

Ankylosing spondylitis and multiple sclerosis in an HLA-B27 negative patient

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Abstract

A 41-year-old man presented with vertigo and gait disturbance. He gave a 10-year history of definite ankylosing spondylitis with low back pain, limitation of spinal mobility, decreased chest expansion and radiological evidence of bilateral sacroiliitis. The vertigo attacks started 3 years before and he had insidious evolution of bilateral leg weakness, increased muscle tension and walking disability during the past 2 years. The HLA haplotypes of the patient were A2, A33, B14, B49, Bw4, Bw6, Cw7 and he was HLA-B27 negative. The axial and sagittal cranial magnetic resonance imaging (MRI) showed multiple foci of increased signal intensity in the periventricular white matter and cerebellar hemispheres, suggesting a demyelinating disease process. The MRI of the spine showed centromedullar high intensity lesions at C7, Th7-8, Th 9-10 levels. The diagnosis was definite MS (primary progressive MS) as the patient had insidious neurological progression, CSF evidence of intrathecal production of oligoclonal bands, conduction defects at VEP, multiple brain and additional spinal cord lesions on MRI and continued progression for more than 1 year.

Key words : Ankylosing spondylitis ; multiple sclerosis ; HLA B-27.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterised by low back pain, limitation of spinal mobility, decreased chest expansion and radiological evidence of sacroiliitis and spondylitis (Van der Linden *et al.*, 1984). It is associated with several neurological syndromes, including cauda equina syndrome, atlanto-axial joint subluxation, spinal fractures, single root lesion, spinal cord compression and monophasic myelopathy (Rosenbaum, 2000). Recently small series have reported the occurrence of multiple sclerosis (MS) in patients with AS suggesting a possible association (Khan and Kushner, 1979 ; Pillay and Hunter, 1986 ; Hanrahan *et al.*, 1988, Whitman and Khan, 1989 ; Dolan and Gibson, 1994 ; Libbrecht and de Bleecker, 1999 ; Cellnerini *et al.*, 2001). Both diseases have an obscure etiopathogenesis and the most likely explanation

for the disease process is cross-recognition of microbial antigens and host proteins that is molecular mimicry (Rosenbaum, 2000 ; Rose and Mackay, 2000 ; Martin *et al.*, 2001). Pillay and Hunter (1986) reported an increased prevalence of abnormal evoked potentials in patients with AS suggesting an increased frequency of MS-like disease, however later studies failed to confirm these results (Hanrahan *et al.*, 1988). Nearly 90% of the AS patients are HLA-B27 positive compared to 8% in normal populations (Hanrahan *et al.*, 1988 ; Calin, 1989 ; Libbrecht and de Bleecker, 1999). We like to report a new case of AS and definite MS in an HLA-B27 negative patient.

Case report

A 41-year-old man presented with vertigo and gait disturbance. He gave a 10-year history of AS and had chronic low back pain, limitation of motion of lumbar spine and bilateral sacroiliitis. He had prominent stiffness and pain in the morning improved by activity. The vertigo attacks started 3 years before and he had insidious evolution of bilateral leg weakness, increased muscle tension and walking disability during the past 2 years.

During general physical examination, there was flattening of the normal lordotic curvature and restriction of movements in lumbar spine. Dorsal kyphosis was also increased and active-passive cervical range of motion was painful and limited. Chest expansion was decreased to 1.5 cm. The anteroposterior radiograph of the sacroiliac joints showed bilateral grade 4 sacroiliitis (Fig. 1). Considering the modified New York criteria (Van der Linden *et al.*, 1984) the patient was diagnosed as definite AS.

Neurological examination revealed spastic paraparesis, hyperactive patella and Achilles reflexes, bilateral Achilles clonus and bilateral (+) Babinski sign. Sense of vibration was bilaterally decreased at lower extremities and an intentional tremor was present bilaterally at upper extremities. Romberg test was also positive.

Routine blood and urine analysis, tumour markers, vitamin B12 levels and thyroid function



FIG. 1. — Pelvic x-ray showing bilateral grade 4 sacroiliitis.

