



Systemic Lupus Erythematosus and hearing disorders: Literature review and meta-analysis of clinical and temporal bone findings

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Abstract

Objective: This literature review and meta-analysis was performed to evaluate the correlations among hearing and vestibular clinical symptoms, temporal bone findings, and pathological mechanisms in patients with systemic lupus erythematosus (SLE).

Study design: Relevant papers in the literature were retrospectively reviewed. Clinical hearing aspects in patients with SLE and relevant temporal bone studies in the same field were analyzed.

Methods: PubMed and Google Scholar searches were performed using the following keywords: “auto-immune disease,” “systemic lupus erythematosus (SLE),” “hearing loss,” “temporal bone study,” “vertigo,” “dizziness,” “tinnitus,” “ear symptoms,” “treatment,” “diagnosis,” “symptoms,” “etiopathogenesis,” “Wegener granulomatosis,” “Sjogren,” “polyarteritis nodosa,” “Cogan syndrome,” and “granulomatosis.” Also included were reviews in which the following terms were present: “SLE,” “temporal bone,” and “hearing symptoms.”

Review and conclusion: This literature review and meta-analysis focused on the pathological mechanisms through which SLE can damage inner ear structures and determinate hearing and vestibular symptoms. The main mechanisms involved in inner ear damage include the autoimmune response, deposition of immune complexes in the vessels and, to a lesser extent, cytotoxic damage.

Keywords

Systemic lupus erythematosus, hearing loss, tinnitus, dizziness, autoimmune disease

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiorgan involvement and an incidence of 12.5–39.0 per 100,000 people in the general population. The incidence of SLE is higher in

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women (82%–96%) than in men (4%–18%),^{1–2} and it is two to three times more prevalent in people of African and Asian descent than those of European one.³ Onset is most frequent from 20 to 39 years of age.⁴

SLE is a multifactorial pathology with different aetiologies, including genetic chromosome alterations, inflammation, drugs, environmental factors, and interactions between the adaptive and innate immune systems.^{1–3}

The hallmark of SLE is the production of autoantibodies that react with self-nuclear and cytoplasmic antigens and culminate in immunologic attacks on body organs, resulting in tissue inflammation and multi-organ damage.⁴ T- and B-lymphocyte disorder plays a central role in this auto-immune dysfunction.⁵ The role of natural killer T cells has also been explored.^{6,7} Autoantibodies are directed toward antigens at the nuclear cell level; one of the most relevant antigens in SLE is double-stranded DNA. Antibody-mediated attacks \ primarily involve tissues and cells; however, they also target the walls of blood vessels, resulting in a generalized vascular alteration defined as vasculitis.⁸

As a systemic disease, SLE can involve different organs including the skin, kidney, neurologic system, and musculoskeletal system. Recent studies have also shown involvement of the inner ear.⁹ The aim of this study was to review the current literature with respect to hearing disorders in patients with SLE and evaluate the correlations among the pathophysiology, clinical symptoms, and temporal bone findings of SLE.

Material and methods

A systematic review was conducted by searching PubMed and Google Scholar. The following keywords were used to identify relevant articles: “autoimmune disease,” “systemic lupus erythematosus (SLE),” “hearing loss,” “temporal bone study,”

Table 1. Study collection data.

| Author | Audiogram |
|---------------------|---------------------------------|
| Type of article | Type of hearing loss |
| Year of publication | Cytochleogram |
| Number of patients | Description of bone preparation |
| Systemic diseases | Involved ear structures |
| Therapy used | Middle ear aspect |
| Otologic symptoms | Inner ear aspect |

“vertigo,” “dizziness,” “tinnitus,” “ear symptoms,” “treatment,” “diagnosis,” “symptoms,” “etiopathogenesis,” “Wegener granulomatosis,” “Sjogren,” “polyarteritis nodosa,” “Cogan syndrome,” and “granulomatosis.” Studies in which the following words were present were included in the review: “SLE,” “temporal bone,” and “hearing symptoms.”

Table 1 summarizes the collected data for each publication selected for inclusion in the review. In total, 49 articles were reviewed.

