

The diagnosis of autoimmune inner ear disease: evidence and critical pitfalls

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Abstract The purpose of this paper is to review the current diagnostic work-up for patients with suspected Autoimmune Inner Ear Disease (AIED). AIED is a rare disease accounting for less than 1% of all cases of hearing impairment or dizziness, characterized by a rapidly progressive, often fluctuating, bilateral SNHL over a period of weeks to months. While specific tests for autoimmunity to the inner ear would be valuable, at the time of writing, there are none that are both commercially available and proven to be useful. Thus far, most of the identified antigens lack a clear association with localized inner ear pathology and the diagnosis of AIED is based either on clinical criteria and/or on a positive response to steroids. For clinical practice, we recommend an antigen-non-specific test battery including blood test for autoimmune disorders and for conditions that resemble autoimmune disorders. Nevertheless, if financial resources are limited, a very restricted work-up study may have a similar efficiency.

Keywords Immunology · Cochlear disorders · Vestibular disorders · Hearing loss

Introduction

AIED is a rare disease accounting for less than 1% of all cases of hearing impairment or dizziness, but its incidence is often overlooked due to the absence of a specific diagnostic test.

Many cases are analogous to rapidly progressive glomerulonephritis, in that inner ear inflammation progresses to severe, irreversible damage within 3 months of onset (often even quicker).

However, steroid responsiveness is high and with prompt treatment, hearing loss may be reversible. Unfortunately, the diagnosis of AIED is still in an experimental phase, as will be discussed in this paper.

Clinical features

The disease seems more common in females between 20 and 50 years of age and manifests itself with the occurrence of a rapidly progressive, often fluctuating, bilateral sensory-neural hearing loss (SNHL) over a period of weeks to months [1]. The progression of hearing loss is often too rapid to be diagnosed as presbycusis and too slow to conclude a diagnosis of sudden SNHL. Generalized imbalance, ataxia, motion intolerance, positional vertigo and episodic vertigo is often present in almost 50% of patients. Bilateral hearing loss occurs in 80% of patients [1], with symmetric or asymmetric audiometric thresholds, although only one ear is usually affected in the early stages. Almost 25–50% of patients also suffer tinnitus and aural fullness, which can fluctuate.

Systemic autoimmune diseases coexist in 15–30% of patients (systemic lupus erythematosus, rheumatoid arthritis, disseminated vasculitis, Sjögren's syndrome, myasthenia gravis, Hashimoto's thyroiditis, Cogan's syndrome, Behçet's disease, sarcoidosis, Wegener's granulomatosis, colitis ulcerosa, relapsing polychondritis).

A detailed history rarely discloses endocrine diseases and/or recurrent fever.

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Otосcopy is usually normal, nevertheless, external ear skin and/or cartilage inflammation and/or facial palsy rarely occurs (e.g., relapsing polychondritis), as well as tissue destruction of the tympanic membrane, middle ear and mastoid (e.g., Wegener's granulomatosis).

Differential diagnosis comprehends : both the sides Menière' disease, luetic inner ear disease, Lyme disease, toxoplasmosis, treatment with ototoxic drugs (gentamicin, cisplatin), Charcot-Marie-Tooth (CMT)-disease (hereditary neuropathy), enlarged vestibular aqueduct syndrome, endocranic hypertension.