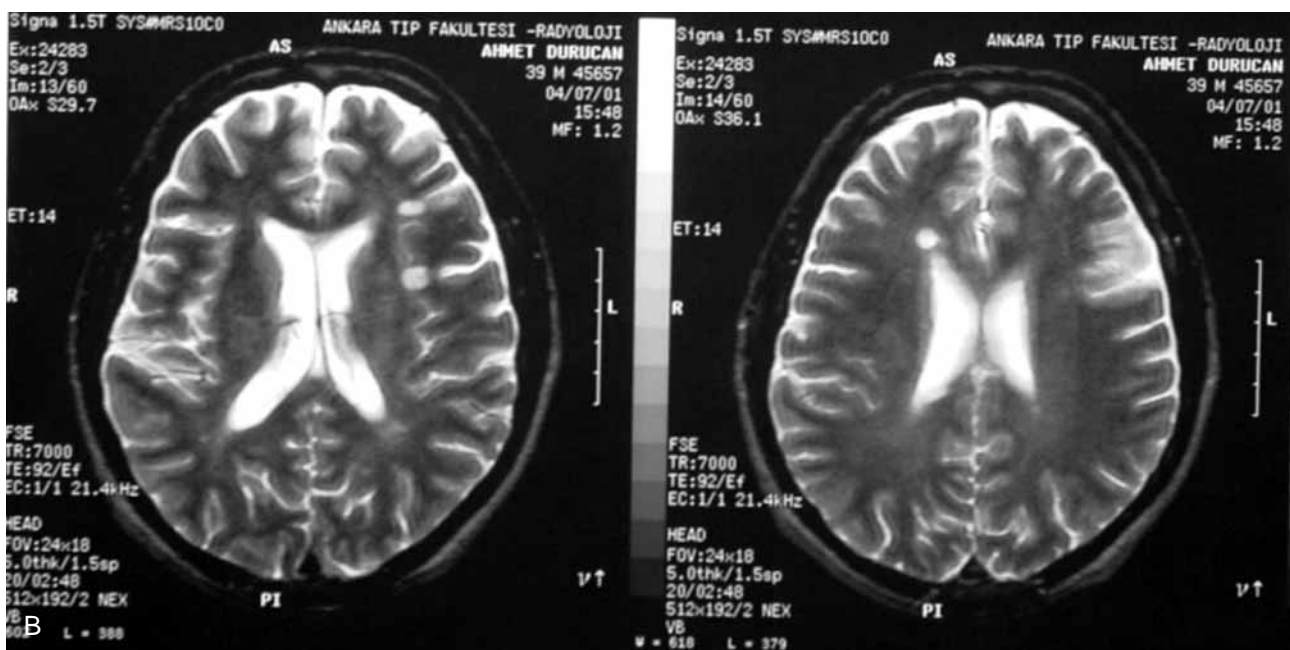
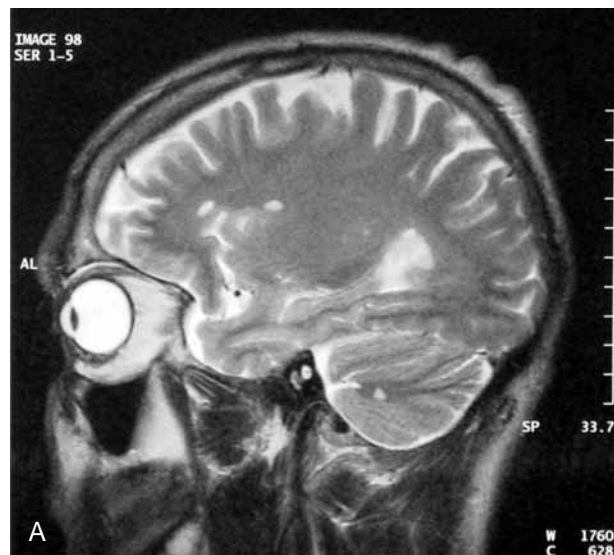


FIG. 2. — Cranial magnetic resonance imaging (MRI). T2-weighted images. Multiple foci of increased signal intensity in the periventricular white matter and cerebellar hemispheres. A : Sagittal ; B : Transverse view.

tests were normal. Blood tuberculosis, Brucella, Lyme, VDRL screening, markers of hepatitis, HIV testing and CSF Brucella and Lyme screening were negative. The HLA haplotypes of the patient were A2, A33, B14, B49, Bw4, Bw6, Cw7 and he was HLA-B27 negative.

The axial and sagittal cranial magnetic resonance imaging (MRI) showed multiple foci of increased signal intensity in the periventricular white matter and cerebellar hemispheres, suggesting a demyelinating disease process (Fig. 2A and 2B). The MRI of the spine showed focal centromedullar high intensity lesions at C7,Th7-8, Th 9-10 (Fig. 3).

Visual evoked potential (VEP) studies showed bilateral conduction defects (P 100 latency for the right eye :103msec and for the left eye :108msec).

The cerebrospinal fluid (CSF) analysis suggested the diagnosis of multiple sclerosis with an IgG index of 0.72 (normal 0.2-0.5) and the electrophoresis was positive for oligoclonal bands. Thus the diagnosis was definite MS (primary progressive form). The patient was put on immunosuppressant therapy and he is still followed.

