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Wegener granulomatosis as possible cause of vertigo: case report and review

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Abstract. *Wegener granulomatosis as possible cause of vertigo: case report and review. Objective:* Wegener granulomatosis (WG) or granulomatosis with polyangiitis (GPA) is a multi-system necrotizing granulomatous vasculitis that classically affects the upper respiratory tract, lungs and kidneys. We report the unusual clinical course of a patient with WG, and we present a literature review on the association between WG and vertigo.
Results: In our case, a 56-year-old female presented with a several-month history of chronic sinusitis and otalgia that was refractory to all initiated outpatient therapies. During hospitalization, a diagnostic evaluation revealed serious nasal crusting, chronic otitis media, and hematuria. Serologic testing showed elevated anti-neutrophil cytoplasmic antibodies (c-ANCAs). The tentative diagnosis of Wegener granulomatosis was confirmed by renal biopsy. Upon admission, the patient developed an acute vertigo with nystagmus, nausea, and vomiting, accompanied by sensorineural hearing loss in one ear.
Conclusions: Vestibular symptoms may be associated with Wegener granulomatosis.

Introduction

Wegener granulomatosis (WG) or granulomatosis with polyangiitis (GPA) is a multi-system necrotizing granulomatous vasculitis that classically affects the upper respiratory tract, lungs and kidneys. Common upper respiratory tract symptoms are nasal obstruction or discharge, bloody crusting, epistaxis and chronic sinusitis. Also middle ear effusion, conductive hearing loss and otalgia are common otologic manifestations of the disease.

A less common otologic symptom is sensorineural hearing loss, and vestibular dysfunction is rather exceptional. We present a case of a patient with WG with classical onset but who developed an unusual course of symptoms with inner ear manifestations. A brief literature review on vertigo in the context of WG is presented.

Case report

A 56-year-old Caucasian female with a medical history of arterial hypertension and reflux disease was referred to our hospital. She quit smoking 7 years prior, with a total exposure of 15 pack years. Her complaints started with a severe cold four months before admission to our hospital. In the following months she experienced a persisting nasal discharge, nose blockage, and headache. A few months after onset, she developed a middle ear effusion in both ears and complained of hearing loss and aural fullness. She mentioned intermittent fever. Before admittance, she had been closely followed by an otolaryngologist. She was treated with several oral antibiotic (amoxicillin/clavulanate, ciprofloxacin) and steroid therapies. Tympanostomy tubes were placed, resulting in ongoing, serous otorrhea. Local eardrops containing dexamethasone, neomycin, and polymyxin B were administered. Several swabs were taken, but cultures remained sterile. All of the therapies that were initiated realized very little or no improvement.

At the time of referral, the main complaints were earache and right-side hemifacial pain, bilateral hearing loss, aural fullness, and limited ear discharge. There was a free nasal airway, watery rhinorrhea, and limited nasal spotting of blood. The throat was sore, and clinical examination of the oral cavity showed a greenish-yellowish post-nasal discharge. The rhinoscopia anterior showed serosanguinous crusting. Crusting was also visualized deeper in the nose by endoscopy, and lymphoid tissue in the nasopharynx was highly inflamed and edematous. There was a whitish discharge in both

external ear canals, the eardrum was thick and opaque bilateral and drains were both patent. Examination of neck did not reveal any pathological lymph nodes.

Laboratory tests showed a normal white blood cell count, thrombocytosis of 475 10^E9/L, elevated blood sedimentation rate of 53 mm/h, C-reactive protein 141.5 mg/L, and a limited disturbed liver panel. Pure tone audiometry showed mixed hearing loss in both ears with a dominant conductive component in the lower and mid frequencies and sensorineural hearing loss, predominantly in the higher tones (Figure 1).

The patient was hospitalized with a working diagnosis of rhinosinusitis with a prolonged course and middle ear involvement. Therapy was initiated with intravenous ciprofloxacin (2×200 mg/day) and oral methylprednisolone. Because of the preceding prolonged course, additional blood tests were performed. Indirect immunofluorescence showed a positive result for antinuclear factor (ANF) with a granular cytoplasmic pattern and titer of 1/400 (normal value <1/100). Screening for anti-neutrophil cytoplasmic antibodies (ANCA) was positive and showed a cytoplasmic pattern (c-ANCA). Further testing showed increased levels of anti-Proteinase 3 (19 IU/ml, normal value <3 IU/ml). Proteinase 3 (PR3) is a common antigen for ANCA. Therefore, Wegener granulomatosis was presumed, and therapy with ciprofloxacine was ceased.

