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Azathioprine in Combination with Steroids in the Treatment of Autoimmune Inner-ear Disease

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A total of twelve patients with a relatively uncommon form of progressive sensorineural deafness (autoimmune inner-ear disease) were treated orally with 1 mg/kg azathioprine, once daily, and with 30 mg prednisolone, every other day, for 4 weeks. Statistically significant increases in the ability to hear pure tones or in discrimination on audiometry took place in 10/12 patients. This condition was initially described as 'sensorineural hearing loss', but it is now clear that the term 'autoimmune inner-ear disease' is more appropriate since the vestibular compartment as well as the cochlear compartment is involved. This relatively uncommon disease is one of the few forms of sensorineural deafness that can be successfully treated.

KEY WORDS: AZATHIOPRINE; PREDNISOLONE; CYTOTOXIC IMMUNOSUPPRESSANTS; INNER-EAR DISEASE; SENSORINEURAL HEARING LOSS; AUTOIMMUNITY

INTRODUCTION

In recent years, evidence has accumulated from case reports and animal models that humoral and cellular immunity, probably in concert, are responsible for some forms of sensorineural hearing loss. It is now clear that with accurate diagnosis and aggressive treatment such forms of sensorineural hearing loss, unlike most other forms, may respond to treatment. McCabe[1] first reported a treatable form of sensorineural hearing loss that appears to have an autoimmune basis and since then studies have focused on the pathogenesis, diagnosis and treatment of this disorder. McCabe[2] and others[3,4] have

reported that autoimmune disease may cause a constellation of audiovestibular symptoms that may be sudden in onset or slowly progressive and that may have a unilateral or a bilateral onset. The symptoms may mimic Menière's disease with fluctuations in hearing and acute, severe vertiginous episodes with nausea and vomiting.

Immunosuppresion with azathioprine seems to result from inhibition of nucleic acid metabolism at stages that are essential to the wave of cell proliferation that follows antigenic stimulation. The purine analogues are thus cytotoxic to stimulated lymphoid cells.

The present report shows that azathioprine in combination with steroids provides an effective treatment for autoimmune inner-ear disease.

PATIENTS AND METHODS

PATIENTS

The 12 patients [eight females, four males; age range 22 – 61 years; mean (± SD) age 32.7 ± 10.4 years] had had sensorineural hearing loss for a mean of 22 ± 11 days at the time of recruitment to the study. The trial was conducted between December 1990 and February 1993. Inclusion criteria were unilateral and bilateral sensorineural hearing loss, established by audiometry, of at least 3 weeks' duration.

TREATMENT AND ASSESSMENT OF TREATMENT

Audiometry was performed every month for 12 months after recruitment. A detailed social, family and patient history was obtained for all patients and laboratory tests including complete blood count, uric acid, multiphasic biochemical screening, serum protein, serum alkaline phosphatase and liver function tests were carried out before the start of the azathioprine treatment. Tests were repeated at the end of treatment and once every month for the subsequent 3 months.

The treatment initially involved the administering of 1 mg/kg azathioprine orally, every 24 h and 30 mg prednisolone every other day for a total of 4 weeks. These doses were relatively small in terms of side-effects but were considered adequate for treatment. If this treatment resulted in any significant increase in ability to hear pure tones or in discrimination on audiometry (by an average of 15 dB in any three frequencies or more than 20% in the discrimination score), the response was considered positive and full treatment was started. Full treatment consisted of continuing the same drugs at the same doses for 3 months. The azathioprine was then discontinued but the prednisone treatment was maintained for a further 2 weeks. If the hearing improvement was maintained, the prednisolone dose was gradually reduced over 2 weeks. If there was a reduction in hearing ability before or after the tapering of the prednisolone, full treatment was reinstituted for an additional 3 months.

STATISTICAL ANALYSIS

The hearing levels (dB) of patients pre- and post-treatment were compared using the paired Student's *t*-test ($P < 0.001$).

