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Early diagnosis and stage-adapted treatment of Wegener's granulomatosis

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Abstract
A case of Wegener's granulomatosis (WG) presenting with hearing loss and right facial nerve palsy is reported. The definitive diagnosis was based upon clinical data and serum cANCA and AECA detection. Early assessment of WG prevented surgical facial nerve decompression to treat a chronic otitis media complication. Immunosuppressive therapy with steroids, cyclophosphamide and methotrexate was required for relief of clinical symptoms and cANCA negativity as an expression of disease remission. The effectiveness of co-trimoxazole for preventing relapses of WG is discussed.

Key words: Wegener's Granulomatosis; Hearing Loss, Bilateral; Antibodies, Antineutrophil Cytoplasmic; Facial Paralysis

Introduction

Wegener's granulomatosis (WG) is a systemic disease characterized by granulomatous vasculitis involving both small arteries and veins. It is of special significance for the otorhinolaryngologist because the disease activity limited to the upper respiratory tract (localized WG) often preceeds systemic vasculitis (generalized WG).[1–5]

Therefore, early diagnosis is decisive to implement stage-adapted therapy, established on the basis of the clinical pattern including serum cytoplasm anti-neutrophilic cytoplasmic antibody (cANCA) and histological findings of granulomatous inflammation with epithelioid cells, granulomas, and systemic vasculitis. Only in a few studies was anti-endothelial cell antibodies (AECA) detection considered in the evaluation of WG.[6]

Facial nerve palsy has been reported during the course of WG but it is extremely rare as a presenting sign.[7–16] Bilateral facial palsy has been reported only once.[17] Previously reported cases of facial palsy as a presenting symptom of WG have involved a protracted diagnostic process including exploratory tympanotomy, mastoidectomy and facial nerve decompression.

We report a case of WG presenting with hearing loss and facial palsy that was diagnosed early and successfully treated with multi-drug therapy.

Case report

A 42-year-old Caucasian male presented with a two-month history of bilateral otalgia and hearing loss. Otoscopy revealed bilateral serous otitis media. An audiogram revealed a moderate bilateral mixed hearing loss (Figure 1). Computed tomography (CT) showed bilateral opacification of middle-ear and mastoid air cells without bone erosion (Figure 2). Laboratory tests showed serum leucocytosis and a high erythrocyte sedimentation rate (ESR). Anti-nuclear antibodies and AECA positivity was observed while cANCA autoantibodies were absent. Hearing loss, middle-ear effusion and inflammation were

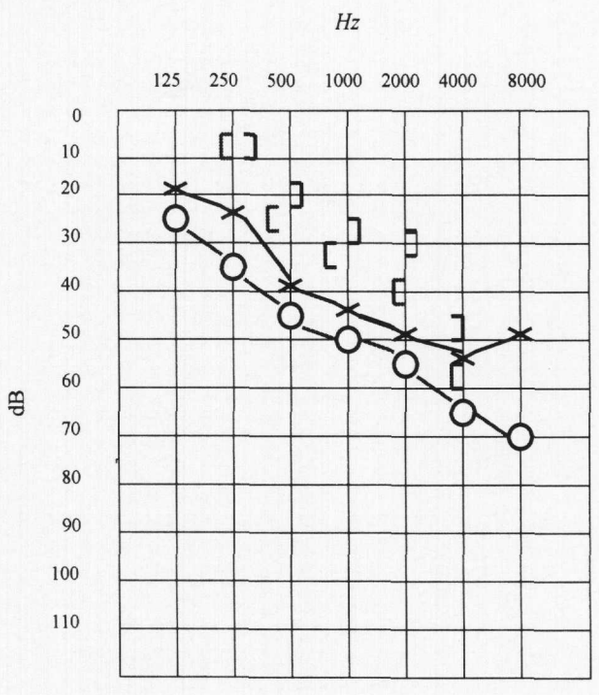

FIG. 1
Left air threshold ×; Left bone threshold ⌐; Right air bone ○; Right bone threshold ⌐

Audiogram showing bilateral mixed moderate hearing loss. The patient complained of deafness and otalgia; both clinical examination and CT of the middle ear showed aspecific bilateral otomastoiditis without complications. cANCA titre was normal and AECA test was positive. A recovery was obtained by anti-inflammatory steroid therapy.

