Genetics In The 3rd Millennium, Vol. 8, No. 4, Winter 2011

Original article

HLA PROFILE AND CLINICAL PRESENTATION OF MULTIPLE SCLEROSIS IN IRAN

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Abstract:
Multiple sclerosis (MS) is a demyelinating disease of the central nervous system, with unknown etiology in which both genetic and environmental factors are thought to be involved. The human leukocyte antigen (HLA) system provides a set of genetic markers which lend themselves to systematic study. In Iran, HLA-A24, HLA-DR2, and HLA- DR15 are significantly increased in MS patients. The disease also has 3 main clinical presentations, consisting of relapsing-remitting (88%) primary progressive (7%) and secondary progressive with a gender ratio of 2.5:1 (female: male) and a mean age at onset of 27+ 7.4 years in our country. Five percent of our patients had a positive family history for the disease, 14% of patients had benign MS, and 12% with disease duration longer than five years had an Expanded Disability Status Scale <2. The opticospinal form of MS was not a common form of presentation of the disease in Iran.

Key words: HLA; Clinical Presentation; Multiple Sclerosis; Iran

Introduction:
Multiple Sclerosis (MS) can be regarded as an organ-specific inflammatory disease probably resulting from an aberrant immune response to myelin antigens (1-4). It is a disease of unknown etiology in which both genetic and environmental factors are thought to be involved (5). The HLA system provides a set of genetic markers which lend themselves to systematic study. Evidence continues to accumulate that MS populations differ from local controls in their HLA allele composition (6).

This association varies in different parts of the world probably due to varying racial susceptibility to MS (78-). Genetic analyses have suggested that the major histocompatibility complex (MHC)/HLA region on chromosome 6p21 contains an MS-predisposing component (9); but how many genes out of all the genes present in this region are responsible for MS susceptibility is still an unsettled issue. However, results from genomic screens suggest that a number of genes of varying and interacting effects will be implicated and these searches reinforce the genetic epidemiology of the disease (10).

The condition is diagnosed clinically from the demonstration of white matter (WM) dysfunction

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Submission Date: 10/3/2011 Acceptance Date: 2/5/2011

separated in time and space (11). It is a cause of chronic neurological disability in young and middle-aged adults with an unequal distribution worldwide (2, 12). The variation in prevalence and clinical pattern according to geographical location, probably related to ethnic and environmental factors, has been observed in several studies (1314-). The prevalence is thought to be low in Iran (15) an in other Middle-East countries (1620-). At present, the current impression in Iran is that more cases are being diagnosed.

The aim of this communication is to highlight the HLA types and clinical course of the disease and its pattern of presentation in the largest sample of cases managed so far in Iran (15, 21).

Factors Contributing to disease susceptibility:

A- Environmental factors: Classic studies indicate that MS exhibits distinct geographic clustering within the temperate zones in northern and southern hemispheres (22). Migration studies have been informative regarding the interaction of genetic susceptibility and environment. An individual who moves from a high-risk to a low-risk area during childhood will acquire a low-risk of developing MS (23). By contrast, an individual moving after adolescence retains the risk of the original location.

B- Genes and susceptibility to MS: the balance of evidence relating to the etiology of multiple sclerosis favors an interplay between the genetic susceptibility and environmental trigger. Just as the twin studies show clearly that almost 60% of monozygotic pairs are not concordant for multiple sclerosis (2426-); so, the low concordance rate in twins, the rarity of conjugal multiple sclerosis (27) the lack of a birth order effect (28) and the identification of resistant groups living in high prevalence zones, all argue against a purely transmissible factor (29). A simple view would be that, of the candidate genes which have been examined as markers of susceptibility, only the DR15 class 2 major histocompatibility complex (MHC) allele association in northern Europeans holds up to critical analysis. The specifically different associations with DR4 in the Japanese (30) and Jordanians (31) have never been confirmed although multiple sclerosis does appear to be DR4 associated in Sardinians (8). There is no evidence that any genetic marker, acting alone or in combination, protects individuals from development of the disease. Reports that the severity of multiple sclerosis correlates with the presence of specific susceptibility alleles, or that the primary progressive form of the disease is associated with a specifically different set of susceptibility markers (3233-), remain unconfirmed.

The role of the HLA system in conferring susceptibility to MS has been demonstrated by population association studies, but these do not resolve the question of which class 2 region allele makes the primary contribution. The association also is varied in different races. For these reasons, we studied the role of HLA system in 79 Caucasoid Iranian patients with definite MS (15).

Seventy- four patients were classified as having relapsing-remitting (RR) MS, with distinct (11) attacks and stable phases in between. This group consisted of 48 females and 26 males with an age range of 18 to 50 years (mean 31 7.3), a disease duration of 4.23.3 years and an EDSS of 1.91.1.

Five patients were classified as primary progressive (PP) MS (11) with a steady progressive course. This group consisted of four females and one male with an age range of 37 to 61 years (mean 48.49.9), a disease duration of 8.66.8 and an EDSS of 4.32.3.

From 51 antigens tested and compared with 100 controls (13A, 18B, 5C, 12 DR, 3 DQ), it was found that the distribution of HLA antigens showed a preponderance for HLA-DR15 and to a lesser degree for HLA- DR2 and HLA- A24 in MS patients. On the other hand, HLA-B15, B40, DR4, DR52 and DQ3 were significantly under- represented in MS patients.