Audiovestibular disorders in patients with SLE

Clinical findings

SLE is characterized by the participation of multiple antibodies in immune-mediated tissue injury in different tissues and organs, including the auditory system. At this level, there are several mechanisms by which antibodies may damage the inner ear: 1) humoral-type antibody attacks on inner ear antigens, 2) cell-mediated cytotoxic damage to cochlear and vestibular hair cells, and 3) immune-complex deposition in the microvessels of the inner ear.⁵

The most common otologic symptom found in clinical studies of patients with SLE is sensorineural hearing loss (SNHL), the reported prevalence of which ranges from 6% to 70%.^{10–16} Table 2 summarizes

the different subtypes of hearing loss found in patients with SLE in multiple studies performed from 1995 to 2013 (Table 2). Various authors have reported different pathways of SNHL in patients affected by SLE: hearing loss may either be slowly progressive or acute. It mainly affects high frequencies, mimicking the typical presbycusis pattern; however, it may also affect the low and middle frequencies. Maciaszczyk et al.¹⁰ described progressive SNHL involving all frequencies except 500, 2000, and

4000 Hz; Roverano et al.,¹² in a series of 31 patients, identified asymptomatic bilateral SNHL affecting high frequencies. Khalidi et al.⁹ reported unilateral SNHL involving 500, 1000, 2000, and 3000 Hz associated with a 16% word discrimination score as demonstrated by speech audiometry. Sperling et al.,¹³ in a series of 84 patients, described bilateral and slowly progressive hearing loss; the same author in a previous paper described patients with SLE who developed sudden unilateral SNHL.

Table 2. Summary of hearing loss results.

| Authors | Patients (n) | Year | Auditory symptoms | Hearing thresholds |
|---------------------------------------|--------------|------|-------------------|--|
| Kataoka et al. ³⁷ | 2 | 1995 | n/a | Bilateral fluctuant SNHL |
| Sperling et al. ¹³ | 84 | 1998 | 31.0% | Unilateral SNHL (15%), bilateral SNHL (17%) |
| Green and Miller ¹⁵ | 1 | 2001 | n/a | Sudden pantonal unilateral SNHL, male |
| Digiovanni and Nair ¹⁴ | 1 | 2006 | n/a | Sudden unilateral SNHL for 3000 and 4000 Hz; male |
| Roverano et al. ¹² | 31 | 2006 | 70.0% | Bilateral symmetric SNHL for 2000, 4000, and 8000 Hz |
| Gomides et al. ¹⁹ | 45 | 2007 | 55.5% | SNHL for all frequencies (14%); SNHL for 500, 1000, and 2000 Hz (57%); SNHL for 4000 and 8000 Hz (28%) |
| Khalidi et al. ⁹ | 1 | 2008 | n/a | Profound bilateral SNHL for 500, 1000, 2000, and 3000 Hz; female |
| Maciaszczyk et al. ¹⁰ | 35 | 2011 | 71.4% | Progressive SNHL with 500-, 2000-, and 4000-Hz frequency preservation |
| Abbasi et al. ¹¹ | 45 | 2013 | 26.7% | SNHL (11.1%), otorrhea (8.9%), tinnitus (6.7%) |
| Lin et al. ² | 7168 | 2013 | n/a | Higher incidence of SNHL in women aged ≤ 34 years. Most frequently affected frequencies: 4000 and 8000 Hz |
| Chawki et al. ¹⁷ | 1 | 2016 | n/a | Sudden bilateral hearing loss for all frequencies (40 dB in right ear, 60 dB in left ear) |
| Lasso de la Vega et al. ¹⁶ | 55 | 2016 | 70.0% | High-frequency hearing loss at 8000 and 18,000 Hz |

SNHL, sensorineural hearing loss; n/a, not available

Digiovanni and Nair¹⁴ and Green and Miller¹⁵ presented case reports of sudden hearing loss in patients affected by SLE; in contrast, Andonopoulos et al.¹⁷ showed that the threshold of SNHL in patients with SLE mimics the presbycusis pattern. In a large population-based, retrospective cohort study from the Taiwan National Health Insurance Research Database, Lin et al.² identified a higher prevalence of sudden SNHL in patients with SLE, especially young women, than in the general population; the most common audiological pattern was loss of high-frequency hearing in women aged <35 years. These results were in accordance with the findings by Vendelman et al.,¹⁸ who reported bilateral SNHL in patients affected by lupus, hypothesizing a role of vasculitis of the internal auditory artery and stria vascularis. Chawki et al.¹⁹ recently presented a case involving a young woman with SLE and bilateral SNHL affecting the 250- to 8000-Hz frequencies. In all studies, the most commonly involved frequencies were in the 4000- to 8000-Hz range (65%), followed by middle frequencies (32%) and low frequencies (3%). The distribution of hearing loss by frequency is shown in Figure 1.

