Abstract

The inner ear may be damaged by several autoimmune mechanisms, the most frequent manifestation being progressive sensorineural hearing loss with good responsiveness to immunosuppressants. Effort work is justified by the need for further studies relating to sensorineural hearing loss mediated (DNSI), since the pathophysiology of this disease entity per obscure manatee but positive response to immunosuppressive therapy enhances the existence of immunological mechanisms and autoimmune diseases. The overall objective of this work was to perform a literature review on sensorineural hearing loss immune-mediated-DNSI, focusing on the presentation forms and clinical manifestations, identifying the possible pathophysiological mechanisms involved in internal ear involvement. The specific focus was to establish a protocol to be followed to conduct a suspected case of DNSI, from diagnosis to treatment. The results found in the consulted literature show that the inner ear may be located within the organ-specific disease groups, or, more commonly, as a compromised organ within the systemic form, and hearing damage may be the first symptom. The index of inner ear impairment in systemic au toimunes is variable. It can be concluded that the hearing loss is neurosensory may occur in patients with autoimmunity disease and should always be taken in cases of hearing loss without apparent cause and the knowledge of autoimmune diseases and their correlation with the sensorineural hearing loss contributed significantly to the demystification of this type of hearing loss, allowing the institution of specific treatment.

Keywords: hearing loss, autoimmunity, sensorineural hearing loss, treatment, otological diseases1

Introduction

Autoimmune diseases-DAI are due to an inadequate response of the immune system, which reacts against organs, tissues or cells, leading to their destruction or impairing their function. They include diseases that simultaneously or sequentially affect these organs or systems and others specifically directed to some of them, such as the nervous system, the digestive and respiratory systems, skin, blood, eye, etc. The immune system is disordered by attacking the body itself and the organs it should protect and, as a whole, ICDS reach three times as many women as men, and are among the top 10 causes of death in women under 65. Symptoms vary from one disease to another and even within the same disease. Because they are diseases that affect several organs, they may have nonspecific symptoms, which make diagnosis difficult. The same disease may have very different symptoms in several people and at different ages.2

Says3 that puma autoimmune disease may present as a prolonged fever over three weeks, which does not give with antipyretics or antibiotics, for joint pain with swelling on the red spots on the face that increase with the sun, mouth ulcers that do not pass, miscarriages with immunosuppressants (Table 3). The determination of the etiology of hearing loss is fundamental for determining prognosis and treatment, which may involve behavioral, clinical, surgical and/or rehabilitation measures with sound amplification.4

In the case of ear manifestations, diseases such as sensorineural hearing loss (Table 1) mediated-DNSI having m was studied and is characterized m generally by bilateral sensorineural hearing loss, progressive, asymmetric or not accompanied by other symptoms of the inner ear.5 It is common for immune-mediated sensorineural hearing loss to be associated with autoimmune systemic diseases, being well characterized in the systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, giant cell arteritis, Wegener’s granulomatosis, ulcerative colitis, Sjögren’s syndrome, Behcet’s syndrome, amyloidosis, sarcoidosis, Cogan syndrome and Berger’s disease.6

Immune-mediated sensorineural hearing loss has been studied in the last two decades in relation to its etiological and pathophysiological mechanisms, maintaining itself as a complex disease and difficult to diagnose (Table 2) and treat.7 According to,8 the main clinical features of DNSI are: unilateral or bilateral sensorineural hearing loss that is rapidly progressive or sudden, asymmetric, commonly affecting severe frequencies. In some cases, buzzing and fullness of headset may be present. It can start at any age, being more common in women with age s between 30 and 45 years. The diagnosis is eminently clinical and based on the positive response to the therapeutic test with immunosuppressants (Table 3). The rationale of the effect of immunosuppressants on DAI con focuses on decreasing the efficiency of the pathological mechanisms of the disease. The response to immunosuppressants is directly related to the presence of specific antibodies that can be measured indirectly with autoantibodies and directly with immunological tests.9

1Immunosuppressants are medicines that lower immunity. They are indicated in the treatment of autoimmune disease, especially when the patient does not respond to conventional medications and are considered the most effective oral remedies.
of the immune system, passing on the latter to attack the body more mildly, which leads to a decrease in the symptoms of the disease (Table 4).

