Cochlear impairment and autoimmune ear disorder in a patient with breast cancer

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Abstract

The purpose of this study was to consider the possible role of autoimmune diseases and paraneoplastic syndrome in the genesis of tinnitus. The incidence of autoimmune inner ear disease (AIED) is rare, accounting for <1% of all cases of hearing impairment and dizziness. In presence of auditory and vestibular deficit in oncological patients, a paraneoplastic syndrome with cochleovestibulopathy should be considered. We described a 50-year-old Caucasian woman came to our attention with complaints of severe disabling bilateral tinnitus (Tinnitus Handicap Inventory, THI: 96), ear fullness and headache. The onset of tinnitus was associated to the last breast implant and prolonged antibiotic therapy. Serological autoimmunity tests were positive and a diagnosis of mixed connective tissue disease with notes of fibromyalgia was made**.** Pure tone audiometry testing revealed bilateral fluctuating mild hearing loss on high frequencies. The tinnitus was successfully treated with bilateral wideband sound generators (listening 8-9 h for day) regulated at the mixing point. At 12 months follow up THI has shrunk considerably (THI: 4) and the patient has continued treatment only with the sound pillow.

In conclusion significant progress is needed to better understand the role of autoantibodies in the pathogenesis and diagnosis of paraneoplastic cochleovestibulopathy. To our knowledge, our study is the first in which hearing loss and tinnitus is considered as a manifestation of a paraneoplastic syndrome.

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Introduction

In the field of audio-vestibular disorders there is a group of diseases, identified for the first time by McCabe in 1979 and named "Autoimmune Inner Ear Disease" (AIED), characterized by the progressive loss of function of the inner ear on autoimmune basis due to the damage of the inner ear's structures.[1]

The incidence is rare, accounting for <1% of all cases of hearing impairment or dizziness.

The limiting factor in the evaluation of autoimmune diseases of the inner ear, is that it is in a bone capsule and therefore inaccessible to most of the immunobiological techniques; all the scientific studies on autoimmune diseases of the inner ear are based mostly on statistical analysis and animal models without a full consensus on the diagnostic and therapeutic aspects.

AIED presents an extreme variability of the clinical onset and evolution.[2] AIED is more common in females and in middle age patients. In most cases it manifests with bilateral sensorineural hearing loss, with rapid progression or fluctuating for periods of several months, fullness and tinnitus. The vestibular symptoms are present in 50% of cases and they are characterized by instability and sometimes by vertigo associated with hearing loss that simulates a Meniere's disease. In 30% of cases there is a systemic autoimmune disorder.[3]

This clinical picture is due to an immunological activity, which is fitted to the inner ear; in particular the endolymphatic sac has all the cell constituents needed to process the antigen and produce a cellular and humoral immune response.[4] In a recent study, audiovestibular disorders like vertigo, hearing loss, fullness and tinnitus are suggested as an attempt of the immune system to develop anti-melanoma response.[5] The immune system produces antibodies that cross-react with both the melanoma cells and the labyrinth melanocytes causing an altered homeostasis of endolymphatic liquids.

The diagnosis of AIED is very problematic in the absence of specific laboratory test for this disease. The gold standard would be represented by the availability of specific tests such as the Western Blot test to identify a portion of a protein of 68 kD which corresponds to the heat shock protein 70 (HSP 70): this would be the target of antibodies in the serum of patients with AIED.[6-8] To date, however, the Western Blot has a low sensitivity regarding the stage of the disease. Of a certain utility may be the execution of a battery of not antigen-specific immunological tests. Even though they are not strictly related to the diagnosis of AIED, these tests may at least indicate a systemic immune dysfunction. Their negativity does not rule out an immune-mediated disease.[9]

Autoimmune diseases and symptoms can sometimes be included within what is called paraneoplastic syndrome of a tumor. They may precede the onset of cancer or be an indicator of its reactiva-

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tion.[10] Different tumors may give a paraneoplastic syndrome such as the small cell cancer, breast and ovarian cancer and seminoma.[11] The paraneoplastic syndrome can affect different organs and tissues with different mechanisms. The majority is due to the production by the tumor of substances that mimic the physiological hormones;[10,12] a small part is immune based. According to this hypothesis the paraneoplastic syndromes would result from activation of the immune system induced by the contact between mesenchymal and epithelial cells or neuroectodermal, invaded by the tumor through the basal membrane or the blood-brain barrier.[11] The inner ear could be affected because the endolynphatic sac is involved in the processing of antigens with immune response.[4]