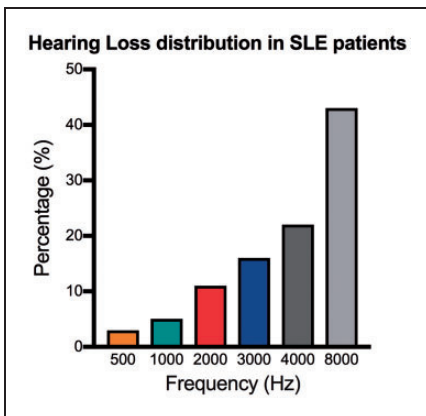


Figure 1. Hearing loss distribution in patients affected by systemic lupus erythematosus.

Besides hearing loss, other audiovestibular symptoms often associated with SLE include tinnitus and vertigo. Tinnitus, a symptom that can be linked to numerous conditions,^{20–22} has been reported in patients with SLE by Gomides et al.,²¹ Sperling et al.,¹³ Dayal and Ellman,²⁰ and Abbasi et al.¹¹ In all cases, tinnitus was associated with hearing loss and may have been a consequence of deafferentation. The vestibular system appears to be involved in SLE, although to a lesser extent; vertigo and dizziness have rarely been reported in patients with lupus. A few authors^{22,23} have described vertigo in patients with SLE and, in all cases, this symptom was always associated with SNHL or tinnitus. Gad and Abdelateef²⁴ found that vertigo in children with SLE was always associated with cochlear symptoms. However, the incidence of vestibular symptoms may be under-reported due to the slowly progressive onset of these symptoms and compensation by the somatosensory system and vision.

Temporal bone findings

Fourteen publications in which the authors analyzed the effects of different autoimmune diseases on inner ear structures were identified using the following keywords: “auto-immune disease,” “systemic lupus erythematosus (SLE),” “hearing loss,” “temporal bone study,” “vertigo,” “dizziness,” “tinnitus,” “ear symptoms,” “treatment,” “diagnosis,” “symptoms,” “etiopathogenesis,” “Wegener granulomatosis,” “Sjogren,” “polyarteritis nodosa,” “Cogan syndrome,” and “granulomatosis.” Only studies in which the following words were present were included in the review: “SLE,” “temporal bone,” and “hearing symptoms.” Of these studies, 6 analyzed the effect of SLE on the inner ear among a total of 52 analyzed specimens and were selected for the present meta-analysis. The numbers of specimens studied according to autoimmune

disease is summarized in Table 3. The different percentages of autoimmune diseases found in the analyzed specimens are shown in Figure 2.

Table 3. Numbers of specimens studied according to autoimmune disease.

| Autoimmune disease | Specimens studied (n) |
|--|-----------------------|
| Systemic lupus erythematosus | 52 |
| Granulomatosis with polyangiitis (Wegener's) | 22 |
| Polyarteritis nodosa | 20 |
| Sjogren syndrome | 8 |
| Cogan syndrome | 7 |
| Autoimmune hearing loss | 4 |
| Total | 113 |

In total, 52 temporal bones, the ones affected by SLE, were included in our meta-analysis. Table 4 summarizes the symptoms that the patients presented before death. The most common condition was hearing loss, found in >70% of patients. Hearing loss was sensorineural in 96% of patients and mixed in 4%. Vertigo and dizziness were reported in 30% of patients. These data are consistent

Table 4. Temporal bone analysis: symptoms reported by patients before death.

| Hearing and vestibular symptoms | Percentage |
|---------------------------------|------------|
| Sensorineural hearing loss | 96% |
| Mixed hearing loss | 4% |
| Vertigo and dizziness | 30% |
| Tinnitus | 8% |
| Aural fullness | 2% |

