Restoration of Immune-mediated Sensorineural Hearing Loss with Sodium Enoxaparin: A Case Report

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The aim of the study was to assess the efficacy of sodium enoxaparin in the treatment of autoimmune sensorineural hearing loss. A small number of patients with unilateral sensorineural hearing loss were selected and divided randomly into two numerically equal groups (groups A and B) if they fulfilled the inclusion criteria, i.e. being between 20 and 65 years of age, had been affected by systemic lupus erythematosus, had presented with a hearing loss of at least 30 dB of audibility threshold involving the medium frequencies (2000–4000 Hz), and had provoked informed consent. Group A received sodium enoxaparin while group B (control) received placebo. In group A, all patients except one showed an improvement in hearing after sodium enoxaparin treatment. In group B, no patients showed an improvement in auditory function. In conclusion, our results underline the important role of sodium enoxaparin in the therapeutic management of this disease. The low number of patients suggests that further studies are required to confirm this initial data but this study suggests that sodium enoxaparin provides encouraging results in the treatment of autoimmune sensorineural hearing loss. Key words: anticoagulant therapy, immune-mediated disorders, systemic lupus erythematosus.

INTRODUCTION

Autoimmune sensorineural hearing loss is characterized by rapidly progressive hearing loss that has no confirmed etiology (1). It can occur as one of the clinical features of systemic immune-mediated disorders or as a distinct clinical entity.

Diagnosis of immune-mediated sensorineural hearing loss is still based on clinical impressions as laboratory testing is not sufficiently diagnostic. The existence of a typical profile patient, including the clinical course, immunological changes and the response to steroid therapy, can facilitate diagnosis: a timely clinical assessment and treatment can positively affect the prognosis of the hypoacusia (2, 3). This is an unsatisfactory situation, leaving the patient and the physician with the difficult problem of using immunosuppressive drugs without clear knowledge that such medication is necessary or likely to be effective. But if left untreated many cases progress to more severe hearing loss and involvement of the opposite ear.

Treatment guidelines are controversial but include corticosteroids, cytotoxic agents and plasmapheresis. These drugs can be effective in reversing such hearing loss, although at the cost of occasionally severe side-effects (4).

Recent developments in understanding the intracellular pathways that participate in damage to the inner ear provide new opportunities for pharmacotherapy of immune-mediated disorders of hearing: the goal of this study was to assess the effects and the efficacy of sodium enoxaparin in the treatment of autoimmune sensorineural hearing loss.

MATERIALS AND METHODS

A 39-year-old man presented with a 6-month history of progressive sensorineural hearing loss in the right ear. During the medical history, the man referred to systemic lupus erythematosus (SLE) treated with medical therapy (cyclophosphamide). There was no history of ear discharge, recent trauma or preceding intake of drugs that could cause ototoxicity or precipitate SLE. There was no family history of deafness or nephritis. The liver was 3 cm in the right midclavicular line. There was no splenomegaly or lymphadenopathy. Examination of fundus, other cranial nerves and central nervous system was normal. He was affected by a hearing loss of 30 dB of audibility threshold involving the medium frequencies (2000–4000 Hz).

When the patient was treated with sodium enoxaparin his hearing was restored. His recovery was more than 25 dB on the right ear audiogram. There was also an improvement in the oto-acoustic emission study.

In this preliminary study, we decided to treat patients who had been affected by unilateral progressive sensorineural hearing loss and tinnitus for at least 6 months. Patients were selected on the basis of the following inclusion criteria: being between 20 and 65 years of age, had been affected by SLE, had presented with a hearing loss of at least 30 dB of audibility threshold involving the medium frequencies (2000–4000 Hz), and had provided informed consent.

We analyzed eight patients who were divided randomly into two numerically equal groups (groups A and B). All patients were hospitalized for 10 days.
To those in group A, enoxaparin was administered subcutaneously at a dose of 2000 IU twice daily for 10 days. Group B (control) patients received placebo (0.2 ml of physiological solution) with the same method of submistration (4, 5).

At the start and end of therapy, all patients underwent the following instrumental examinations: laboratory tests (prothrombin and fibrinogen levels); liminal tonal audiometry; typanometry; oto-acoustic emissions with linear click emission; oto-acoustic products of distortion; and subjective assessment of symptoms on a scale from 0 to 4 (0 = absence of tinnitus, 1 = low tinnitus, 2 = medium tinnitus, 3 = high tinnitus, 4 = incapacitating tinnitus).

Daily, during the treatment period, we performed liminal tonal audiometry, oto-acoustic emission with linear click emission and oto-acoustic products of distortion. Each patient returned after 30 days for a physical examination, liminal tonal audiometry and oto-acoustic emissions to evaluate the efficacy of the therapy.

Exclusion criteria included: a history of thrombocytopenia following heparin treatment; hemorrhagic manifestations or tendencies due to disorders of hemostasis that are not heparin-dependent or related to consumption coagulopathy; organic injuries at risk of bleeding; renal failure; acute infectious endocarditis (excluding endocarditis due to mechanical prostheses); hemorrhagic cerebrovascular events; allergy to enoxaparin; concurrent use of ticlopidine, salicylate or non-steroidal anti-inflammatory drugs (NSAIDs) with sodium and association with platelet anti-coagulants (such as dipyridamole, sulfiprynazine).

