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Wegener's granulomatosis in two siblings: a family study

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Abstract
Two brothers with Wegener's granulomatosis are presented. HLA status and associated genes in the brothers and the immediate family are explored. No specific association could be found with tissue types within the family.

Introduction

As long ago as 1931 a report appeared of a patient suffering from a disseminated vasculitic process which was defined by Wegener as a distinct disease entity (Wegener, 1936). The early work and subsequent developments in our understanding and treatment of the disease have recently been reviewed by the original author (Wegener, 1990).

Generalized Wegener's granulomatosis is a necrotizing granulomatous vasculitis affecting the upper and lower respiratory tract and kidneys. It is a rare condition, but its true incidence is difficult to estimate since it is probably under-reported.

Its natural history is of a median survival of five months (Walton, 1958), but with aggressive treatment with cytotoxic drugs and steroids long term survival can be achieved. In a study over 18 years (Fauci *et al.*, 1983) only six out of 85 patients died of active disease.

There has also been a more recent appreciation that localized forms of the disease can exist. Ocular features (Coutu *et al.*, 1975; Spalton *et al.*, 1983) otological features (Kornblut *et al.*, 1982; Bradley, 1983; Ridley *et al.*, 1988; Kempf, 1989) and even subglottic stenosis (Hoare, 1989) can be the presenting features of Wegener's.

Diagnosis has always been difficult mainly because of the inability to detect the typical histological features, especially in the early stages. Clinical diagnosis has been the rule in the past, aided by crude measures of disease activity such as the erythrocyte sedimentation rate.

Most recently, the discovery and development of tests for anti-neutrophil cytoplasmic antibodies have provided a powerful tool for the recognition of cases. A recent study (Noelle *et al.*, 1989) gave a specificity of 98 per cent or better, and a sensitivity of 93 per cent or better for generalized active disease and 60 per cent or better for localized active disease. Hence false positives are rare but can occur (Mains, 1989), whereas a negative result is of limited value in localized disease.

It is now understood that Wegener's is an autoimmune-mediated disease, with the antibody being directed against intracytoplasmic components of leucocytes. Because of the leucocyte connection there have been studies into possible associations between the HL-A tissue typing phenotypes and Wegener's. A significant association between HL-A B8 and DR2 has been shown. (Strimlan *et al.*, 1978; Katz *et al.*, 1979; Beigel *et al.*, 1981; Elkon *et al.*, 1983).

We present two cases of Wegener's granulomatosis occurring in brothers; possible hereditary factors are investigated with the use of tissue typing.

Patients

Case 1

A 42-year-old male baker (D.Q.) presented with a 12 month history of a gradual onset of significant bilateral deafness, worse on the left, and a four month history of right otalgia with headaches which interfered with his sleep. Ear, nose and throat examination was normal except for dull tympanic membranes. There was significant conductive deafness and flat tympanograms bilaterally. A diagnosis of bilateral serous otitis was made. Sinus X-rays were normal, there was a mild leucocytosis and the ESR was 47 mm.

On myringotomy, there was pale granular tissue in both middle ears and some serous fluid on the left side where a grommet was inserted. EUA of the post-nasal space showed swollen posterior ends to the inferior turbinates and a granular surface to the soft palate. Biopsies were reported as showing oedematous connective tissue and normal lymphoid tissue. Post-operatively he improved symptomatically. A CT scan performed because of the granulations was suggestive of an infective process, with opacity of the right mastoid cells and destruction of some septa.

He was given a course of steroids as a therapeutic trial, and was well while on this. He was readmitted three weeks later with a recurrence of his symptoms, however, when the presumptive diagnosis was of Wegener's granulomatosis. He had a leucocytosis of 17.6 and an ESR of 59 mm; urea, electrolytes and a chest X-ray were normal. A right cortical mastoidectomy and tympanotomy were performed to obtain more tissue for histology; granulations were found in the epitympanum and hypotympanum but the mastoid was normal apart from some bone destruction. Histology was of granulations, with no evidence of granulomas or vasculitis. He was discharged feeling clinically well, on a dose of 20 mg prednisolone a day. Relapse occurred when the dose was reduced, with otalgia, generalized musculoskeletal pains and nasal pain. His tympanic membranes, right external meatus and nasal septum were all thickened. A nasal biopsy again showed non-specific inflammatory changes.