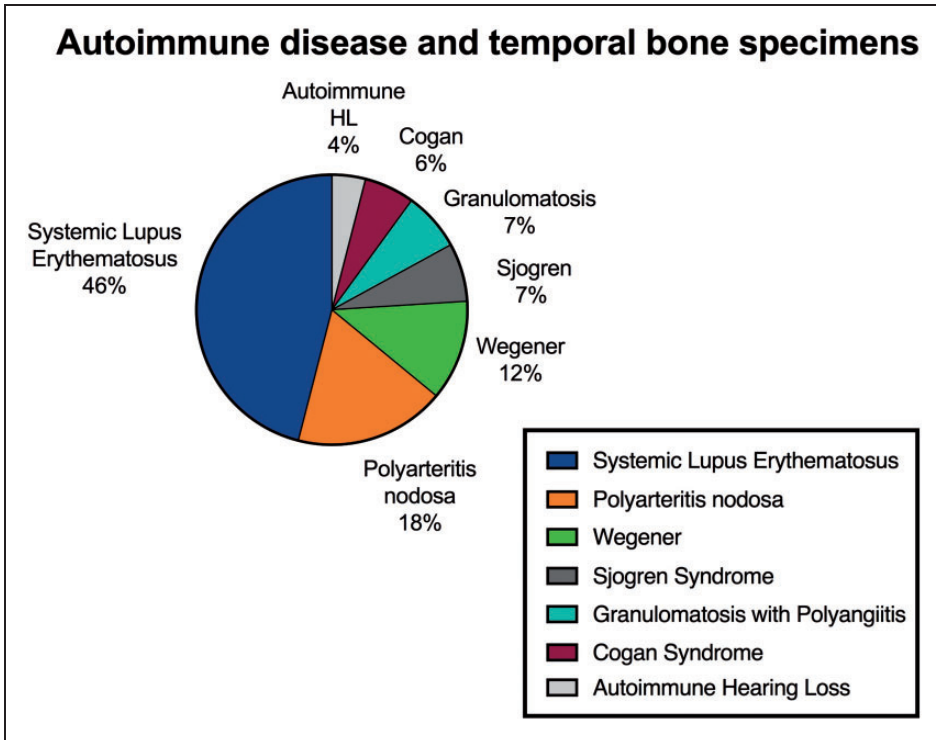


Figure 2. Autoimmune disease and temporal bone specimens.

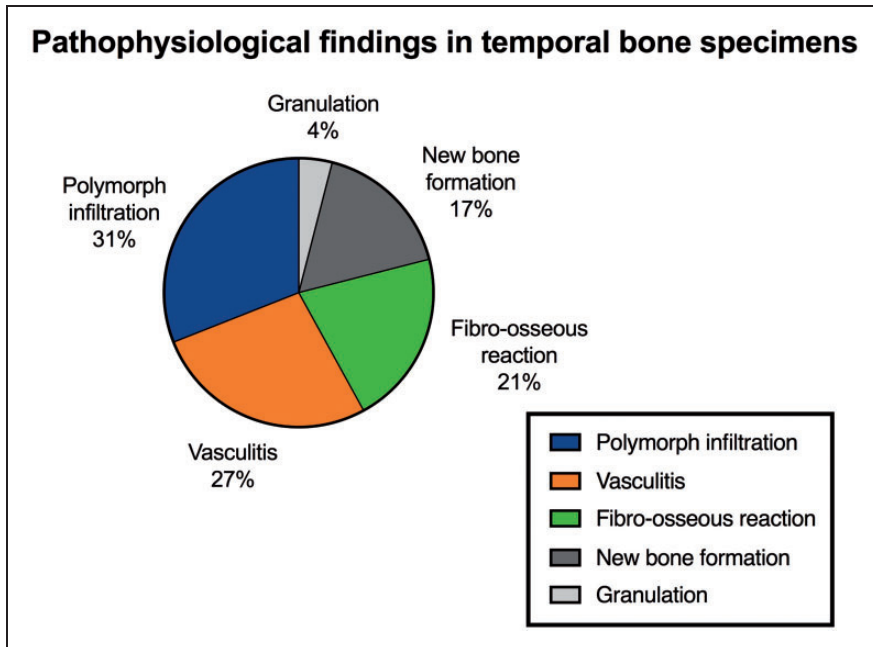


Figure 3. Pathophysiological findings in temporal bone specimens.