In an attempt to confirm the diagnosis histologically, tissue biopsies were taken from the nasal septum and nasopharynx a few days after admission. Septal biopsies showed severe acute ulcerative and chronic inflammation with formation of inflammatory granulation tissue, and nasopharyngeal biopsies showed signs of acute and chronic inflammation. Pathognomonic features of Wegener vasculitis (granulomas, vasculitis and geographical necrosis) were absent. Immunohistochemistry to detect CD68, a marker for various cells of the macrophage lineage, showed scattered macrophages but no granuloma formation.

A chest CT scan revealed a pulmonary opacity in the left apex, suspected to be a granuloma, with bibasal thickening of the bronchial wall and limited bronchiectasis. No signs of interstitial lung disease were observed, and spirometry tests were normal. Ultrasound revealed no abnormalities in the liver or in the remaining abdomen, and hepatitis serology was also negative; the disturbed liver values were presumed to be related to prior therapies with amoxicillin/clavulanate. During the course of hospitalization the patient gradually developed an active urinary sediment with progressive hematuria and proteinuria. A renal biopsy was performed, which revealed a segmentary necrotizing glomerulonephritis and necrotizing vasculitis from the small arteries. Immunofluorescence test on the renal tissue was negative, and renal function tests remained normal.

Based on clinical, biochemical, and histopathological findings, the diagnosis of Wegener granulomatosis was made, mainly with upper respiratory tract involvement. A more intensive work-up could not detect major organ involvement,

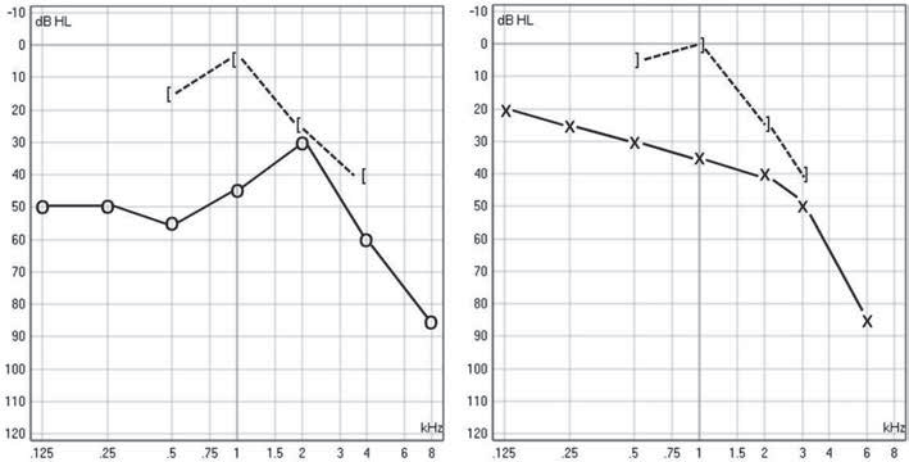

Figure 1
Pure tone audiometry at admission

except for limited renal damage. Immunomodulation therapy was initiated. Induction therapy started with cyclophosphamide (1.5 mg/kg/day for at least 12 weeks until remission), methylprednisolone (1 mg/kg/day for 1 month, then 16 mg/day in month 2-3, and 5-10 mg/day in month 4-6), trimethoprim/sulfamethoxazole (800/160 mg given 3 times/week), and calcium/vitamin D (1000/880 mg daily) for bone protection.

Just before initiation of the immunomodulation therapy, the patient developed acute vertigo with nausea and vomiting. She also mentioned increased hearing loss in her left ear and an altered taste. Examination with Frenzel goggles showed a spontaneous nystagmus to the right side with a torsional component in 3 gaze directions. The nystagmus declined by fixation. Upon performing the head impulse test to the left-hand side, there was a corrective saccade visible, indicative of an inadequate vestibulo-ocular reflex due to disturbed semicircular canal function of the left side. During the Romberg test the patient exhibited a tendency to fall to her left-hand side, and Unterberger's test showed a leftward rotation. A hearing test confirmed sensorineural hearing loss in her left ear (Figure 2).