Diagnostic criteria

Gloddek [2] suggested that the diagnosis of an autoimmune disease relies on three levels of evidential factors which are, in descending order of importance: (1) direct proof; (2) indirect proof; and (3) circumstantial evidence. Direct proof means the induction of disease in humans by the transfer of auto-antibodies or auto-reactive T cells, which is ethically unacceptable. Indirect proof derives from the induction of autoimmunity in animal models, using the transfer of auto-antibodies or reactive cells. Circumstantial evidence refers to: (1) the association with other autoimmune diseases, (2) lymphocytic infiltration of the target organ, which is impossible to access because the inner ear is not amenable to diagnostic biopsy, (3) genetic restriction to hearing loss and autoimmune disease and (4) response to immunosuppressive therapies [2]. Nowadays, experimental models of autoimmune hearing loss have been developed in a variety of animals [2–4]. The correlation between experimental models in animals and serological findings in humans might be significant [5]. Several studies seem to demonstrate that genetically controlled aspects of the immune system may increase or otherwise be associated with increased susceptibility to different inner ear diseases [6]. Moreover, autoimmune activity in patients with idiopathic hearing loss has been assessed by several different laboratory techniques. Viral infections of the labyrinth are considered a major cause of auditory and vestibular system pathology. Theoretically, an immune response directed against a virus might cross-react with self-protein or auto-antigen, evoking an autoimmune response. However, there is no evidence that serologic studies to role out the involvement of viruses in the development of AIED could be of clinical utility [7].

Therefore, there is now strong evidence to suggest that immune mechanisms are involved in the aetiopathogenesis of inner ear damage, however, at the time of writing, none of the proposed tests for the diagnosis of AIED is either useful, or feasible in clinical practice.

Laboratory studies

Antigen specific tests include: migration inhibition test (MIT), lymphocyte transformation test (LTT) and Western blot analysis for antibodies to inner ear antigen. MIT use is limited because of inherent technical difficulties. Results obtained by LTT are still greatly controversial [1, 8, 9]. Western blot analysis has been extensively used in clinical practice.

In reality, a commercially available test, called “anti-68 kD (hsp-70) Western blot” (OTOblot™) was reported to detect a local autoimmune inner ear process in the absence of any systemic autoimmune process and to be correlated with steroid responsiveness [10, 11]. The test uses purified hsp-70 kDa antigen from a bovine kidney cell line and is based on the assumption that the 68-kDa protein is the heat shock protein 70 (hsp-70) [12, 13]. Unfortunately, this assumption has now been refuted: there is, in fact mounting evidence that the target antigen of the 68-kDa antibody is not the HSP 70 (as was believed over the last 15 years), but the human “choline transporter-like protein 2” (CTL2) [14]. Furthermore, the sensibility reported in different studies is either very low (22% in a study by Gottschlich et al. [11] or positivity is similar in patients with clinical AIED and the normal population [14, 15]. Specificity is also controversial: 5% of the general population is positive as well as 33% of patients suffering from Menière's disease [11, 16]; however, anti-hsp was not found in patients with otosclerosis or Cogan's syndrome [10].

Regarding Menière's disease, it has been demonstrated that the endo-lymphatic sac has an important role in the immuno-mediated reaction and it is believed that an immunological mechanism may be involved in the development of endo-lymphatic hydrops. Several studies demonstrated raised values of circulating immune complexes in a percentage varying from 21 to 96% of Menière's suffering patients. Nevertheless, other serological non-specific immune tests are generally either negative or non-significant [17, 18].

A 30-kDa protein [19] has also received particular attention. This protein was demonstrated to be the major peripheral myelin protein P0, possibly an autoantigen in autoimmune inner ear disease. Despite the initial enthusiasm [20], a recent multi-centric prospective study [21] demonstrated that, in patients with rapidly progressive hearing loss (HL), P0 positive bands were not statistically different from the control group (genetic HL) and in patients with Menière's disease, the prevalence was lower than that of the control group represented by patients with paroxysmal positional vertigo. The authors stress the fact that the recognition of antibodies to myelin P0 is not a useful tool in the diagnosis of autoimmune inner ear disease.

Identification of an antibody to an inner ear supporting cell antigen with immunofluorescence microscopy [22, 23] of guinea pig organ of Corti has been shown to be more sensitive and specific than Western blot [24, 25]. Patients with IF-positive serum are nearly three times more likely to experience improved hearing with corticosteroid treatment than those who are IF negative [24]. Unfortunately, this technique is also not practicable in current clinical practice.

