Sodium Enoxaparin Treatment of Sensorineural Hearing Loss: An Immune-Mediated Response?

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Abstract: The authors propose the existence of a new entity of autoimmune sensorineural hearing loss on the basis of diagnostic study and treatment experience with a series of 30 patients. Immunological mechanisms play an important role in the pathogenesis and natural course of various inner-ear diseases. Patients may present clinically with symptoms resembling Ménière's disease or even with sudden deafness. Currently, no widely used standard protocol for treatment of this autoimmune sensorineural hearing loss exists. Prompted by such observations, we implemented a protocol using a particular kind of heparin—sodium enoxaparin—with a low molecular weight. Patients were randomly assigned to two groups; to those in the first group, enoxaparin was administered subcutaneously at a dose of 2,000 IU twice daily for 10 days; the patients in the second group were treated with placebo. At the beginning and at the end of the therapy period, the patients were evaluated by instrumental examinations. Specifically excluded were patients with abnormal known coagulation. On discharge, all patients treated with enoxaparin presented both a subjective and objective decrease in symptoms. No patient experienced side effects from this treatment. The results indicate that administration of sodium enoxaparin abates sensorineural hearing loss in patients with autoimmune diseases. The clinical response to therapy can confirm diagnosis.

Key Words: autoimmunity; immune-mediated sensorineural hearing loss; inner-ear disease; sodium enoxaparin

The audiovestibular system can be affected by an immunological etiology. The clinical presentation of immune inner-ear disease is extremely variable and depends on the type of immune reaction and on the site of injury within the inner ear [1]. Immune-mediated inner-ear disease, first described by McCabe [2] in 1979, typically presents with an idiopathic, progressive unilateral and successive bilateral rapidly progressive sensorineural hearing loss; the course of the hearing loss occurs over weeks to months and is most common in middle-aged women. It may be accompanied by tinnitus and vertigo [2,3].

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We propose the existence of a new entity of immune-mediated sensorineural hearing loss (IMSNHL), on the basis of clinical presentation, diagnostic study, and treatment experience. In each case, the clinical pattern did not fit with known entities and thus seemed to merit distinctive categorization. The 30 patients presented a clinical symptoms fairly different from that described by McCabe [2]: These patients were affected by a bilateral, slowly progressive sensorineural hearing loss, or SNHL (the course of the hearing loss occurring over years) with tinnitus, without involvement of balance function, most common in middle-aged men and with a usually normal clinical examination. Only two patients had a history of a preexisting systemic autoimmune disease (systemic lupus erythematosus [SLE]).

A positive response to treatment is a criterion for the diagnosis of immune inner-ear disease; treatment guidelines are controversial but include corticosteroids, a

cytotoxic agent, and plasmapheresis. These drugs can be effective in reversing such hearing loss, although at the cost of occasionally severe side effects. For these reasons, we decided to analyze the efficacy of sodium enoxaparin in the treatment of IMSNHL [4].

SUBJECTS AND METHODS

We performed the study in Italy during the period from April 2002 to May 2003. Patient selection was based on the following inclusion criteria for 30 patients with bilateral, slowly progressive immune-mediated hearing loss: between 20 and 65 years of age; having a history of a specific immunological disorder with an alteration of 6 of 12 immune blood parameters examined at the beginning of the protocol; having been affected by bilateral slowly progressive hearing loss of at least 30 dB of audibility threshold involving the medium and high frequencies (2,000–4,000 Hz) for at least 1 year; and having provided informed consent. All the patients confirmed a complaint of tinnitus, and no patient noted balance disorders (Table 1). Only two patients were affected by SLE; these two patients had no specific characteristic that would qualify them as a subgroup.

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

Others laboratory tests were performed at the beginning of the treatment: erythrocyte sedimentation rate (ESR), C-reactive protein, rheumatoid factors, antinuclear and antithyroglobulin antibodies, anti-double-stranded DNA antibodies, circulating immunoglobulins—class G, M, A (IgG, IgM, IgA), and complement levels (CH_{50}, C3, C4; see Table 1).