A brain MRI did not reveal any signs of meningeal enhancement, meningitis or venous thrombosis. There were normal findings in the internal auditory meatus. It revealed a bilateral otomastoiditis without complications, no pathological staining of the labyrinth or cochlea was observed. On neurologic examination no abnormalities could be detected except for a hyperesthesia in the right trigeminal region (V_I, V_{II}, V_{III}) and a sense of blurred vision in the right temporal quadrant. Cerebrospinal fluid (CSF) examination was normal, as was ophthalmologic examination.

So the patient exhibited a vestibulocochlear deficit and limited signs of cranial neuropathy; however, there was a rapid recovery from the cranial neuropathy after initiation of the immunosuppressive therapy. The dizziness and hearing loss resolved only at a later stage. One month after the onset of vertigo, an electronystagmography was performed. There was no spontaneous nystagmus, and both oculomotor tests and a rotary chair test were normal. No caloric testing was performed because of the tympanostomy tubes and unfortunately we did not have the possibility of caloric air irrigations. We did not perform vestibular evoked myogenic potential (VEMP) testing to evaluate the structures innervated by the inferior vestibular nerve because the device was not at our disposal. Caloric irrigations will be performed in the near future when the tubes are expelled. Five weeks after starting therapy, the patient's hearing returned to normal (Figure 3). Her nasal complaints also resolved completely.

Discussion

Wegener granulomatosis, also known as granulomatosis with polyangiitis (GPA), is a vasculitis that affects small- and medium-sized vessels in many organs. The vessels are attacked by circulating pathologic antibodies, named antineutrophil cyto-