Hearing loss can be classified in two ways:

a. Sensory: when the inner ear is affected
b. Neural: when there is impairment of the auditory nerve or its complementary pathways.4

c. Sensorineural loss, in general, can be caused by viral infections, labyrinthitis, damage to the auditory nerves, exposure to noise, use of some medications or the correlation with diseases such as:

- Diabetes
- Autoimmune diseases
- Viral diseases
- Exposure to intense noises
- Hypertension
- Oto and sclerosis
- Trauma in the head region
- Aging (which is one of the most common causes).2

| Table 1 | Main entities involved in the differential diagnosis of sensorineural hearing loss |
|---|---|
| Characteristics | Clinical manifestations |
| Genetic deafness | Autosomal dominant or recessive (most common). |
| Infections | CMV, rubella, toxoplasmosis, gestational or perinatal syphilis |
| Presbycusis | Hearing loss associated with aging intensity and progression influenced by: infections, drug use, genetics, exposure to noise throughout life, comorbidities. |
| Menière’s disease | Abnormality of ionic hemostasis and internal ear fluid Excess of endolymph and distension of the membranous labyrinth. |
| Noise-induced hearing loss (NIHL) | Occupational, use of headphones at high volume Hearing loss in susceptible individuals, if the intensity and time of exposure are sufficient. |
| Tumors | Generally benign Most common: acoustic neurinoma (vestibular schwannoma). |
| Systemic and metabolic changes | Diabetes mellitus, hyperinsulinism, atherosclerosis, peripheral vascular disease, hypertension, dyslipidemia, thyroid changes: factors possibly associated with hearing loss. |
| Immune-depleted deafness | It may be associated with other systemic autoimmune diseases Substances that may affect the auditory and vestibular system. |
| Ototoxicidade | Antibiotics and chemotherapeutics: gentamicin, streptomycin, tobramycin, cisplatin, amikacin, neomycin, among others. Some diuretics (furosemide) and salicylates are also classically associated. |
| Neurological | Stroke (stroke), multiple sclerosis and Arnold-Chiari malformation may manifest with hearing loss and vertigo. |

Table 2 Epidemiological data

| Epidemiological data |
|---|
| Age between 30 and 45 years |

Table 3 Clinical characteristics of hearing loss

| Clinical features of hearing loss |
|---|
| Usually affects severe frequencies |
| Asymmetric |
| Floating |
| Neurosensory |
| Rapidly progressive (weeks to months) or sudden |
| Unilateral or bilateral |
| Tinnitus, ear fullness and vertigo |

The degree of hearing loss varies from person to person and is usually linked to:

a. Genetic inheritance
b. The abnormal conditions to which the ear was exposed during life
c. General disorders such as hypertension and diabetes, which may also affect the inner ear.2
d. Problems in the inner ear usually cause difficulty in separating speech from external noises, difficulty hearing high frequency sounds and the need to repeat what has been said.3
e. The early diagnosis is essential for treatment to be instituted as early as possible, aiming at a better end result. When deterioration of inner ear structures is noted, hearing loss is almost always irreversible. It is estimated that in about 95% of cases the use of hearing aids is effective in reducing the impact of the problem. In the case of severe to profound sensorineural hearing loss, the solution may be the cochlear implant (Table 5).3
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**Anti-proteína antibody 68kD (Western Blot)**

Results

If increased, they suggest the presence of autoimmune disease. Positivity suggests presence of DNSI.

**Temporal bone MRI**

Immunosuppressants

| Exams                      | Results                                                                 |
|----------------------------|-------------------------------------------------------------------------|
| Non-specific               | FAN, FR, Hemogram, Mucoproteins, HSV/PCR                               |
| Specific                   | Anti-proteína antibody 68kD (Western Blot)                             |
| Image                      | Temporal bone MRI                                                      |

In the presence of inflammatory process, there is presence of cochlear hypersignal in the images obtained in T1.