Patients were divided randomly into two numerically equal groups (A and B). All patients were hospitalized for 10 days. To those in group A, enoxaparin was administered subcutaneously at a dose of 2,000 IU twice daily for 10 days. Group B (control) patients received placebo (0.2 ml of physiological solution) via the same method of administration [5,6].

Daily during the treatment, we performed the three aforementioned audiometric examinations: liminal tonal audiometry, otoacoustic emission with linear click emission, and otoacoustic products of distortion. We did not treat patients with (1) a history of thrombocytopenia after heparin treatment; (2) hemorrhagic manifestations or tendencies that are due to disorders of hemostasis but are not heparin-dependent or related to consumption coagulopathy; (3) organic injuries at risk of bleeding; (4) renal failure or acute infectious endocarditis; (5) hemorrhagic cerebrovascular events; (6) allergy to enoxaparin; (7) use in the last 6 months of cortisone or immunosuppressive drugs; or (8) concurrent use of ticlopidine, salicylate, or nonsteroidal antiinflammatory drugs associated with sodium enoxaparin and with platelet anticoagulants (dipyridamole, sulfinpyrazone, etc.).

Table 1. Patient Characteristics, Including Modifications of Some Blood Parameters

Characteristic	No. of Subjects	
	Group A*	Group B*
Male	10	9
Female	5	6
Smoker	5	6
Bilateral hearing loss	15	15
Tinnitus	15	15
Vertigo	0	0
Systemic lupus erythematosus	1	1
Erythrocyte sedimentation rate	15	15
C-reactive protein	8	5
Rheumatoid factors	15	15
Anti-double-stranded DNA	11	9
Antithyroglobulin antibodies	6	5
IgG	15	15
IgM	13	12
IgA	14	13
CH_{50}	8	9
C3	9	8
C4	5	6

*Mean age in group A, 47.5 yr; in group B, 42.5 yr.

RESULTS

At the beginning of treatment, all patients in the two groups presented with modifications of some blood immune parameters (see Table 1). No single blood immune parameter can support a diagnosis of immune-mediated disease: we considered the possibility of an immune-mediated disease when the patients showed a modification of at least four blood immune parameters.

After therapy, the patients in group A showed an improvement of some immune parameters. The results of the pretherapeutic and posttherapeutic blood tests are summarized in Table 2.

On discharge, 13 group A patients (87%) treated with sodium enoxaparin presented a subjective abate-

Table 2. Summary of Blood Parameters Before and at the End of Therapy in Group A

	Before Therapy		After Therapy	
Blood Parameter	**Mean**	**±SEM**	**Mean**	**±SEM**
Erythrocyte sedimentation rate (mm/hr)	64.8	2.26	13.8	3.24
C-reactive protein (mg/dl)	8.3	3.25	<3.2	
Rheumatoid factor (IU)	280.4	3.66	189.1	3.78
C3 complement component (mg/dl)	193.3	0.98	177.7	0.74
Fibrinogen (mg/dl)	311.6	11.89	312.3	12.01
Prothrombin (sec)	98.5	0.69	98.7	0.66
IgG (mg/dl)	1850.1	5.15	1629.3	4.69
IgM (mg/dl)	282.3	3.21	239.6	2.78
IgA (mg/dl)	410.7	4.13	406.2	3.35
C4 complement component (mg/dl)	48.6	0.23	37.2	1.27
CH_{50} complement component (U)	198.5	4.88	197.3	3.60
Antithyroglobulin antibodies (IU/ml)	240.3	2.75	109.3	2.77

SEM = standard error of the mean.

ment of tinnitus. In group A, hearing improved in 11 patients (73%) and was unchanged in 4 (27%); mean hearing improvement for these patients ranged from 18.6 to 23.8 dB (±4.79 standard error of the mean in the 2,000-Hz range and ±4.60 in the 4,000-Hz range examined).