Alternatively, there is seldom convincing evidence from broader laboratory tests indicating autoimmunity. A non-specific antigen-screening test is useful for evidence of systemic immunologic dysfunction; yet does not strictly correlate with the diagnosis of immune-mediated inner ear disease. In clinical practice the antigen-non-specific tests usually recommended are:

1. blood tests for autoimmune disorders: levels of circulating immune complexes, sedimentation rate, antinuclear antibodies (ANA), Raji cell, rheumatoid factor, complement C1Q, smooth muscle antibody, TSH and anti-mitochondrial antibodies, anti-gliadin antibodies (for celiac disease), HLA testing;
2. blood tests for conditions that resemble autoimmune disorders: FTA (for syphilis), Lyme titer, HbA1c (for diabetes, which is often autoimmune mediated also), HIV (HIV is associated with auditory neuropathy).

Nevertheless, García-Berrocal et al. [26] confronted the efficiency of two immunologic work-up study in patients with a high clinical suspicion of autoimmune inner ear disease (AIED). The restricted examination consisting of ANA and immunophenotype of peripheral blood lymphocytes (PBL), demonstrated similar efficiency when compared to a classical work-up study, which costs about five times more. Therefore, an exhaustive immunologic work-up study is not recommended if financial resources are limited.

Conclusion

Based on the clinical and experimental data, today there is strong evidence that immune mechanisms are involved in the aetiopathogenesis of inner ear damage, together with viral infection, trauma, vascular damage and genetic factors. In the cases of AIED, the inner ear inflammation progresses to severe, irreversible damage within a few months of onset (and often much more quickly). At the same time, steroid responsiveness is high and with prompt treatment, hearing loss may be reversible. While specific tests for autoimmunity to the inner ear would be valuable, at the time of writing, there are none that are both commercially available and proven to be useful [5, 27, 28]. Thus far, most of the identified antigens lack a clear association with

localized inner ear pathology and the diagnosis of AIED is based either on clinical criteria and/or on a positive response to steroids. For clinical practice, we recommend an antigen-non-specific test battery including blood test for autoimmune disorders and for conditions that resemble autoimmune disorders. Nevertheless, if financial resources are limited, a very restricted work-up study may have a similar efficiency.

Conflict of interest statement The authors declare that they have no conflict of interest to report.

References

1. Hughes G, Kinney S, Barna B, Calabrese L, Hamid M (1983) Autoimmune reactivity in Menière's disease: preliminary report. *Laryngoscope* 43:410–417
2. Gloddek B, Arnold W (2002) Clinical and experimental studies of autoimmune inner ear disease. *Acta Otolaryngol Suppl* 548:10–14
3. Soliman A (1992) Immune-mediated inner ear disease. *Am J Otol* 6:575–579
4. Hefeneider SH, McCoy SL, Hausman FA, Trune DR (2004) Auto-immune mouse antibodies recognize multiple antigens proposed in human immune-mediated hearing loss. *Otol Neurotol* 25:250–256
5. Soliman A (1989) Experimental autoimmune inner ear disease. *Laryngoscope* 99:188–193
6. Bernstein JM, Shanahan TC, Schaffer FM (1996) Further observations on the role of the MHC genes and certain hearing disorders. *Acta Otolaryngol* 116(5):666–671
7. García-Berrocal JR, Ramírez-Camacho R, González-García JA, Verdaguier JM, Trinidad A (2008) Does the serological study for viral infection in autoimmune inner ear disease make sense? *ORL J Otorhinolaryngol Relat Spec* 70:16–19
8. Berger P, Hillman M, Tabak M, Vollrath M (1991) The lymphocyte transformation test with type II collagen as a diagnostic tool of autoimmune sensorineural hearing loss. *Laryngoscope* 101:895–899
9. Harris J, Sharp P (1990) Inner ear autoantibodies in patients with rapidly progressive sensorineural hearing loss. *Laryngoscope* 100:516–524
10. Moscicki RA, San Martin JE, Quintero CH, Rauch SD, Nadol JB, Bloch KJ (1994) Serum antibody to inner ear proteins in patients with progressive hearing loss. *JAMA* 272:611–661
11. Gottschlich S, Billings PB, Keithley EM, Weisman MH, Harris JP (1995) Assessment of serum antibodies in patients with rapidly progressive sensorineural hearing loss and Meniere's disease. *Laryngoscope* 105:1347–1352
12. Billings P, Keithley E, Harris J (1995) Evidence linking the 68 kilo Dalton antigen identified in progressive sensorineural hearing loss patient sera with heat shock protein 70. *Ann Otol Rhinol Laryngol* 104:181–188
13. Bloch DB, San Martin JE, Rauch SD, Moscicki RA, Bloch KJ (1995) Serum antibodies to heat shock protein 70 in sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg* 121:1167–1171
14. Yeom K, Gray J, Nair TS, Arts HA, Telian SA, Disher MJ, El-Kashlan H, Sataloff RT, Fisher SG, Carey TE (2003) Antibodies to HSP-70 in normal donors and autoimmune hearing loss patients. *Laryngoscope* 113:1770–1776
15. García Berrocal JR, Ramírez-Camacho R, Vargas JA, Millan I (2002) Does the serological testing really play a role in the diagnosis immune-mediated inner ear disease? *Oto-Laryngologica* 122:243–248