Discussion

Some AS patients were reported to present with a spectrum of disease like MS thus some workers have suggested a possible association between both diseases (Pilay and Hunter, 1986 ; Hanrahan *et al.*, 1988 ; Calin 1989 ; Libbrecht and de Blecker, 1999). Both diseases share an obscure etiopathogenesis while a T-cell based autoimmunity is the



FIG. 3. — The MRI of the spine. T2-weighted image. Focal high intensity lesion (arrow) at thoracic spinal cord.

most likely explanation for the disease process (Rosenbaum, 2000 ; Rose and Mackay, 2000 ; Martin *et al.*, 2001). In all cases the diagnosis of AS preceded the initial symptoms of MS and the majority of cases were reported to have probable MS, possible MS or MS-like syndrome rather than definite MS (Libbrecht and de Bleecker, 1999 ; Cellierini *et al.*, 2001). In our case the diagnosis fits to definite AS by the modified New York criteria (Van der Linden *et al.*, 1984). According to the criteria a patient with bilateral grade 2-4 sacroiliitis and any clinical criteria ; i) low back pain of ≥ 3 months duration improved by exercise and not relieved by rest ii) limitation of lumbar spine in sagittal and frontal planes iii) decreased chest expansion, has definite AS like our patient. The patient also has definite MS (primary progressive

form) by fulfilling the criteria : insidious neurological progression, CSF evidence of intrathecal production of oligoclonal bands, conduction defects at VEP with multiple brain and additional spinal cord lesions on MRI and continued progression for more than 1 year (Mc Donald *et al.*, 2001). In 1986 Pillay and Hunter reported an increased prevalence of abnormal evoked potentials in patients with AS and suggested a possible increased frequency of MS-like disease. Libbrecht and de Bleecker (1999) reviewed 10 cases of concomitant AS and MS. Four of them were definite MS and the others have either probable MS (monophasic myelopathy) or MS-like syndrome. Hanrahan *et al.* (1988) investigated radiological evidence of AS in a series of 20 HLA-B 27 positive MS patients and reported that 5 cases fit the criteria for AS. However in the same study 16 AS patients were subjected to VEP studies and all except 2 were found to be normal contrary to Pillay and Hunter's (1986) series. At present although there is a suggestion of increased frequency of MS in AS patients, it has not yet been proven by definitive epidemiological studies (Calin, 1989).

Molecular mimicry is described as the resemblance of antigenic determinants of certain microorganisms to the host proteins to elicit an autoimmune disorder. Certain disease states like rheumatic fever give serological evidence for the autoimmune process while ankylosing spondylitis and multiple sclerosis represent a different category with presumably T-cell based autoimmunity. The former concept of molecular mimicry did focus on shared amino acid sequences between the accused antigen and the host proteins. Thus attempts to isolate etiological factors for the disease states were disappointing. The new concept of molecular mimicry is a more general term based on T-cell degeneracy (Rose and Mackay, 2000 ; Martin *et al.*, 2001). To recognize a large number of antigens present in the environment the T-cell has a wide repertoire for antigen recognition and after a certain threshold any antigen could induce an autoimmune response whether they have common amino acid sequences with host proteins or not. Genetic and environmental factors might then determine the occurrence of the disease (Calin, 1989). Ankylosing spondylitis and MS were both reported to be associated with certain HLA antigens but a great degree of geographical and racial variance was noted (Whitman and Khan, 1989). While the prevalence of HLA-B27 in AS patients was reported up to 90%, this prevalence was 10.2% for MS patients similar to 8% of normal population (Hanrahan *et al.*, 1989). However all AS-MS patients presented in the literature were shown to be HLA-B27 positive. Several workers have also pointed out a possible HLA cross-reactivity between AS and MS especially for HLA-B7 (Libbrecht and de Bleecker, 1999). Our patient's

HLA haplotypes are HLA A2, A33, B14, B49, Bw4, Bw6 and Cw7. None of our patient's HLA haplotypes fit to the common HLA haplotypes listed for MS and AS. The prevalence studies were based on the presence of HLA-B27 thus the incidence of both diseases might be higher than expected (Calin, 1989). Similarly Hanrahan *et al.*'s (1988) study was conducted in HLA B-27 positive patients ignoring the possible presence of HLA B-27 negative cases. Thus the association between multiple sclerosis and ankylosing spondylitis is probably more complex than expected. Accordingly the presence of common or certain HLA antigens (like B7 or B27) might not be a necessary factor for the coexistence of both diseases. However the rare concomitant presence of both diseases in the literature and epidemiological studies did not support a strong association (Calin, 1989).

In conclusion present literature could not provide convincing evidence for an association between AS and MS. Assuming a common immunopathogenesis and genetical predisposition for both diseases, larger epidemiological studies are necessary to provide data for explaining the coexistence of both diseases. Our case might be an important contribution to the literature with definite MS and AS, magnetic resonance demonstration of the lesions and HLA-B27 negative haplotype that is to our knowledge probably never reported before.

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