**Table 5 Treatment**

| Corticoterapia             | Immunosuppressants          | Plasmapheresis             |
|----------------------------|----------------------------|---------------------------|
| Initial: 1 to 2mg/Kg/day   | Cyclophosphamide 2 to 6mg/Kg/day; for non-responsive cases. | 10 sessions for 1 month, in conjunction with corticoid and cyclophosphamide; for cases still resistant. |
| for 4 weeks.               |                            |                           |
| Patients with good response should continue to receive high doses for another 1 or 2 months; | |                           |
| Later, the corticoid should be withdrawn gradually and decreasingly. | | |

**Goals**

To identify the possible pathophysiological mechanisms involved in the involvement of the inner ear in autoimmune disease; and there was a protocol to be followed to conduct a suspected case of DNSI, from diagnosis, to treatment.

**Material and methods**

This research was a bibliographic review, exploratory, descriptive of qualitative method, involving articles published between the years of 2002 and 2014. The keywords used for electronic literary search involved combinations with the following words: hearing loss, autoimmunity, sensorineural hearing loss. In this step were selected bibliographies, selection of texts, websites, journal articles, with the purpose of gathering information related to the theme chosen for the work proposed here.

**Development**

Most cases of hearing loss in adults are sensorineural. This type of hearing loss affects the inner ear and / or the neural pathways. In this case, the sound is usually conducted through the outer ear and middle ear, but the inner ear presents less efficiency in the transmission of sounds, usually due to the reduction or damage to the nerve endings within the cochlea. This leads to a lower perception of the intensity and quality of the sound. The result is a deficiency in listening and understanding. Sensorineural hearing loss can be treated with hearing aids, the most frequent symptom is a sensorineural hearing loss, usually bilateral, progressive rapidly and resposta varied to immunosuppressant’s, since it depends on the degree of hearing loss.

**Dysacusis immunomedial neurosensory-DNSI**

Immune- mediated sensorineural hearing loss-DNS I is classified as a form of acquired DNS, not late genetics and manifests as sensorineural, fluctuating, bilateral hypoacusis, rapidly progressive and responsive to treatment with immunosuppressive drugs. Approximately 65% of cases occur in women aged between 20 and 40 years, being extremely rare in the pediatric population. In their studies characterized the clinical picture of immune-mediated sensorineural hearing loss-DNS I as sensorineural hearing loss, aural fullness symptoms such as tinnitus, and not tissue destruction or not the middle ear or external and pa and ralisisa face. Sudden or progressive deafness, fluctuating and, uni-or bilateral, does not rule out the autoimmune etiology.

In many ways, the immunity of the labyrinth resembles that of the brain. The hetero-labyrinthine barrier separates the labyrinth from the bloodstream, maintaining the ionic characteristics of the cochlear environment. Immunoglobulins are present in the peri-lymph, at a ratio of 1/1,000, similar to the level of cephalo-rachidial fluid.

According Woolf the inner ear seems to be more immunorresponsive than the brain, because the antigen present in the cochlea rapidly stimulates systemic immunity. When an antigen is introduced into the inner ear of previously sensitized animals, there is an immune response characterized by cellular infiltration, inflammatory reaction, cochlear damage, increase of antibodies in the perilymph, and elevation of local AC production. The inner ear is capable of presenting humoral immune response against a local or systemic antigenic stimulation; send to endolymphatic sac the area with the greatest potential to immune processing. According Tomiyama the end lymphatic sac has a fixed population of lymphocytes, but curiously, the lymphocytes that appear in the inner ear during the immune response come from the bloodstream. The entry point of the white blood cells in the inner ear seems to be the spiral modiolar vein-VME which, in the cochlea, has a similar function to the post-capillary veins of other tissues. During the secondary immune response, the endothelial cells of the EMV are activated, assuming the characteristics of differentiated endothelial veins. These express intercellular adhesion molecules, recruiting circulating lymphocytes, with the likely contribution of other surface molecules.