RESULTS

Of the 12 patients recruited into the study, one (8.3%) had been receiving low molecular weight dextran and vitamins B_1, B_2, and B_6 at the time of entry into the study, and two (16.6%) patients had been previously treated with corticosteriods: one patient had received vitamins B_6 and B_{12} in addition to prednisolone 1 mg/kg; the other patient had received prednisolone 1 mg/kg alone.

TABLE 1

Systems other than the ear involved in an autoimmune inflammatory process in seven patients with autoimmune hearing loss (one symptom per patient)

Symptoms	Characteristics
General	Malaise, weight loss
Allergic	Inhalation allergies
Musculoskeletal	Arthralgias, arthritis
Gastro-intestinal	Diarrhoea
Ocular	Conjunctivitis
Pulmonary	Respiratory failure
Nervous system	Peripheral neuropathies

TABLE 2

Improvement in hearing in 12 patients before and after treatment with 1 mg/kg azathioprine orally every 24 h and 30 mg prednisolone every other day for 4 weeks

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Hearing level before treatment (dB)	34	43	45	48	50	63	78	78	80	85	93	98
Hearing level after treatment (dB)	10	5	8	12	10	26	75	32	10	14	15	96

All patients underwent behavioural testing, with both air and bone conduction threshold testing. The mean sensorineural hearing loss level was 63 ± 8 dB. In total, ten patients (83%) had both bilateral asymmetric sensorineural hearing loss and bilateral reduced vestibular response; five patients with auditory symptoms also complained of dizziness. Asymmetric rapidly progressive sensorineural hearing loss had been experienced by two (16.6%) patients (Table 1) and seven patients (58%) had other systems involved in an autoimmune inflammatory process (Table 1).

Azathioprine was used for all patients and no adverse events of the drug were reported. Statistically significant ($P < 0.001$) increases in ability to hear pure tones or in discrimination on audiometry by an average of 15 dB in any three frequencies, or more than 20% in the discrimination score were recorded in 10 of the 12 patients at an 83% confidence level. In two patients, there appeared to be no significant differences between the audiograms before and after treatment. Minor hearing loss of 30 to 50 dB was found to have improved to normal or near normal in five patients post-treatment. Three patients who had suffered more severe hearing loss of 80 to 100 dB experienced good hearing improvement in both ears post-treatment. Leucocyte counts (including

neutrophils) were made throughout treatment. The leucocyte count was always $\geq 3000/m^3$ in each patient and the neutrophil count remained $\geq 1500/m^3$. No adverse events were observed or reported. There was no evidence of rash, fever, gastro-intestinal side-effects, or hepatic dysfunction.

Discussion

The causes of autoimmunity are not clear. Autoreactivity may be the consequence of the breakdown of an individual's immunological homeostasis, in which regulatory mechanisms prevent the stimulation of self-reactive lymphocytes. An autoimmune immunological response may follow an earlier tissue injury; antigens that were sequestered within the organ and lacked previous contact with the immune apparatus are thus released and immune reactivity may occur, e.g. after certain eye diseases. Antigens may also be modified by drugs or viruses, resulting in a new antigen of non-self character giving rise to autoimmune reactivity.

In a recent study, Harris and Sharp[5] found that 19/54 (35%) patients with progressive sensorineural hearing loss showed evidence of a specific anticochlear antibody in their serum. This finding was confirmed by Moscicki[6] who not only showed by Western blot analysis that the same auto-antibody was present in the 11 patients that he studied but also found that the hearing of these patients was improved by immunosuppressive therapy.

Autoimmune inner-ear disease is a relatively uncommon disorder of the labyrinth that mainly affects young adults and those in early middle age; it is one of the few such diseases for which a treatment is available. It would appear that a combination of moderate dosage azathioprine and low-dose prednisolone gives the most favourable results. The present results are gratifying, with a statistically significant improvement in hearing in the majority of patients and a cessation of the progress of hearing loss in the remainder. It is not possible to diagnose the disease unequivocally before treatment.

In the present study, treatment over a period of 3 – 24 months was necessary. Complications were minor. The clinician should be aware of the possible emergence of diseases of other systems, which will probably be present in one in four patients.

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