The same was true for HLA-A28, B5, B14, and CW2, but to a lesser degree. Segregating patients, according to age at onset, revealed no significant differences in the distribution of HLA antigens. Thus, the 65 MS patients with age at onset before 35 years had HLA-DR15, DR2 and A24 frequencies of 36.5, 43 and 31.08%, respectively. Corresponding frequencies for the 14 patients with onset after 35 years were 37, 43 and 29.9%, respectively. When HLA types were analysed for RR and PP subgroups, no significant differences were noted.

No MS patients had severe disease with a Kutzke score of five or more within 5 years of their first symptoms.

Clinical symptoms and physical findings: Although the clinical syndrome of MS is classically described

as a relapsing- remitting disorder that affects multiple white matter tracts within the CNS, with usual onset in young adults, the disorder displays marked clinical heterogeneity. This variability includes age at onset, mode of initial manifestation, frequency, severity and sequealae of relapses, extent of progression and certain specific clinical and neuro-immunological features. For these reasons, we decided to study the clinical course and pattern of presentation of the disease in an Iranian MS population. The study period was form July 1996 to July 2001, during which 200 cases were evaluated (21).

The RR from was the most common clinical presentation with 179 cases (88%) followed by PP with 14 cases (7%) and SP with 10 cases (5%). The mean age of onset for the entire group of 200 patients was 277.4 years, with a disease duration of 5.54.7 years and an EDSS score of 2.11.4.

The PP group had a higher age at onset (37.1 8.8 years) with a female preponderance (10 out of 14). In 12 cases, spinal signs were first presented in the form of paraparesis with or without sphincter or sensory disturbance. In two cases, the presenting symptom was of cerebellar nature followed by spinal signs.

Women represented 72% of the cases giving a gender ratio of 2.5:1 female: male. While the yearly number of attacks in the RR groups was 0.4, SP patients had an average of 1.2 attacks per year, for their average of 10 6.1 years before entering this phase. Almost all of the SP cases had spinal or cerebellar signs at the onset of the disease.

The most common presenting symptoms were weakness in one or more limbs (33%) followed by sensory impairment (24%), sphincter disturbance (20%), visual impairment (20%), ataxia (15%), vertigo (10%), diplopia (5%), Bell›s palsy (3%) and seizure (3%). Twenty- seven percent of cases had more than one symptom. Eight patients had optico-spinal presentation of RR type with simultaneous or consecutive visual and spinal impairments of motor and/or sensory nature, with a mean disease duration of three years and an EDSS score of 1.3. Ninety per cent of patients were of middle- income class, 65% had a high school diploma and 30% were educated at the university level. Ten patients (5%) had a positive family history, each one with one first- degree affected relative. While 28 (14%) benign cases were recorded (34) with an EDSS score of 3 or less after 10 years, 24 patients had a disease duration of five years or more with an EDSS score of 2 or less.

Discussion:

HLA typing, the natural course and clinical findings of 79 and 200 definite MS cases in Iran were respectively reviewed (15, 21).

Results, drawn from our 79 Iranian MS patients, revealed an association between MS and HLA types-A24, DR2, and DR15, each with a relative risk of 1.9 times that of controls. This genetically determined increased risk is best explained by assuming the existence of an MS susceptibility gene which has been identified in linkage studies with HLA-DR15 and DR2 loci on chromosome 6. This association of DR2 and DR15 HLA types with MS in Iranian patients is in line with studies done in other parts of the world (3437-). In the analysis of HLA class I, we found a positive association with A24 but no association with B locus alleles. The association of HLA-A locus in Iranian MS differs from previous studies in other parts of the world (35, 3839-) as well as Asian countries (4041-). In fact, Indian investigators identified an association between HLA B12 and MS (40).

Of interest is the under-representation of the following alleles in Iranian MS patients: HLA-A28, B5, B14, CW2 ($P<0.05$) and HLA-B15, B40, DR-4, DR-52, and DQ3 ($P<0.005$).

Whether these alleles have any protective role against MS in this geographic region is to be determined.

Iran is traditionally though to be situated in a low risk zone for MS (21). In Iran, MS presents with involvement of multiple sites in the central nervous system (CNS), including the cerebrum, cerebellum or brainstem, which is similar to its behavior in the Caucasian population. Having RRMS as the most frequent type of presentation, followed by the PP form with a higher age at onset and worse prognosis, and female preponderance in both types, are in agreement with European and Latin American studies (4245-). The most common presenting symptoms of pyramidal and sensory involvement in the present cases have also been reported from neighboring Middle East countries and Europe (12, 42). Compared with the RR group, SP had more annual attacks with pyramidal or cerebellar dysfunction as their presenting signs. The presence of

28 patients with an EDSS score 3 after 10 years and 24 with an EDSS score 2 after five years indicates a benign course for MS in this country. Optico-Spinal MS, which is a common presentation of the disease in Asian countries and is called Asian type (46), is not a prominent feature here, probably due to different HLA typing.

It is believed that we are facing a rising incidence of MS similar to other countries (12, 45, 47). This may be explained by increased survival, and improved laboratory and radiological diagnoses. However, a decreased number with SP form, which is a natural endpoint of the RR type, may indicate that more new cases are being diagnosed, and other possibilities should be looked for (21).

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