16. Shin SO, Billings PB, Keithley EM, Harris JP (1997) Comparison of anti-heat shock protein 70 (anti-hsp70) and anti-68-kDa inner ear protein in the sera of patients with Menière disease. *Laryngoscope* 107:222–227
17. Yoo TJ, Yazawa Y (2003) Immunology of cochlear and vestibular disorders. In: Luxon L., Furman JM, Martini A, Stephens D (eds) *Audiological medicine clinical aspects of hearing and balance*. Martin Dunitz, Taylor and Francis, London, pp 74–75
18. Savastano M, Giacomelli L, Marioni G (2007) Non-specific immunological determinations in Meniere's disease: any role in clinical practice? *Eur Arch Otorhinolaryngol* 264(1):15–19
19. Cao M, Gersdorff M, Deggouj N, Warny M, Tomasi J (1995) Detection of inner ear disease autoantibodies by immunoblotting. *Mol Cell Biochem* 24(146):157–163
20. Passali D, Damiani V, Mora R, Passali FM, Passali GC, Bellussi L (2004) P0 antigen detection in sudden hearing loss and Meniere's disease: a new diagnostic marker? *Acta Otolaryngol* 124(10):1145–1148
21. Pham BN, Rudic M, Bouccara D, Sterkers O, Belmatoug N, Bebear JP, Couloigner V, Fraysse B, Gentine A, Ionescu E, Robier A, Sauvage JP, Truy E, Van Den Abbeele T, Ferrary E (2007) Antibodies to myelin protein zero (P0) protein as markers of auto-immune inner ear diseases. *Autoimmunity* 40(3):202–207
22. Plester D, Zanetti F, Berg P et al (1988) Diagnostic laboratory tool for immune-mediated sensorineural hearing loss. In: Veldman JE, McCabe BF (eds) *Immunobiology, histopathology and tumor immunology in otolaryngology*. Kugler Publications, Amsterdam, pp 33–37
23. Arnold W, Weidauer H, Seelig H (1976) Experimentellerbeweis einer gemeinsamen Anti-genizität zwischen Innenohr und Niere. *Arch Otorhinolaryngol* 212:99–117
24. Zeitoun H, Beckman JG, Arts HA et al (2005) *Arch Otolaryngol Head Neck Surg* 131:665–672
25. Gray et al (1999) ARO abstracts #246
26. García-Berrocal JR, Trinidad A, Ramírez-Camacho R, Lobo D, Verdaguer M, Ibáñez A (2005) Immunologic work-up study for inner ear disorders: looking for a rational strategy. *Acta Otolaryngol* 125(8):814–818
27. Agrup C, Luxon LM (2006) Immune-mediated inner-ear disorders in neuro-otology. *Curr Opin Neurol* 19(1):26–32
28. Bovo R, Aimoni C, Martini A (2006) Immune-mediated inner ear disease. *Acta Otolaryngol* 126(10):1012–1021