Case Report

A 50-year-old Caucasian woman came to our attention complaining about severe disabling bilateral not pulsatile tinnitus, ear fullness, headache and mild imbalance. The patient reported previous thyroidectomy for autoimmune thyroid disease (ATD) at 29 years and 3 breast surgeries for a triple negative invasive breast ductal carcinoma followed by breast implant. The onset of tinnitus had taken place 1 month after the last breast surgery (breast implant asportation after infection with prolonged antibiotic therapy). In spite of different medical therapies, there was no tinnitus improvement. Meanwhile the tinnitus worsened with a pitch of 8 kHz, loudness of 15 dBSL, minimum masking level (MML) of 35dB and complete residual inhibition. TEOAE were bilateral pass, DPOAE were pass on the right and refer on the left. Insomnia and concentration problems due to tinnitus lead to severe disability and a poor quality of life. The impact of tinnitus on quality of life was evaluated with the Tinnitus Handicap Inventory (THI) (Table 1). Usually we use psychological questionnaires for anxiety and depression, to evaluate a patient affected with tinnitus but in this case, as she was a psychologist, we decided to use the THI as main outcome measure. Pure tone audiometry testing revealed bilateral fluctuating mild hearing loss on high frequencies (Figure 1). Tympanogram was normal bilaterally. Auditory evoked potentials were normal. Computed tomography (CT) of temporal bone was normal. Magnetic resonance imaging (MRI) and angio-MRI resulted normal and negative for cerebral ischemia and acoustic neuroma. The positive serological markers of autoimmunity are reported in Table 2. A diagnosis of mixed connective tissue disease with notes of fibromyalgia was made. Results of diagnostic tests are reported in Table 3.

The tinnitus was successfully treated with bilateral wideband sound generators (listening 8-9 hours per day) regulated at the mixing point. The sound generators were adjusted everyday from the patient in such a way that it equalized the level of the perceived tinnitus. These devices were wearable using thin tubes (open fit). The patient used them for 4 months. Shortly after 1 month of a standard fitting procedure the patient reported a significant reduction of her tinnitus (THI: 36). The tinnitus worsened after 2 months (THI: 65) in relation to two transient facial hemipareses, hearing fluctuations and ear fullness. The hemipareses were promptly treated with corticosteroids (prednisone) and completely resolved. A fourth breast cancer recurrence (triple-negative breast cancer, T1 with high histological grade G3 N1 M0), created a suspicion of a paraneoplastic syndrome in relation to the complex symptomatology (Table 4): weight loss, transient visual loss, transient facial hemiparesis, tinnitus, ear fullness, fluctuating mild hearing loss on high frequencies, stomatitis, chronic bronchitis. Subsequently, the patient underwent mastectomy, medical therapy with pregabalin and tapentadol and then chemotherapy with cyclophosphamide,

Table 1. THI at T0 and follow up after 1 month (T1), 2 months (T2) and 4 months (T4), one year (T5).

	T0	T1 (1 month)	T2 (2 months)	T3 (4 months)	T5 (1 year)
THI	96	36	65	36	4

Table 2. Serological autoimmune markers.

Serological autoimmune markers	
Antinuclear antibodies (ANA)	+
Anti-extractable nuclear antibodies (ENA)	+
Anti-smooth muscle antibodies (ASMA)	+
Scl-70 antibodies	+

Table 3. Diagnostic tests.

Diagnostic tests	
Tympanogram	Normal
TEOAE	Pass bilateral
DPAOE	Pass right
Refer left	
ABR	Normal
Brain MRI	Normal
Angio-MRI	Normal
PET-CT	Normal
CT of the temporal bone	Normal

Table 4. Symptoms related to the paraneoplastic syndrome.

Symptoms related to the paraneoplastic syndrome
Weight loss
Transient visual loss
Transient facial hemiparesis
Tinnitus
Ear fullness
Fluctuating mild hearing loss on high frequencies
Stomatitis
Chronic bronchitis

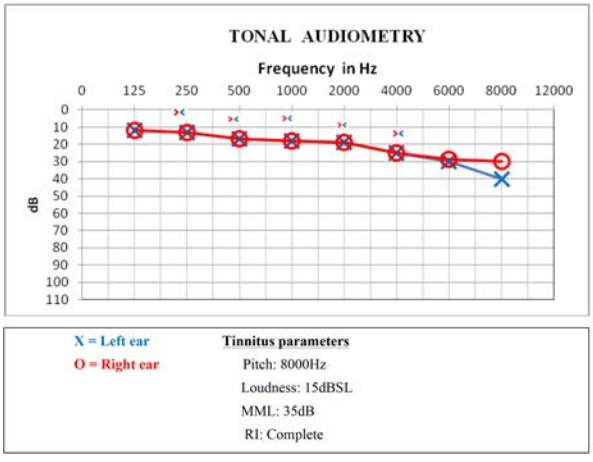


Figure 1. Audiometric test.