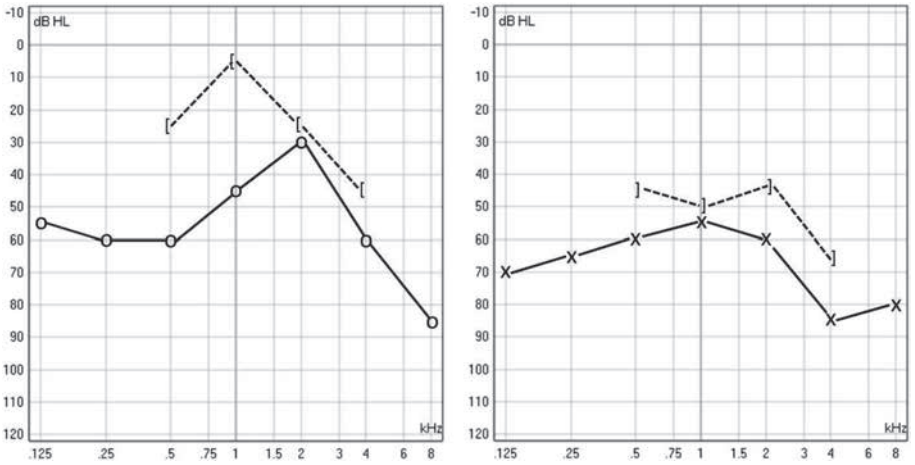

Figure 2
Pure tone audiometry at time of vestibulocochlear deficit

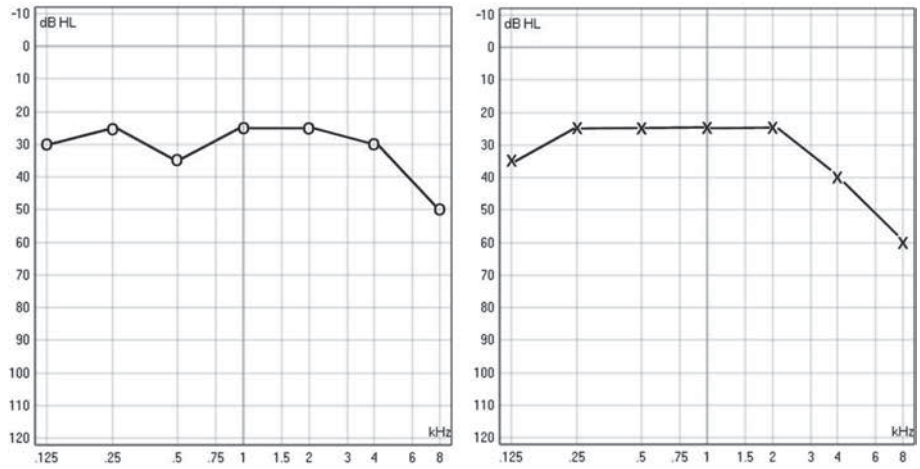

Figure 3
Pure tone audiometry after immunosuppressive treatment

plasmic antibodies (ANCA). Classically it affects the triad of upper airway, lower airway, and kidneys, although any organ system can be involved. It has an incidence of 1 in 25.000, with a mean age at onset of 41 years. Ninety percent of the patients are Caucasian.[1,2] Diagnostic criteria are summarized by the Chapel Hill Consensus Conference.[3] The diagnosis is based on the presence of typical organ involvement and histopathological proof of vasculitis, granulomatous inflammation, and necrosis. The presence of c-ANCA has a high specificity for GPA (80-98%), with PR3 as target antigen. However, c-ANCA are also associated with other diseases, and some cases of GPA remain seronegative. Therefore, a positive identification of c-ANCA is suggestive of GPA but it is not definitive, and cannot replace a biopsy.[1,3,4]

ENT symptoms in GPA

More than 90% of patients with GPA have upper airway involvement.[2,3] Very often the symptoms are nonspecific, such as nasal obstruction or discharge, bloody crusting, epistaxis, chronic sinusitis, middle ear effusion, and otalgia. That is why diagnosis is frequently delayed. Otologic symptoms in GPA have an incidence of 30-50%. Most common otologic symptoms include serous and purulent otitis media, conductive hearing loss, and otalgia. The middle ear problems are due to the presence of the granulomatous necrotic tissue in the middle ear or granulomatous nasopharyngeal involvement with secondary Eustachian tube dysfunction.[2,6] Less common symptoms are sensorineural hearing loss (in 13-43%) and facial palsy.[4,5] Vestibular dysfunction is rather exceptional. In contrast to middle ear disease, the mechanisms of inner ear disturbance are poorly understood.[3] Inner ear damage is presumed to be the consequence of necrotizing vasculitis of the small vessels, along with deposition of immune complexes and granulomatous involvement (loco-regional extension of middle ear inflammation) of the cochlear and/or the vestibular nerves. The rich vascular network of the stria vascularis probably makes the cochlea more susceptible for the damage caused by GPA than the vestibulum.[2,4,9]

Inner ear pathology

Unfortunately, only a limited number of studies of human temporal bones derived from patients with GPA are available to explore the inner ear damage. The morphologic changes found are consistent with two different pathogenic mechanisms in the inner ear. The first is fibrosis and osteoneogenesis within the scalae, which is consistent with the end stage of inflammation caused by vasculitis. There are other changes most likely caused by ischemia, including cellular atrophy with no evidence of inflammation. The vascular compromise is then probably secondary to a nonspecific vasculopathy, with occlusion of the labyrinthine artery, without signs of vascular inflammation and necrosis.[7] One report, by Leone *et al*.,[8] describes postmortem findings from a patient with GPA and sensorineural hearing loss, in which an obvious

thickening of the vessels adjacent to the endolymphatic sac was observed, with otherwise normal-appearing cochlear vessels. Leone and co-workers claimed that immune complex deposition in the capillaries of the endolymphatic sac induced alterations in the composition of endolymph, thus altering the vestibule-cochlear microenvironment.[8,9] This could be an alternative explanation for the vertigo and sensorineural hearing loss. The labyrinthine artery, originating from the anterior inferior cerebellar artery, provides the principal blood supply to the inner ear. Depending on the particular branches involved, vasculitic, thromboembolic, or other pathologic processes of the inner ear may present with a variety of vestibular and auditory signs and symptoms.[10]