RESULTS

On discharge, all patients treated with enoxaparin presented a subjective abatement of symptoms. In group A, the mean value of scores on the subjective symptom scale fell from 3.1 to 1.5; in group B the mean value fell from 3.2 to 2.9. Hearing improved in three (75%) group A patients and was unchanged in one patient; the mean hearing improvement for these patients ranged from 17.9 to 22.7 dB across the 2000–4000 Hz range examined. In group A patients, the evoked oto-acoustic emissions revealed an improvement from ‘fail’ to ‘pass,’ and oto-acoustic distortion products, which were previously absent, were evoked at frequencies of the tonal field normally examined.

In group B, no patient showed an improvement in auditory function and the evoked oto-acoustic emissions revealed an improvement from ‘fail’ to ‘pass’ in only two patients.

No significant alteration of the examined parameters was discovered during the last control.

Comparison of groups was made by the unpaired t-test and correlations were analyzed by regression analysis: probability values at less than 0.05 were regarded as significant. The comparisons of groups were also made for repeated measures by analysis of variance.

No patient experienced side-effects from this treatment.

DISCUSSION

Immune-mediated inner ear disease, first described by McCabe in 1979, typically presents with an idiopathic, progressive, unilateral or bilateral sensorineural hearing loss. It may occur in both sexes and at a variety of ages, but is most common in middle-aged females. It may be accompanied by tinnitus, Menière’s-like vertigo, or, more commonly, ataxia or unsteadiness. Hearing loss can be caused by autoimmune disorders localized to the inner ear or secondary to systemic immune diseases (6–8).

Sensorineural hearing loss due to immune-mediated inner ear disease, although unusual as a cause of hearing loss, is important to recognize because early diagnosis and treatment can have a marked effect on the clinical outcome. When a more common clinical diagnosis cannot be reached in suspicious patients, immune laboratory tests should be made. Positive test results and beneficial response to therapy support a presumptive diagnosis of immune inner-ear disease (9). Ear damage in SLE patients has been occasionally reported but the frequency and the mechanisms of ear involvement are not well documented (10).

Although the pathogenesis of sensorineural hearing loss in patients with SLE is not clear, several reports suggest an association with the antiphospholipid antibody (aPL). Several authors suggest an anticoagulation treatment of these patients (11). The antiphospholipid syndrome (APS) was first described by Hughes in 1983 (12). It has two types: primary and secondary. Secondary APS is associated with autoimmune disease. APS is characterized by the presence of various autoantibodies whose specificity is directed not only against phospholipids but their complex with plasma proteins. Anticardiolipin antibodies (aCL) and lupus anticoagulant tests are widely performed to diagnose APS (13).

The first case of SLE with aCL and deafness was described by Hisashi et al.: aCL affect platelet membranes or the endothelium and lead to reduced levels of prostacyclin release and this in turn leads to thrombosis. It is postulated that thrombosis may cause
dysfunction of the cochlea and this may result in deafness (14).

The success of unfractionated heparin with pregnancy outcomes in women with antiphospholipid antibody syndrome has stimulated our interest to implement a protocol using an anticoagulant, sodium enoxaparin, for patients with sudden autoimmune sensorineural hearing loss (15). Sodium enoxaparin is a particular kind of heparin with a low molecular weight (LMWH) and endowed with a high antithrombotic activity. Like all the other types of heparin, it belongs to the class of anticoagulants, but offers a number of clinical advantages and has therapeutic effects superior to the other types of non-fractionated heparin. Sodium enoxaparin shows a reduction of antifactor IIa activity relative to antifactor Xa activity and superior pharmacokinetic properties. Sodium enoxaparin produces its anticoagulant effect by the activation of antithrombin and in comparison with unfractionated heparin (UFH) it has less ability to inactivate thrombin; in particular, sodium enoxaparin has lower properties than UFH to bind cellular and circulating proteins.

This drug exerts its effects essentially on capillary blood viscosity, erythrocyte deformability, thrombocyte aggregation and aPL activity (16). The possible side effects are slight hemorrhaging, usually due to pre-existing risk factors; thrombocytopenia; sometimes serious cutaneous necrosis near the injection site; cutaneous or systemic allergy; and increased transaminase levels (17).

Published experience suggests that LMWHs are generally safe and effective when administered for thromboprophylaxis during pregnancy. Several physiologic mechanisms have been proposed to explain the beneficial effects of heparin in antiphospholipid antibody syndrome (18, 19). Investigators who have followed aPL levels during pregnancy in women with antiphospholipid antibody syndrome have recorded declining levels of aPL; these data suggest that sodium enoxaparin may directly block the binding of antibodies to phospholipids and facilitate the clearance of aPL in vivo (17–20). Besides, sodium enoxaparin shows an anti-inflammatory action in subcutaneous administration, and for this reason we consider this type of treatment to be highly efficacious and innovative (21).

The literature does not report any therapeutic protocols for autoimmune sensorineural hearing loss treatment with sodium enoxaparin or other kinds of unfractionated heparin. Our decision to use sodium enoxaparin was based both on the pathogenesis of this condition and on the evaluation of the other classes of drugs currently used.

We have tested sodium enoxaparin in these patients affected by autoimmune sensorineural hearing loss and a high number of patients have shown a marked improvement of their symptoms. This preliminary study warrants further studies to confirm these data but this therapy appears to give encouraging results in the treatment of autoimmune sensorineural hearing loss.

REFERENCES

16. Franklin RD, Kutteh WH. Effects of unfractionated and low molecular weight heparin on antiphospholipid


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