In the same 13 patients, the evoked otoacoustic emissions revealed an improvement from "fail" to "pass," and otoacoustic distortion products, which previously were absent, were evoked at frequencies of the tonal field normally examined. The mean value of scores on the subjective symptom scale fell from 3.8 before the therapy to 1.5 at the end of the therapy. In the patients with hearing improvement, the scores fell from 3.8 before the therapy to 1.1 at the end of the therapy.

In group B, no patient showed an improvement in auditory function, and the evoked otoacoustic emissions revealed an improvement from "fail" to "pass" in only two patients. Only two patients (13%) reported a subjective abatement of tinnitus, and these patients had no particular characteristics to qualify as a subgroup. The mean value of scores on the subjective symptom scale fell from 3.7 before therapy to 3.2 at the end of therapy.

We made a comparison of groups by the unpaired *t*-test, and we analyzed correlations by regression analysis. Probability values at less than .05 were regarded as significant. We also made comparisons of groups for repeated measures by analysis of variance. No patient experienced side effects from this treatment.

DISCUSSION

The presence of SNHL as part of or in combination with other autoimmune diseases is well documented in the literature [7–10]. Hearing loss can be caused by autoimmune disorders localized to the inner ear or secondary to systemic immune diseases (Cogan's syndrome, juvenile chronic arthritis, ulcerative colitis, Wegener's granulomatosis, scleroderma, pulseless disease, and SLE). A systemic autoimmune disorder can be present in fewer than one-third of cases [2,7–11].

The clinical presentation of immune-mediated inner-ear disease can be fairly variable and may include symptoms similar to those of Ménière's syndrome or clinical conditions associated with unilateral or bilateral rapidly progressive forms of SNHL [1,2].

Currently, evaluating the importance of an autoimmune phenomenon in the genesis of inner-ear disease is difficult because the clinical and biological criteria of autoimmune deafness have not yet been well defined. Individual diagnostic criteria (clinical presentation, laboratory studies, and response to treatment) are nonspecific but, when used in combination, can diagnose immune-mediated inner-ear disease with reasonable success [1,5].

Immunoserological assays of patients with sudden deafness and progressive hearing losses have revealed the presence of different antibodies, leading to the assumption that immunological processes may be involved. Recent investigations have demonstrated that these patients have phospholipid antibodies that can cause venous or arterial vasculopathies [12,13]. Antiphospholipid antibodies are immunoglobulins of IgG, IgM, and IgA isotypes that target phospholipid [14–16]. They are thought to induce thrombosis by binding to phospholipids on the surface of platelets and the vascular endothelium. This binding complex is characterized by decreased prostacyclin production by endothelial cells, increased thromboxane production by platelets, and decreased protein C activation, resulting in vasoconstriction [17–19].

The success of unfractionated heparin in pregnancy outcomes in women with antiphospholipid antibody syndrome has stimulated our interest in implementing a protocol using an anticoagulant—sodium enoxaparin—for patients with sudden IMSNHL [20,21]. Sodium enoxaparin is a particular kind of heparin with a low molecular weight and is 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 unfractionated heparin. This drug exerts its effects essentially on capillary blood viscosity, erythrocyte deformability, thrombocyte

aggregation, and antiphospholipid antibody activity and shows an antiinflammatory action in subcutaneous administration [21–25].

Although refinements in laboratory tests for specific inner-ear antigens are being made, nonspecific laboratory indicators of inflammatory or systemic immune disease may be useful in confirming the diagnosis. For these reasons, we decided to execute the previously listed blood tests at the beginning and at the end of treatment.

The subjective abatement of tinnitus and the improved hearing observed in the patients treated with sodium enoxaparin (group A) led us to evaluate all the blood parameters so as to justify the effects of sodium enoxaparin and to confirm the diagnosis of IMSNHL. In those in group A, the final observed reduction of the ESR (13.8 mm/hr), C-reactive protein (<3.2 mg/dl), and rheumatoid factor (189.1 IU) confirms the antiinflammatory action of the drug in subcutaneous administration (see Table 2).