Central nervous system and cranial nerve involvement

Central nervous system (CNS) involvement is infrequent but can have disastrous consequences including stroke, cerebrovascular events, and seizures. More common CNS symptoms are meningeal involvement and cranial nerve anomalies such as neuropathy. The incidence of CNS anomalies in GPA patients is 2-8%. CNS and meningeal involvement can be explained by three different pathogenic patterns. First, it can be due to contiguous invasion of granuloma originating from the upper respiratory tract in meninges, brain, and cranial nerves (e.g., optic nerve). Secondly, remote intracranial granulomatous lesions can develop in intracerebral tissues, such as brain or meninges. Third, as a manifestation of generalized disease, the vasculitis may affect small- to medium-size vessels in the brain or in the vasa nervorum of cranial nerves.[11,12]

Cranial nerves seem to be affected along their extracranial route by local granulomatous and/or destructive inflammation. Cranial neuropathy occurs in 5-10% of cases. Most frequently, cranial nerve anomalies occur in the optic nerve due to local granuloma extension from the orbit. Next to the optic nerve, palsies are described in the third, fifth, sixth, seventh, and eighth nerve, usually in combination with pachymeningitis.[12]

Pathogenic hypothesis for the presented case

The question of whether the vestibulocochlear deficit was due to localized extension of middle ear inflammation, endolymphatic toxicity from inflammatory metabolites, to vasculitis of the inner ear, or to neuropathy of the vestibulocochlear nerve, remains unresolved. However, the presenting nystagmus was a pathognomonic sign of involvement of at least the lateral semicircular canal (horizontal nystagmus to the right side) and probably also the superior semicircular canal (torsional component) or even to a reversible neuropathy of the superior vestibular nerve. The total recovery achieved after initiation of therapy suggests that no sensory cells or neural fibers were destroyed. In addition to the vertigo, the patient also developed mild signs of other cranial neuropathies, which might have been due to meningeal irritation or to a minimal vasculitis neuropathy. However, a brain MRI did not disclose any abnormalities as such, and the CSF was normal. Involvement of the brainstem is less probable because we expect that an extended lesion affecting the cochlear and the various vestibular nuclei should have been visible on central imaging or by lumbar puncture. In this report, we attempted to document the vestibular deficit, but since we could not perform caloric tests, the presence of a vestibular hyporeflexia could not be proved. VEMP testing and brainstem auditory potentials would also have added information about cochlear and vestibular nerve involvement.

Treatment and prognosis

Treatment involves induction therapy and maintenance. The first goal is to achieve complete remission with corticosteroids and cyclophosphamide. Alternately, rituximab or methotrexate can also be administered instead of cyclophosphamide. This can take 2-6 months. After obtaining remission, maintenance therapy is used to prevent relapse. Maintenance therapy consists of less toxic immunosuppressive medication such as azathioprine or methotrexate, if necessary administered with low doses of steroids. The duration of the maintenance therapy is at least 2-4 years after remission. Cotrimoxazole is given to prevent pneumocystosis, which is a risk associated with the CD4 deficiency that is caused by cyclophosphamide.[1,14] Untreated, GPA mortality up to 90%.[1] The remission rate ranges from 30-93% depending on the precise definition of remission and the remission induction therapy used. Unfortunately, relapse is not uncommon, up to half of patients

experience a relapse within 5 years.[13] Absence of renal involvement correlates with a 100% 5-year survival rate, compared with a 5-year survival rate of 70% in individuals with renal disease. Overall, the 10-year survival rate ranges from 75-88%, with some of the mortality due to toxicity of treatment.[15]

Conclusion

Although this patient presented with a fairly typical onset of WG, it took several months to establish a correct diagnosis. The remarkable feature of this case was the unusual course of symptoms, with development of vertigo. Otitis media and conductive hearing loss are frequent otologic symptoms in WG. Sensorineural hearing loss may also occur in this context, but the association with vestibular symptoms is uncommon. There are only a few reports in the literature on this subject. Despite the cochlea and labyrinth forming one solid structure, the cochlea is preferentially the target in WG.

It is important to remember that in cases involving prolonged symptoms of chronic rhinosinusitis that are refractory to therapy, especially when present in combination with chronic otitis media, the possibility of WG should be considered. The vertigo observed in this case warrants further research on the mechanisms of vestibular disorders in WG, as it can lead to new treatment options such as the possible benefit of intratympanic corticosteroids.

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