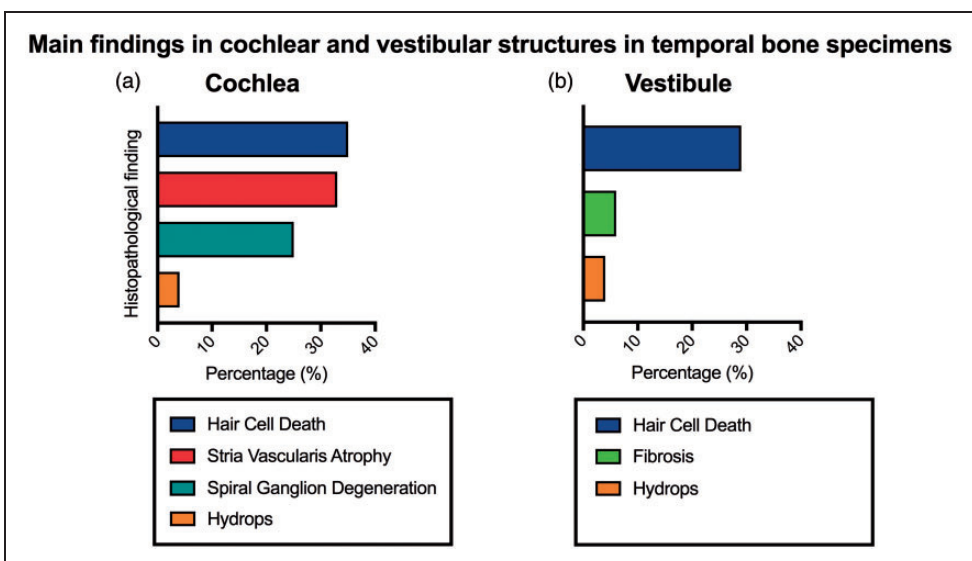


Figure 4. Main findings in cochlear and vestibular structures in temporal bone specimens.

Table 5. Correlations among hearing disorders, temporal bone analysis, and physiopathological mechanisms.

| Hearing and vestibular symptoms | Temporal bone findings | Physiopathological mechanisms |
|---------------------------------|--|---|
| Hearing loss and tinnitus | Hair cell damage | Anti-DNA antibodies Cytotoxic damage Variation of perilymph concentration |
| | Spiral ganglion Degeneration Stria vascularis atrophy | Anti-DNA antibodies Immune complex deposition |
| Vertigo and dizziness | Type I hair cell damage | Anti-DNA antibodies Cytotoxic damage Variation of perilymph concentration |

with those reported in the clinical studies described in the previous paragraph. With respect to histopathological findings, polymorphonuclear infiltration (31%) and vasculitis (27%) were the most common, followed by fibro-osseous reaction (21%), new bone formation (17%), and granulation (4%) (Figure 3).

A deeper analysis of cochlear structures showed moderate to severe inner hair cell damage and, mainly, outer hair cell damage in a large portion of studied temporal bones; alterations involved the middle and apical turns of the cochlea in most of the studies,²⁵⁻²⁸ and all turns were involved in one study.²⁷ Stria vascularis atrophy (33%) and spiral ganglion degeneration (23%) were two other consistent findings. Cochlear hydrops was the least frequently identified histopathological finding (Figure 4a). When focusing on the vestibular system, type I vestibular hair cell damage was the most common finding (29% of cases),²⁸ followed by vestibular fibrosis (6%) and hydrops (4%) (Figure 4b).

Pathophysiology of inner ear involvement in SLE

SLE can damage tissues and organs through three different mechanisms: 1) antibody/antigen direct reactions, 2) cytotoxic action, and 3) immune complex deposition. These mechanisms represent the basis of inner

ear damage in patients with SLE, and a schematic of their connection with specific hearing and vestibular disorders is summarized in Table 5.

The autoantibodies produced in patients with SLE are mainly anti-DNA antibodies; their effect changes the DNA conformation, modifying the resultant protein production and inducing apoptosis in cochlear and vestibular hair cells and in the spiral ganglion. In 1988, Barna and Hughes³¹ identified increased antibody activity in the perilymph of patients with SLE; furthermore, this higher concentration of antibodies increased the protein concentration. These authors also reported that antibodies circulating in the perilymph were associated with the action of cytotoxic molecules and induced a variation in endolymph proteins strictly linked to hair cell degeneration.³¹

Immune complex deposition plays a central role in the development of inner ear vasculitis and is associated with atrophy of the stria vascularis. Immune complex deposition in the auditory artery reduces the vessel calibre with a consequent decrease in blood flow. This blood flow reduction induces an oxygen deficit followed by the release of oxidative molecules responsible for damage to the hair cells^{10,11,32,33} and spiral ganglion.^{34,37} In addition, the progressive reduction of the vessel calibre increases the resistance in the circulatory system, eventually increasing the blood pressure

and contributing to damage and fibrosis of the stria vascularis as shown by the temporal bone findings.³⁵

Sudden hearing loss in patients with SLE can be explained by a temporary blood flow reduction in the inner ear, with complete or partial recovery after restoration of normal perfusion. Instead, recurrent vasculitis permanently damages the structure of the ear because of the chronic oxygen deficit.³⁰ Vasculitis appears to be the major factor involved in cochlear and vestibular damage.^{2,12,13,25,36,37}

Green and Miller,¹⁵ Karatas et al.,²² Gazquez et al.,³⁸ and Kataoka et al.³⁹ supported the hypothesis that the antibody mechanism can explain cochlear and vestibular hydrops and related hearing/vestibular disorders. However, hydrops seems to be the least common finding in patients with SLE reported in the literature.