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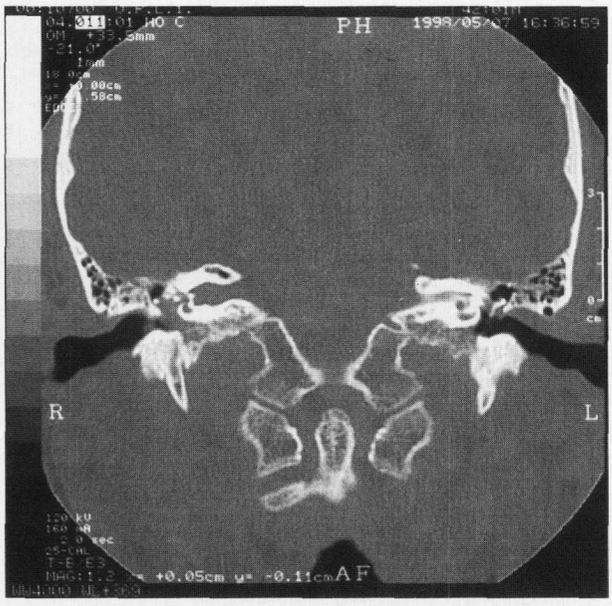

FIG. 2

Frontal CT scan showing bilateral opacification of the middle ear and mastoid ear cells without bone erosion.

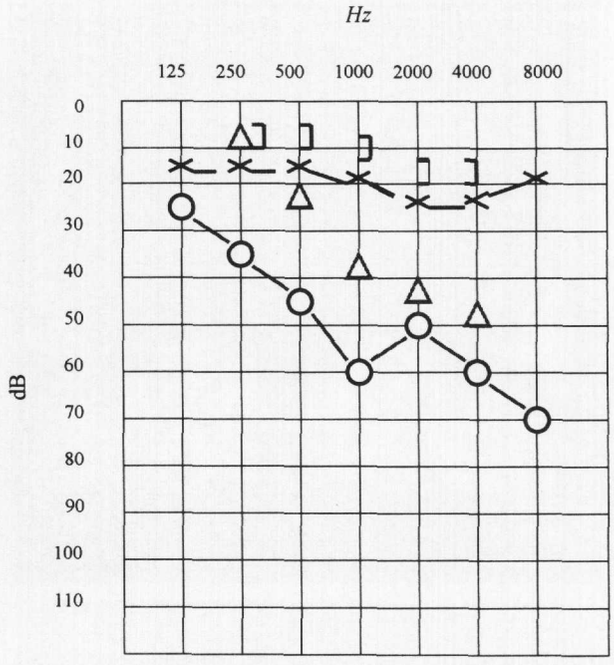

FIG. 4

Left air threshold ×; Left bone threshold ⌉; Right masked air bone ○; Right masked bone threshold △

Audiogram showing a right mixed moderate hearing loss associated to the facial palsy after three weeks from first remission. At this time cANCA titre was abnormal.