The immune response of the inner ear is critical in protecting against infection; however, the associated inflammatory process can produce damage to the delicate cochlear tissue. In addition, there is evidence that cochlear tissue itself may be the target of autoimmune reaction. Cecatto et al. says that in the inner ear may be the site of organ-specific disease, or more commonly present in a disease that takes a systemic way. This autoimmune mechanism is capable of triggering DNSI by self-injury of the inner ear. The main autoimmune mechanisms involved in internal ear dysfunction include: immediate hypersensitivity, with production of IgE immuno-globulins against cochlear antigens, immuno-complex deposits in the vascular stria and spiral ligament, direct action of cytotoxic T cells in the cochlea and hypersensitivity delayed immunological reactivity mediated.
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by type II collagen. These mechanisms can act complementarily and often simultaneously. The main histopathological findings are degeneration of the spiral ganglion, cortiorgan atrophy, vascular stria degeneration, endolympathic duct precipitation and atrophy, presence of macrophages and precipitates in the endolympath, as well as perivascular infiltrate and deposition of circulating immune complexes in the vascular stria. Table 1 summarizes the main entities involved in the differential diagnosis of sensorineural hearing loss.

Source

Incidence

The DNSI usually affects middle-aged women. A study by Hughes et al. showed a predominance of females (65%) in relation to males (35%). Harris et al. also observed, in a series of 279 patients, 63% of women. This fact agrees with the female prevalence found in other autoimmune pathologies of the organism.

Diagnosis

What is essential in the diagnosis of DNS I is the clinical history, since there are no definitive laboratory tests yet. Histopathological examination is not yet possible, since the inner ear is unavailable for tissue biopsy. A DNSI may initially present isolated oto logical symptoms. But it is most commonly part of an immune-mediated systemic disease. Stephens et al. (2009), through a clinical study, showed a high incidence of cochlear-vestibular symptoms (in 13 of 17 patients with ICD). And yet, studies that investigated risk groups for developing DNS did not attempt to correlate otological clinical history with their audiological research findings. QUPrev to the suspected DNSI, a complaint phase clinic without audiometric expression, it should be Initials air treatment with immunosuppressive corticosteroids or go or exist go important clinical suspicion, can be with this reversal or stabilization of the degenerative process of the inner ear still in an incipient stage, preventing irreversible deafness. Recovery is directly related to cochlear lesion, more specifically to hair cells. Once occurring death of these cells, or immunosuppression restore auditory function. In patients with defined cochlear lesions, we should consider the interruption of the progression of the condition satisfactory, which will allow eventual rehabilitation with a hearing aid.

The tests

In laboratory tests between which can aid in the diagnosis of DNSI can cite complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-neutrophil cytoplasmic antibody assay (ANCA), anti-factor nucleus (FAN), rheumatoid factor (RF) and mucoproteins. The increase in these markers is suggestive of autoimmune disease. The Ac-anti 68kD is a highly specific test for DNSI, using the Western B lot method against 68kD hsp-70 (anti-cochlea antibody evaluation), and its positivity is around 89% in the active phase of the disease. Approximately 70% of the patients who present the positive test have a good response to treatment with corticosteroids, compared to 15% in patients who present a negative test.

The anti-68kD (70hsp) anti-protein AC research is currently the most specific test in otoimmunity, although rarely performed because of its high cost and difficult access.

Since lymphocyte transformation in Consist method that exposes mononuclear leukocytes prepared from the patient’s blood, various dilutions of antigen. The evaluation (of the test is done through positive and negative controls. Lymphocytes are then examined from scintigraphy techniques and compared to controls by statistical evaluations (Table 6). Its predictive value is around 80% and is considered alongside Western blot, one of the most specific tests in the diagnosis of modern otomimunology. The literature is controversial relative to the role of anti-type II collagen antibody. Some authors publish ram results revealed a large percentage of patients with idiopathic progressive DNS Bilateral with high titers of anti collagen II Ac, observing also correlation between high titers of Ac and good response to therapy with corticosteroids fronts.