Treatment of hearing and vestibular disorders in SLE

Different treatments for SLE-related hearing disorders have been proposed in the literature. These treatments are mainly focused on prevention, especially for slowly progressive hearing loss, and hearing restoration for cases of sudden hearing loss.

Corticosteroid therapy is the most prevalent therapy for sudden hearing loss and for the prevention of further worsening of progressive hearing loss in patients with SLE.^{11,37,40-43} Sudden hearing loss, as widely reported in the literature, is also subject to spontaneous recovery; Digiovanni and Nair¹⁴ reported a case of spontaneous recovery of sudden hearing loss in a patient with SLE.

Other treatments of hearing disorders in patients with SLE include plasmapheresis as reported by Kobayashi et al.⁴⁴ and Sichkareva et al.,⁴⁵ anticoagulant therapy,¹⁵ and cyclophosphamide.⁴⁶ These drugs mainly contribute to a reduction in the progression of SNHL.

More recently, the use of monoclonal antibodies such as rituximab or alemtuzumab has been proposed in SLE treatment.⁴⁷ The suppressive effects of the immune system are able to consistently reduce activation of the inflammatory mechanisms that underlie inner ear damage.

Identification of the pathogenic mechanisms at the basis of audiovestibular symptoms in patients with SLE is crucial for selection of the correct treatment.⁴⁸⁻⁴⁹ Steroids have different activities: anti-inflammatory, immunosuppressive, and anti-oedema effects. Immunosuppression reduces the formation of immune complexes, while anti-inflammatory and anti-oedema actions restore the normal caliber of affected vessels. Additionally, corticosteroid therapy increases blood pressure as a side effect; however, this has a therapeutic effect in patients with SLE because high systemic blood pressure increases blood flow in all structures, including the auditory artery, thus improving the oxygen concentration. Plasmapheresis also improves the oxygen concentration in the inner ear; and anticoagulant therapy improves blood fluidity by increasing vascularization in smaller vessels that have a reduced calibre secondary to SLE. Immunosuppressant drugs such as cyclophosphamide reduce autoimmune activity and the formation of immune complexes.

In the authors' opinion, corticosteroids should be considered as the first treatment option to restore hearing in patients with sudden hearing loss and prevent worsening of progressive hearing loss in patients with SLE because of the large availability of these drugs worldwide and their much lower cost compared with monoclonal antibodies. In patients with progressive hearing loss, cyclophosphamide should be used if steroid therapy is unsuccessful. Plasmapheresis and anticoagulant treatments can be useful for the prevention of sudden hearing loss and treatment of tinnitus and vestibular symptoms; however, their use should be

carefully evaluated on an individual basis depending on the patient's systemic involvement and SLE history. Monoclonal antibodies can be a valid choice, especially for aggressive forms of SLE or in patients with proven resistance to other treatments.

Conclusion

The temporal bone studies examined in the present review confirm the aetiopathological mechanisms of SLE in inner ear structures. Two mechanisms are undoubtedly involved at this level: the autoimmune response, supported by the presence of polymorphonuclear leukocytes in the inner ear and the death of hair cells, and the deposition of immune complexes in the vessels, as demonstrated by the presence of vasculitis in the inner ear and by atrophy of the stria vascularis. An understanding of the aetiopathology of SLE through temporal bone findings is certainly helpful in identifying the most effective treatment for SLE in patients with auditory and vestibular disorders. If we assume that temporal bone findings are an exact representation of SLE mechanisms, it appears clear that although corticosteroid therapy is still routinely used for hearing disorders, future research will show that monoclonal antibodies are the gold standard treatment for systemic and specific SLE-related alterations such as inner ear damage.

The use of monoclonal antibodies is often limited to cancer treatment because of their high cost and financial impact on healthcare systems. Although current findings are encouraging, further studies involving larger numbers of patients are necessary to better define the correlations among clinical symptoms, temporal bone findings, and pathological mechanisms in patients with SLE.

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