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methotrexate and 5-fluorouracil (CMF). After mastectomy and chemotherapy there were no more episodes of facial hemipareses or hearing fluctuations, and the patient was subjected to controls over time. At 4 months follow up the tinnitus was stable (THI: 36) and it was treated with sound enrichment. One year after the tinnitus onset, the THI has shrunk considerably (THI: 4) and the tinnitus was treated only with the sound pillow. The patient followed a self-modified CBT approach in addition to the sound therapy. She refused the cognitive-behavioral counseling with the psychologist. Instead, being a psychologist, she decided to apply the principles of CBT to identify, challenge and modify her unhelpful thoughts in response to tinnitus. The clinician also offered to the patient a complete education based on the outcomes of her audiological, radiological and serological investigations and the theoretical basis of habituation based on the Jastreboff neurophysiological model. Of course we have to acknowledge that this adaption had a presumably positive effect, even if we cannot measure the true impact of the "self-treatment". Therefore, it is impossible to say the extent our TRT with sound therapy helped the patient aside from her own "self treatment."

Discussion

Our work yielded two major findings: (i) a possible role of AIED should be considered in patients with audiovestibular disorders (ii) tinnitus in oncological patients may be undervalued in a context of a paraneoplastic syndrome. AIED presents an extreme variability of the clinical onset and evolution.[2] In accordance with reports from the literature about AIED cases our patient is female, in middle age, she presented with bilateral sensorineural hearing loss, with rapid progression or fluctuating for periods of several months, fullness and tinnitus, she had postural instability and in the past she had ATD.

Regarding the treatment of auditory symptoms in AIED cases, the literature does not retain a clear evidence from high-quality prospective trials of an effective treatment for AIED. Some authors suggest in case reports an effective treatment of hearing loss and tinnitus in patients with AIED using respectively infliximab[13] and adalimumab.[14]

In the literature a rare case of pulsatile audible tinnitus is reported, caused by metastatic breast carcinoma of the temporal bone.[15] Although characterized as type VI (non-immune rapidly progressive sensorineural hearing loss) within the Harris autoimmune inner ear disease classification system, the mechanism of paraneoplastic cochleovestibulopathy is not well understood.[16] Autoantibody production would lead to such damage to the involved tissues and organs and would explain the appearance of certain well-defined symptoms. In particular the endolymphatic sac has all the cell constituents needed to process the antigen and produces a cellular and humoral immune response.[17,18] The "cross-reaction" theory is the most favored; antigen induces the release of interleukin, particularly IL-2, which filters through the endothelium attracting lymphocytes, with a progressive increase in number.[19] This phenomenon would result in a damage of the acoustic and vestibular system cells, causing tinnitus, vertigo or dizziness and hearing loss; in some cases it can lead to cochlear fibrosis and ossification.[20] The cochlin protein seems to be a more likely candidate as the target of the autoimmune response.[21]

Some authors reported the occurrence of a paraneoplastic cerebellar syndrome characterized by vertigo and anti-Purkinje cell antibodies (anti Yo) related to a breast cancer.[22,23] In tinnitus pathogenesis also the pharmacologic therapy could play an important role. The effects of cochlear damage by intense sounds (acoustic trauma), ototoxic drugs (carboplatin, but some data for salicylate, kanamycin, and neomycin) on neurotransmission in the central auditory system have been studied as a cause of tinnitus in a study on different species of rodents.[24] The main results obtained on chemical changes after cochlear damage induced by ototoxic drugs were the altered levels of glutamate, aspartate and Gaba together with high levels of glycine, taurine, glutamine and serotonin. The conclusion of the authors is that tinnitus comes from an imbalance between excitatory and inhibitory neurotransmission system. The American Tinnitus Association has distributed a list of drugs that have demonstrated tinnitus side effects as indicated in the 1995 "Physicians Desk Reference"; methotrexate is included in this list.[25] It is a folic acid antagonist. Low folic acid levels can cause different effect such as vertigo, dizziness and tinnitus. We also must consider the psychological aspect of the patient in tinnitus perception. For example, the severity, loudness and annoyance of tinnitus seem to be important factors reflecting psychological problems. Tinnitus-related anxiety and depressive symptoms and handicap may be significantly associated with proneness to negative affective emotional states and catastrophic thinking if specific problems are actual and present. Major limitations of the study are: (i) the lack of psychological tests used to complete the evaluation of the patient, (ii) a major confounding variable in the treatment outcome because the patient was a psychologist and she applied CBT to herself. Due to the lack of specific diagnostic tests for AIED, we strongly recommend to evaluate patient with steroid-responsive fluctuating asymmetrical sensorineural hearing loss including a detailed history and physical examination, audiogram, MRI and routine serology tests for autoimmune diseases.

