the tympanic cavity.

TABLE 2. *Patients' profiles of vestibular symptoms (+) Group I and (−) Group II patients*

		Group I n = 11	Group II n = 20	*p* Value
Age	Median (range)	70 (46–81)	73 (41–81)	0.640
Sex	Male/female	3/8	9/11	0.282
Affected side	Bilateral/unilateral	8/3	17/3	0.484
ANCA-status	PR3-ANCA (+)	1	3	0.590
	MPO-ANCA (+)	7	15	0.483
Hearing level of worse hearing ear before treatment (dB)		80 ± 23.4	78 ± 22.2	0.640
Involvement of other organs	Facial palsy	3	5	0.606
	Hypertrophic pachymeningitis	3	4	0.429
	Lung	3	11	0.134
	Kidney	1	7	0.124
Treatment	Steroid with immunosuppressant	3	9	0.200
	Others	8	11	
Follow-up period (mo)	Median (range)	26 (1–127)	25 (5–74)	0.502

ANCA indicates antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

Eleven of 31 OMAAV patients had subjective vestibular symptoms; three of these patients had acute vertigo with sudden hearing loss, and eight had chronic dizziness along with progressive hearing loss (Table 3). No patient had episodic vertigo.

Because of the retrospective nature of the study, vestibular tests were performed only for 19 of the 31 OMAAV patients (i.e., 10 patients in symptomatic Group I and 9 patients in asymptomatic Group II). Among 10 patients with vestibular symptoms (Group I), the auditory inner ear was bilaterally affected in seven patients, and the vestibular periphery was damaged unilaterally (n = 6) or bilaterally (n = 4), resulting in at least unilateral vestibular involvement in all 10 patients (Table 4). In Group II patients without vestibular symptoms, eight of nine patients had bilateral hearing disturbance, and only three of nine patients had normal caloric response (Table 4). The remaining six of nine patients had ipsilateral (n = 3) or bilateral (n = 3) caloric weakness (Table 4). In total, 16 of 19 (84%) OMMAV patients with or without vestibular symptoms had unilateral or bilateral caloric weakness. Concerning the VOR test in patients with vestibular symptoms (Group I), VOR gain for both the right and left direction was significantly lower compared with the gain observed in Group II patients (Table 4). In the EET, one patient had ataxic and one had saccadic pattern in Group I and Group II, respectively (Table 4). The maximum SPEV in OKN was under 40°/s in one Group II patient (Table 4). Regarding the pathophysiological mechanisms underlying vestibular symptoms in OMAAV patients, there were no differences in each parameter except for VOR gain between the symptomatic Group I and asymptomatic Group II (Table 4).

Table 5 shows the age, treatment, and follow-up period of symptomatic Group I patients according to the final outcome of the vestibular symptoms. We failed to conduct a follow-up for one patient. Three of 10 patients had intractable persistent dizziness at the final follow-up (median, 23 mo). There were no differences with respect to each of the factors between the intractable vestibular patients and those who recovered from vestibular symptoms (Table 5). Though not statistically significant, all three patients who received immunosuppressive therapy (with steroids) recovered from vestibular symptoms, whereas three of seven patients who received steroid therapy only progressed to develop intractable dizziness (Table 5).

As shown in Figure 1, the hearing threshold before treatment was 83 ± 28.4 dB in Group I patients who had intractable vestibular symptoms (n = 3, thick lines), whereas the hearing threshold was 77 ± 23.6 dB in Group I patients who recovered from vestibular symptoms (n = 7, thin lines). There were no differences in pretreatment hearing levels between the two groups. The posttreatment hearing threshold was 79 ± 57.8 dB in the former patients (n = 3, thick lines) and 60 ± 33.0 dB in the latter patients (n = 7, thin lines). There was no difference in the posttreatment hearing threshold ($p = 0.667$), or hearing recovery ($p = 0.833$) between the two groups.

TABLE 3. *Vestibular symptoms of OMAAV patients*

	Group I n = 11		Group II n = 20
Vestibular symptoms	(+)		(−)
	Acute vertigo attack with sudden HL	Chronic dizziness	
	n = 3 (9.7%)	n = 8 (25.8%)	n = 20 (64.5%)

TABLE 4. *Vestibular tests of vestibular symptoms (+) Group I and (−) Group II patients*

			Group I n = 10	Group II n = 9	*p* Value
Age		Median (range)	70 (46–78)	71 (65–81)	0.497
Sex		Male/female	2/8	2/7	0.667
Affected side		Bilateral/unilateral	7/3	8/1	0.333
Hearing level of worse hearing ear before treatment (dB)			78 ± 23.7	82 ± 19.1	0.720
ENG	Caloric weakness	Bilateral/unilateral	4/6	3/3	0.087
	VOR	Rt.- VOR gain	0.57 ± 0.22**	0.8 ± 0.12	0.002**
		Lt.- VOR gain	0.61 ± 0.27*	0.81 ± 0.10	0.014*
	Eye tracking test		1 Ataxic	1 Saccadic	0.737
	Optokinetic nystagmus		Normal	1 Poor	0.474

ENG indicates electronystagmography; Lt, left; Rt, right; VOR, vestibulo-ocular reflex.
*$p < 0.05$, **$p < 0.01$ versus Group II.