The elevated levels of C3 (193.3 mg/dl) and C4 (48.6 mg/dl) indicated an activation of the first part of the complement cascade and, therefore, suspected inflammatory causes; their final reduction (C3: 177.7 mg/dl; C4: 37.2 mg/dl) highlighted the antiinflammatory action of sodium enoxaparin in subcutaneous administration (see Table 2) [4,5]. The normalization of the ESR, C-reactive protein, and rheumatoid factor supports the combined interaction of the drug with the immune system and inflammatory mechanisms.

At the end point, group A patients showed a decrease of IgG (1629.3 mg/dl) and IgM (239.6 mg/dl) plasmatic levels; reduction of the initial high titers of IgG (1850.1 mg/dl) and IgM (282.3 mg/dl) highlights the possible role of sodium enoxaparin in the antiphospholipid syndrome in patients with immune-mediated inner-ear disease (see Table 2).

Hearing loss accompanies some thyroid gland diseases, especially those involving hypothyroidism. Some authors state that it correlates with the autoimmune background of certain thyroid gland disturbances. In accord with the literature, our data suggested an association between the immune-mediated disease and the thyroid blood hormone level [26]. The final reduction of plasmatic levels of antithyroglobulin antibodies (109.3 IU/ml) highlights the combined antiinflammatory and immunologically modulated action of sodium enoxaparin (see Tables 1 and 2). We found no significant difference in the other parameters (see Table 2).

The possible side effects are slight hemorrhaging, usually due to preexisting risk factors; thrombocytopenia; sometimes serious cutaneous necrosis near the injection site; cutaneous or systemic allergy; and increased transaminase levels [27].

The blood tests performed at the beginning of therapy highlighted modifications of the single immune parameters in all patients. The hematic alterations of the immune parameters, the positive response to treatment in group A patients, and the specific mechanisms of action of sodium enoxaparin can support a diagnosis of immune-mediated inner-ear disease (see Tables 1 and 2).

At the beginning of the treatment, our data showed a high incidence of high blood values of ESR, C-reactive protein, and rheumatoid factors. The final normalization of these three parameters highlighted their greater importance in the diagnosis of IMSNHL.

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

CONCLUSIONS

We have tested sodium enoxaparin in all our patients affected with IMSNHL, and all have shown a marked lessening of their symptoms (hearing loss and tinnitus). Because of that outcome, we believe enoxaparin has a very important role in the therapeutic management of IMSNHL. Avoidance of the need to monitor anticoagulation appears to be the major advantage of this agent over unfractionated heparins (see Table 2).

Diagnosis of IMSNHL is still based on insufficient diagnostic parameters. Clinical impressions and laboratory tests and the existence of a typical patient profile (including clinical course, immunological changes, and response to therapy) can facilitate diagnosis. The low number of patients suggests the need for further studies to confirm the first data that we obtained, but we believe that this kind of therapy produces encouraging results in the treatment and diagnosis of IMSNHL.

REFERENCES

1. Dornhoffer JL, Arenberg JG, Arenberg IK, Shambaugh GE Jr. Pathophysiological mechanisms in immune ear disease. *Acta Otolaryngol* 26:30–36, 1997.
2. McCabe BF. Autoimmune sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 88:585–589, 1979.
3. Ryan AF, Keithley EM, Harris JP. Autoimmune inner ear disorders. *Curr Opin Neurol* 14:35–40, 2001.
4. Ryan AF, Harris JP, Keithley EM. Immune-mediated hearing loss: Basic mechanisms and options for therapy. *Acta Otolaryngol Suppl* 548:38–43, 2002.
5. Van Den Belt AG, Prins MH, Lensing AW, et al. Fixed dose subcutaneous low molecular weight heparins versus

adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev (2):CD001100, 2000.