Table 6 Prognostic evaluation

Corticosteroid test

| Criteria indicative of responsiveness to corticosteroid therapy (Month monitoring with audiometry) are: |
| Improvement in tritone mean for pure tone by 15dB or more; |
| Increase in vocal discrimination by 20% or more; |
| Stabilization of hearing with complete resolution of vertigo. |

Circulating immunocomplexes-ICC have an important role in vasculitis and glomerulonephritis, and has been frequently related to hearing loss. Evidence of this fact includes the detection of CHF in the blood and its deposition in the organs, resulting in tissue damage due to the activation of the complement cascade. The complement system-C1q is activated para there is precipitation of the ICC and tissue damage, there must be precipitation after consumption of specific complement fractions.

In this sense, we investigated the fraction C1q, which has a special affinity for the immunocomplexes, being reduced in the blood levels of the patients with DNSI.

Another test is the HLA. We have already reported the incidence of 51% of HLA CW7 in patients with DNS I when compared to the control group. And studos point out the higher incidence of HLA B16 and B18 in carriers of DNS I, in addition to HLA DR2 and CW4, much more frequently than in the rest of the population.

Although it is recommended carrying out the tests mentioned often gets If no definitive diagnosis, as serum levels indicated for positivate exams are rarely achieved in the case of localized and limited process, as is the case of the endolympathic sac. Thus, there is little relation between the positivity of the cited tests and the response to treatment.

Thus, the clinical suspicion persist going DNSI, although no confirmation laboratory ots if the therapeutic test with corticosteroids as a means of confirming the initial diagnostic hypothesis. It is worth mentioning the use of imaging methods for diagnosis, such as Magnetic Nuclear Resonance (NMR) of temporal bones. We note the hypersignal cochlear, after infusion of paramagnetic contrast (gadolinium), in the images obtained in Table 1, when in the presence of inflammatory process. In cases of ICD, MRI may show other systemic changes of the central nervous system, as such vasculature of small vessels.

ICC can be detected in plasma and electrodensing deposits in tissue through immunofluorescence. Its presence in the blood determines the suspected autoimmune process in progress.

It consists of observing the type of audiometric response to the use of prednisone. The test is performed with the administration of prednisone at a dose of 1mg/kg/day for a period of 15-20days. The positivity is given by the improvement of the tonal thresholds at the end of the test, which closes the autoimmune reaction diagnosis of the inner ear.

Citation: Rezende CEB, Sio BTD, Sio GTD, et al. Immunoided otological diseases: when to suspect, how to diagnose and treat? J Otalaryngol ENT Res. 2019;11(2):97–102. DOI: 10.15406/joentr.2019.11.00416
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Different minds systemic therapies, intratympanic therapy allows direct and specific action in the ear affected being treated. In addition to glucose intolerance and a vascular necrosis of the hip, other adverse effects of systemic corticosteroids such as insomnia, irritability, gastritis and mood changes can be avoided through intratympanic therapy. The main disadvantage of intratympanic corticosteroid therapy is still the lack of evidence that it would have a superior efficacy when compared to systemic therapy. Other disadvantages include pain, vertigo and even rare possibility of perforation of the tympanic membrane and serous otitis media. In studies effect was not observed with the ADD al concomitant oral corticoid of the anode and intratimp.

Conclusion

It can be concluded that the sensorineural hearing loss may occur in patients with autoimmune disease and should always be remembered in cases of discusses with no apparent cause. Knowledge of autoimmune diseases and their correlation with the picture of disabuse sensorineural a major contributor in the demystification of this type of hearing loss allowing specific treatment institution more precocem one, with better results. The main autoimmune mechanisms involved in internal ear dysfunction include: immediate hypersensitivity, with production of IgE immunoglobulins against cochlear antigens, immunocomplex deposits in the vascular stria and spiral ligament, direct action of cytotoxic T cells in the cochlea and hypersensitivity delayed immunological reactivity mediated by type II collagen. These mechanisms can act complementarily and often simultaneously.

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None.

Conflicts of interest

The author declares there is no conflict of interest.

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