His condition deteriorated in spite of reinstitution of high dose steroids, with chest pain and haematuria. The ANCA test was strongly positive at 76 per cent. He was started on i.v. cyclophosphamide in addition to the steroids.

Soon after starting on the steroids he presented with sudden loss of vision in his left eye. A CT scan showed no evidence of orbital granulomas and a presumptive diagnosis of retinal artery occlusion due to vasculitis was made.

Initially good remission was obtained with the steroids and

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cyclophosphamide, but he has had relapses, with his nasal disease being the most difficult to control. He therefore had a course of radical radiotherapy to the nose. At present he continues with a maintenance dose of azathioprine and steroids.

Case 2

A 30-year-old male ambulance driver (W.N.Q.) presented in May 1984, with epistaxis, nasal obstruction and deafness. Initially he had a submucosal resection of his nasal septum and had bilateral grommets inserted in another hospital. By July he was losing weight, and a subsequent biopsy showed small vessel vasculitis and multinucleated giant cells consistent with a diagnosis of Wegener's granulomatosis. ESR at presentation was 50 mm. He developed conjunctivitis and uveitis in addition.

Initial treatment was with radiotherapy, being given 4000 cGy to the nose. A relapse in October 1984 with sore throat, muscular aches, arthritis in his hands and conjunctivitis was associated with an ESR of 102. This was brought under control with i.v. cyclophosphamide and steroids with a maintenance of oral cyclophosphamide and prednisolone.

In September 1986, he had a reactivation of disease with pain and swelling around the nose and granulations in the nasal cavity. This responded to increased doses of cyclophosphamide and prednisolone.

From December 1986, he had several episodes of chest infection but without any evidence of involvement with Wegener's. The possibility of pulmonary fibrosis secondary to cyclophosphamide was raised and therefore he was changed to azathioprine maintenance.

Since then he has remained well until recently when he had a recurrence of disease with granulations in the nasal vestibule and an ulcer on the nasal tip, requiring further cyclophosphamide.

The Family

There are two other living siblings, one of each sex. They were interviewed and examined and had no clinical evidence of disease. Their mother is alive and well, similarly free of clinical evidence of disease, and their father died in 1966 of lung cancer.

Results of tissue typing studies

The patients, siblings and mother were tested for their HL-A phenotypes. (See Table I) The two patients share the A31; Bw60; DR4 haplotype derived from their mother but have inherited different haplotypes from their father. The other two siblings are HL-A identical.

Discussion

A search of the literature has only revealed one case of siblings being affected by Wegener's granulomatosis (Muniain *et al.*, 1986), though there are other unreported family associations (Lockwood, 1990 personal communication). It is an attractive thought that there may have been a genetic predisposition in these families which led to the clustering of cases. In our investigation of tissue antigens in our patients; however, although the brothers did share tissue antigens, they were not HLA identical, and we found neither of the antigens previously reported to be of higher incidence of Wegener's (HLA B8 and DR2).

The present study, although of interest, is of no direct help in the search for a gene locus. This must await more powerful techniques, and to this end DNA has been banked from the family.

TABLE I
HLA PHENOTYPES

W.N.Q.	(patient)	HLA-A3, A31; Bw60, B14; DR4, DRw6
D.Q.	(patient)	HLA-A11, A31; Bw60, B44; DR4, DRx
J.Q.	(mother)	HLA-A3, A31; Bw60, B51; DR4, DRw8
R.V.Q.	(sibling)	HLA-A3, A11; B51, B44; DR4, DRw8
J.C.	(sibling)	HLA-A3, A11; B51, B44; DR4, DRw8

Key words: Wegener's granulomatosis

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