TABLE 5. *Age, treatment, and follow-up period of intractable versus recovered vestibular patients*

		Vestibular Symptoms		
		Intractable (n = 3)	Recovery (n = 7)	*p* Value
Age	Median (range)	75 (68–77)	69 (46–78)	0.383
Treatment	Steroid with immunosuppressant	0	3	0.292
	Steroid only	3	4	
Follow-up period (range) (mo)		23 (18–39)	29 (3–127)	0.905

DISCUSSION

One-third of OMAAV patients had vestibular symptoms (Group I, Table 2) and one-third of OMAAV patients with vestibular symptoms developed intractable persistent dizziness (Table 5). Irrespective of the presence or absence of vestibular symptoms, bilateral or at least unilateral vestibular periphery was affected in 84% of the OMAAV patients (Table 4); this suggests that OMAAV is not just an ''otitis media'' with AAV, but may also be a vestibular disease. It was difficult to predict the development of vestibular symptoms based on age, sex, affected side (unilateral or bilateral), ANCA status, involvement of other organs, or hearing level before treatment (Table 2). Regarding the final vestibular outcome among the symptomatic vestibular patients, all three patients who developed persistent and intractable dizziness received a less intensive treatment without immunosuppressive agents, and all three patients who received intensive combination therapy with steroids and immunosuppressants recovered from the vestibular symptoms (Table 5). This indicates that aggressive combination therapy may prevent the development of intractable persistent dizziness in OMAAV patients.

Our findings suggest that there might be two types of vestibular symptoms in OMAAV patients (Table 3): chronic dizziness accompanied by progression of hearing loss and acute vertigo attack with sudden hearing loss that mimics sudden deafness. In the latter case, vertigo may be caused by acute dysfunction of the vestibular periphery, and, it would be difficult to make a correct diagnosis of this condition as an OMAAV at the early stage. Clinicians should consider OMAAV as a differential diagnosis of sudden deafness, if faced with atypical clinical course such as fluctuation of the hearing level, and the contralateral occurrence of acute hearing disturbance. Chronic dizziness occurred along with progressive hearing loss, suggesting that these types of vestibular symptoms may be due to insufficient compensation, especially in the bilaterally affected patients. It is notable that episodic vertigo mimicking Ménière's disease with

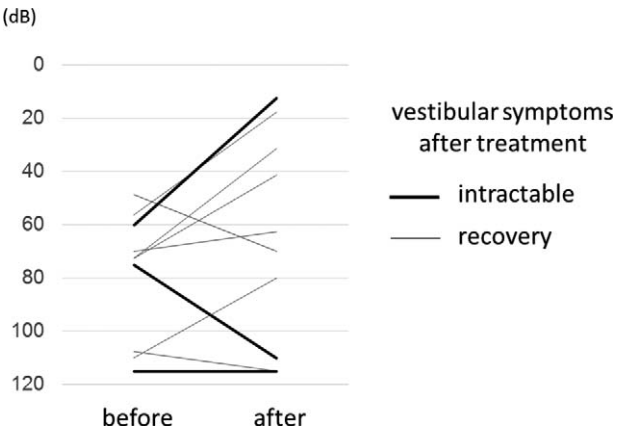

FIG. 1. Hearing outcome of worse hearing ear (dB) in symptomatic Group I patients. Hearing threshold before treatment was not different between patients who had intractable vestibular symptoms (n = 3, *thick lines*) and those recovered from vestibular symptoms (n = 7, *thin lines*). There was also no difference in the posttreatment hearing threshold or hearing recovery between the two groups.

suspected endolymphatic hydrops was not observed in OMAAV.

Regarding the origin of vestibular symptoms in OMAAV patients, there might be two mechanisms, namely peripheral and central. It has been reported that AAV can affect the central nervous system and cause complications such as hypertrophic pachymeningitis, pituitary involvement, and cerebral vasculitis in 7 to 11% of GPA patients (12). In our study, unilateral or bilateral caloric weakness was observed in 84% of OMAAV patients, and VOR gain for both directions was reduced in symptomatic patients (Table 4). Moreover, there was no obvious abnormality in ETT and OKN (Table 4). These results suggest that the symptoms may be due to a peripheral vestibular disorder. Regarding the findings observed in the inner ear, the temporal bone histopathological studies in GPA patients revealed hemorrhage in the stroma of the crista of semicircular canals, changes in vessel caliber, and lymphocytic infiltration (13). With respect to the intractability of vestibular symptoms in OMAAV patients, hearing improvement tended to be better in the final vestibular asymptomatic group (Fig. 1); all three patients who developed intractable persistent dizziness did not receive combined therapy (steroid plus immunosuppressant) (Table 5). We suppose that the significant changes observed in the inner ear would be resistant to steroid therapy, and that a combination with immunosuppressive agents should be administered to OMAAV patients for treatment of auditory and vestibular disturbances.

A limitation of this study was that the number of patients who ultimately developed intractable dizziness was small. Although immunosuppressive therapy in addition to steroid treatment may be effective for preventing progression to intractable dizziness, other variables such as general health, lifestyle, other systemic diseases, and genetics might also influence the rate of recovery. In future studies, these parameters should be investigated using a multivariate analysis.

CONCLUSION

One-third of OMAAV patients showed vestibular symptoms of peripheral origin. Acute vertigo attack or chronic dizziness can occur in OMAAV patients, whereas episodic vertigo may be rare in these patients. One-third of symptomatic patients ultimately developed intractable persistent dizziness. Initial intensive treatment with combination therapy using steroids and immunosuppressive agents may be effective in preventing the development of intractable persistent dizziness.

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