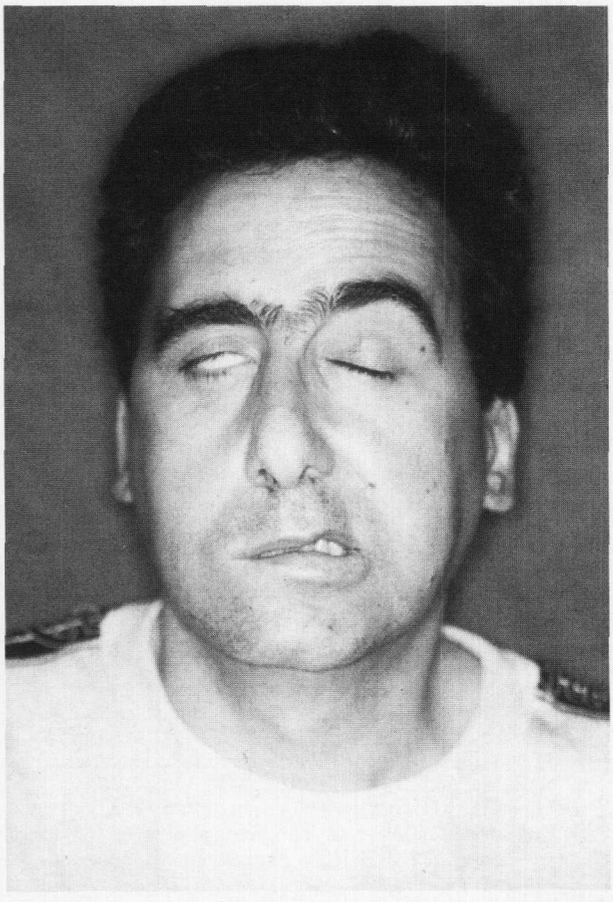

FIG. 3

Right facial palsy compared in association with ipsilateral hearing loss. The patient presented right facial palsy and hearing loss after three weeks after dimission. Clinical examination and CT showed right otomastoiditis.

resolved with steroid anti-inflammatory (16 mg/die methylprednisone) therapy for a week. Three weeks later the patient showed right facial palsy (Figure 3) associated with hearing loss. The audiogram revealed a right moderate mixed hearing loss (Figure 4). CT showed right otomastoiditis without evidence of bone erosion (Figure 5). A reactive enhancement of the right facial nerve in its first

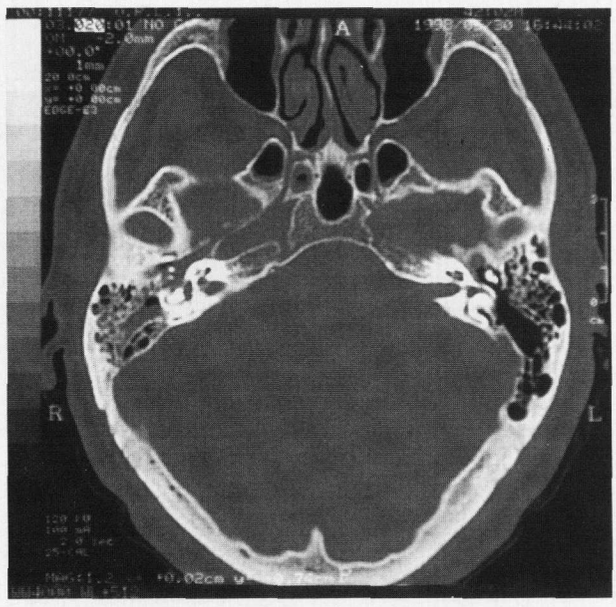

FIG. 5

Axial CT scan showing opacification of the right middle ear and mastoid air cells without bone erosion.

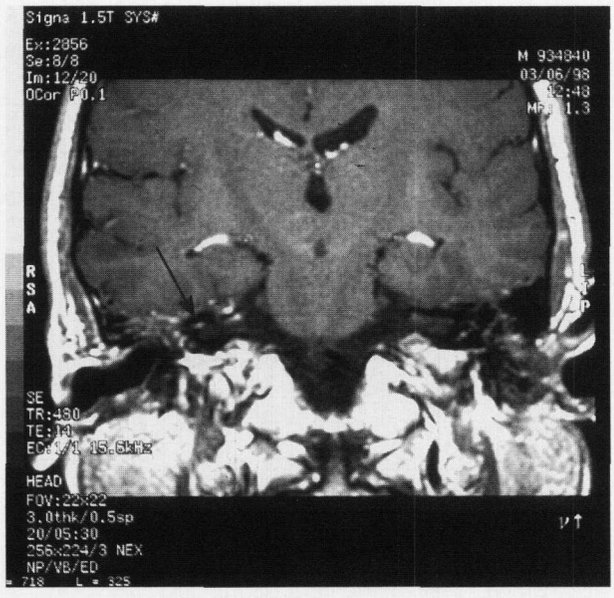

FIG. 6

Frontal MR scan showing flogistic enhancement along the first and second tracts of the right facial nerve temporal course. cANCA titre was abnormal.