6. Chan WS, Ray JG. Low molecular weight heparin use during pregnancy. Issues of safety and practicality. *Obstet Gynecol Surv* 54:649–654, 1999.
7. Cogan DG. Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. *Arch Ophthalmol* 33: 144–149, 1945.
8. Weber RS, Jenkins HA, Coker NJ. Sensorineural hearing loss associated with ulcerative colitis. A case report. *Arch Otolaryngol* 110:810–812, 1984.
9. Leone CA, Feghali JG, Linthicum FHJ. Endolymphatic sac: Possible role in autoimmune sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 93:208–209, 1984.
10. Hughes GB , Barna BP, Kinney SE, et al. Clinical diagnosis of immune inner-ear disease. *Laryngoscope* 98:251–253, 1988.
11. Veldman J. Immune-mediated sensorineural hearing loss. *Auris Nasus Larynx* 25:309–17, 1998.
12. Moine A, Mohcini M, Beal C, et al. Deafness and autoimmunity: What is the role of antiphospholipid syndrome? Apropos of 35 cases. *Ann Otolaryngol Chir Cervicofac* 111:363–70, 1994.
13. Heller U, Becker EW, Zenner HP, Berg PA. Incidence and clinical relevance of antibodies to phospholipids, serotonin and ganglioside in patients with sudden deafness and progressive inner ear hearing loss. *HNO* 46:583–586, 1998.
14. McIntyre JA, Wagenknecht DR, Faulk WP. Antiphospholipid antibodies: Discovery, definitions, detection and disease. *Prog Lipid Res* 42:176–237, 2003.
15. Bick RL. Antiphospholipid thrombosis syndromes. *Hematol Oncol Clin North Am* 17:115–147, 2003.
16. Cadoni G, Fetoni AR, Agostino S, et al. Autoimmunity in sudden sensorineural hearing loss: Possible role of anti-endothelial cell autoantibodies. *Acta Otolaryngol Suppl* 548:30–33, 2002.
17. Lockshin MD. Antiphospholipid antibody. *JAMA* 277: 1549–1551, 1997.
18. Chamley LW, McKay EJ, Pattison NS. Inhibition of heparin/antithrombin III cofactor activity by anticardiolipin antibodies: A mechanism for thrombosis. *Thromb Res* 71:103–111, 1993.
19. Shibata S, Harpel P, Bona C, Filit H. Monoclonal antibodies to heparin sulfate inhibit the formation of thrombin-antithrombin III complexes. *Clin Immunol Immunopathol* 67:264–272, 1993.
20. Kutteh WH, Wester R, Kutteh CC. Multiples of the median: Alternate methods for reporting antiphospholipid antibodies in women with recurrent pregnancy loss. *Obstet Gynecol* 84:811–815, 1994.
21. Mora R, Salami A, Barbieri M, et al. The use of sodium enoxaparin in the treatment of tinnitus. *Int Tinnitus J* 9(2):109–111, 2003.
22. Franklin RD, Kutteh WH. Effects of unfractionated and low molecular weight heparin on antiphospholipid antibody binding in vitro. *Obstet Gynecol* 101:455–462, 2003.
23. Ensom MH, Stephenson MD. Low molecular weight heparins in pregnancy. *Pharmacotherapy* 19:1013–1025, 1999.
24. Masamoto H, Toma T, Sakumoto K, Kanazawa K. Clearance of antiphospholipid antibodies in pregnancies treated with heparin. *Obstet Gynecol* 97:394–398, 2001.
25. Ermel LD, Marshburn PB, Kutteh WH. Interaction of heparin with antiphospholipid antibodies (APA) from the sera of women with recurrent pregnancy loss (RPL). *Am J Reprod Immunol* 33:14–20, 1995.
26. Gawron W, Pospiech L, Noczynska A, Klempous J. Two cases of hearing loss following Hashimoto disease. *Wiad Lek* 55:478–482, 2002.
27. Depasse F, Samama MM. Heparin-induced thrombocytopenia. *Ann Biol Clin (Paris)* 58:317–326, 2000.