Conclusions

As reported in the literature the frequency of autoimmune diseases seems to be higher in patients suffering from ATD and the frequency of fibromyalgia is higher in women with breast implant rupture or extracapsular silicone. It remains to clarify the exact mechanism that determines the appearance of cochleovestibular disorders in a context of a paraneoplastic syndrome. The evaluation of auditory and vestibular function in these patients can lead to a proper diagnosis and therapy. Significant progress is needed to better understand the role of autoantibodies in the pathogenesis and diagnosis of paraneoplastic cochleovestibulopathy.

References

1. McCabe BF. Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol 1979;88:585-9.
2. Bovo R, Ciorba A, Martini A. Vertigo and autoimmunity. Eur Arch Otorhinolaryngol 2010;267:13-9.
3. Mijovic T, Zeitouni A, Colmegna I. Autoimmune sensorineural hearing loss: the otology-rheumatology interface. Rheumatology (Oxford) 2013;52:780-9.
4. Takahashi M, Harris JP. Anatomic distribution and localization of immunocompetent cells in normal mouse endolymphatic sac. Acta Otolaryngol 1988;106:409-16.
5. Barozzi S, Ginocchio D, Socci M, et al. Audiovestibular disorders as autoimmune reaction in patients with melanoma. Med Hypotheses 2015;85:336-8.
6. Bovo R, Aimoni C, Martini A. Immune-mediated inner ear disease. Acta Otolaryngol 2006;126:1012-21.

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7. Moscicki RA, San Martin JE, Quintero CH et al. Serum antibody to inner ear protein in patients with progressive hearing loss. JAMA 1994;272:611-6.
8. Block DB, San Martin JE, Rauch SD, et al. The target of antibody in the serum of patients with idiopatic, progressive, bilateral, sensorineural hearing loss (IPBSNHL) is heat shock protein 70 (HSP70). J Allergy Clin Immunol 1995;95:149-56.
9. Hoffer ME, Balough BJ, Gottshall KR. Laboratory testing in the diagnosisand treatment of dizziness. In: Weber PC, ed. Vertigo and disequilibrium. A practical guide to diagnosis and management. Thieme 2008:53-5.
10. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349:1543-54.
11. Ketchandja Ngonga G, Ferrari D, et al. Sindromi paraneoplastiche: teorie eziopatogenetiche, inquadramento clinico e approccio terapeutico. Ann Ital Med Int 2005;20:28-38.
12. Gagel RF. Manifestazioni endocrine dei tumori: secrezione ormonale "ectopica". In: Goldman L, Bennett JC, eds. Cecil. Trattato di medicina interna. Roma: Verduci; 2001. pp 1148-52.
13. Heywood RL, Hadavi S, Donnelly S, Patel N.Infliximab for autoimmune inner ear disease: case report and literature review. J Laryngol Otol 2013;127:1145-7.
14. Marsili M, Marzetti V, Lucantoni M, et al. Autoimmune sensorineural hearing loss as presenting manifestation of paediatric Behçet disease responding to adalimumab: a case report. Ital J Pediatr 2016;42:81.
15. Vasama JP, Pitkäranta A, Piilonen A. Pulsatile audible tinnitus and metastatic breast carcinoma of the temporal bone. ORL J Otorhinolaryngol Relat Spec 2001;63:56-7.
16. Greene JJ, Keefe MW, Harris JP, Matsuoka AJ. Paraneoplastic syndrome: a masquerade of autoimmune inner ear disease. Otol Neurotol 2015;36:3-10.
17. Tomiyama S, Harris JP. The role of the endolymphatic sac in inner ear immunity. Acta Otolaryngol 1987;103:182-8.
18. Arnold W, Altermatt MJ, Gebbers JO, et al. Secretory immunoglobulin A in the human endolymphatic sac. An immunohistochemical study. ORL 1984;46:286-8.
19. Harris JP, Ryan AF. Fundamental immune mechanisms of the brain and inner ear. Otolaryngol Head Neck Surg 1995;112:639-53.
20. Chen MC, Harris JP, Keithley EM. Immunohistochemical analysis of proliferating cells in a sterile labyrinthitis animal model. Laryngoscope 1998;108:651-6.
21. Beak MJ, Park HM, Johnson JM, et al. Increased frequencies of cochlin-specific T cells in patients with autoimmune sensorineural hearing loss. J Immunol 2006;177:4203-10.
22. Adama D, Moussa B, Emmanuel M, Dennis U. Breast cancer revealed by a paraneoplastic cerebellar syndrome: about one case and literature review. Pan Afr Med J 2015;22:25.
23. Key RG, Root JC. Anti-Yo mediated paraneoplastic cerebellar degeneration in the context of breast cancer: a case report and literature review. Psychooncology 2013;22:2152-5.
24. Lee AC, Godfrey DA. Cochlear damage affects neurotransmitter chemistry in the central auditory system. Front Neurol 2014;5:227.
25. Ototoxic Drug Information. American Tinnitus Association: ATA.org

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