and second temporal tracts was observed on magnetic resonance imaging (MRI) (Figure 6). At this stage, the diagnosis of localized WG was achieved based on high ESR and cANCA titre and detection of AECAs, allowing early immunosuppressive therapy while unnecessary and potentially hazardous middle-ear surgery was prevented. Systemic steroid therapy (1 mg/Kg/die methylprednisolone) was instituted with remission of facial palsy and hearing loss after six weeks.

Two months later the patient complained of joint pain and fever. Cyclophosphamide (150 mg/die) therapy was therefore added to methylprednisolone. After three months of therapy, due to a chemical cystitis, cyclophosphamide was substituted by methotrexate (10 mg/week). Remission of clinical symptoms and normalized cANCA levels were obtained after 13-month treatment with methotrexate and methylprednisone; therefore only steroid therapy (2 mg/die) was continued. After 16 months the patient had the first relapse; he complained again of fever and joint pain; high cANCA and ESR levels were detected, and microbiological examination of nasal secretions revealed a *Staphylococcus aureus* infection. Therefore steroids (prednisolone 63 mg/die) and cyclophosphamide (50 mg/die for three weeks in decreasing doses) were administered for five months. When normalized cANCA levels were detected cyclophosphamide was replaced by co-trimoxazole (1 gr/die). The patient did not show lung and kidney involvement.

Discussion

Hearing loss and facial nerve palsy associated with acute or chronic middle-ear inflammation should be considered in the early diagnosis of WG.

The early diagnosis of WG should be based on the presence of specific cANCA but we also hypothesize the possible diagnostic role of AECAs. In fact, AECA positivity is observed in systemic vasculitis with WG.[18] The detection of AECAs in the present case report supports their hypothesized role in the pathogenesis of immune-mediated ear function disorders associated to well-known systemic autoimmune diseases such as WG.[6]

In this case report, non-specific inflammatory disease of the mastoid delayed the correct diagnosis of WG, which was then confirmed by a high serum level of cANCA. In fact, a fundamental element in the diagnosis of WG is serum positivity for cANCA studied by indirect immunofluorescence techniques.[19] The close relationship between antibody titre and the clinical course suggests a possible role of these antibodies in the pathogenesis of the disease.[3] Therefore negative c-ANCA tests do not necessarily exclude the diagnosis of WG,[20] as they often become positive during the course of the disease, as happened in the case here described.

MRI scan showed the VIIth cranial nerve inflammation without bone erosion and facial nerve palsy was resolved with steroids. This led to the hypothesis that the pathogenesis of facial nerve palsy was related to Wegener's granulomatous involvement of the nerve.

Generalized WG therapy includes steroids, cytotoxic drugs (cyclophosphamide, methotrexate), immunosuppressants such as cyclosporin, tacrolimus, mycophenolate mofetil, plasmapheresis or anti-lymphocytic monoclonal antibodies. The tumour necrosis factor inhibitor etanercept is now being explored as a therapeutic agent.[21] Bone marrow and stem cell transplantation may find a role in refractory disease.

Anti-inflammatory doses of steroids are used in localized WG whereas cytotoxic drugs with immunosuppressive doses of steroids are administered when WG becomes a systemic disease. As in our case, fever and joint pain can characterize the evolution of WG from localized to generalized disease.

Because of the apparent correlation between infection and WG activation, the management of infections – especially those caused by *Staphylococcus aureus* – requires special attention especially in the localized variant of WG[22] and co-trimoxazole is considered the drug of choice for the prevention of relapses. In view of the high incidence of lethal adverse effects of cytotoxic drugs, co-trimoxazole may be worth trying not only in the initial stage of WG but also in the generalized form with careful follow-up when the patient is not acutely ill.[23]

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