Review Article

Multiple sclerosis in India: An overview

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Abstract

Multiple sclerosis (MS) is being increasingly diagnosed in India mainly due to increase in the number of practicing neurologists and easy and affordable availability of magnetic resonance imaging (MRI). The clinical features and course are largely similar to those seen in the West. The term optico-spinal MS (Asian MS) was coined in the pre-MRI days. Many such patients turn out to be cases of neuromyelitis optica — a distinct disorder and not a variant of MS. Others have shown the classical features of MS on MRI scan. Several of the disease-modifying agents, not all, are now available in India. Their use, however, has been limited in view of the high cost.

Key Words

Asian MS, MS in India, optico-spinal MS

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Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system. It has been well known in the West since its first description by Charcot[1] in 1868. In India, the disease came to be recognized only in the 1960s when physicians who received training in Neurology in the West, returned to India. Baldev Singh,[2] Bharucha[3] and Ramamurthy[4] were the ones who first described the manifestations of MS in Indian context.

The prevalence data has shown that the frequency of MS varies in different populations. In the USA and UK, the frequency is about 90 to 150/100,000. In contrast, calculations based on the hospital data in the 1970s suggested an approximate prevalence rate of only 0.17 to 1.33 per 100,000 in different parts of India.[5] With increased awareness, a significant increase in the number of neurologists and relatively easy availability of magnetic resonance imaging (MRI) the current estimate stands at about 7 to 10/100,000. This figure may still be higher as large sections of the Indian population still do not have access to adequate medical facilities especially in the rural sector. No large epidemiological studies have been reported from India. In the small Parsi population of around 70,000 in India, Bharucha *et al.*,[6] reported a higher prevalence of ~21/100,000 with wide confidence limits. Another study of the same Parsi community by Wadia and Bhatia[7] reported a higher incidence of ~26/100,000. In a recent epidemiological survey, a prevalence of 8/100,000 was noted in urban Mangalore.[8]

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The precise cause of MS is still unknown. Extensive research has shown that both environmental and genetic factors play a significant role. The studies in concord twins and a higher prevalence among the siblings of MS patients have suggested a role of genetic factors in the causation of MS[9,10] Studies of HLA class II genes, located on chromosome 6, which participates in the presentation of antigens to T cells, has been of special interest to MS researchers. The HLA linkage studies in the West, especially among North and West Europeans have suggested a role of HLA DRB*1501, DQA1*0102, DQB1*0602 in MS.[11] There are few reports of HLA linkage in Indian subjects. Kankonkar *et al.*,[12] in a small study from Mumbai region in Western India demonstrated the association between DRB1*1501 allele and MS and also suggested association for two novel DRB1*15 alleles, DRB1*1506 and DRB1*1508. In a more recent study of primary HLA class II alleles associated with MS, Pandit *et al.*,[13] concluded that the risk effects attributable to the HLA-DRB1*1501 and DRB1*03 alleles seen in Europeans are also seen in Indian patients.

Several studies have also emphasized the role of environmental factors in the causation of MS. Alter[14] suggested that persons living in developing countries with relatively poor hygiene possibly develop protective immunity. This might explain the higher frequency of MS in the Parsi population of India who have higher standards of hygiene and better sanitary

conditions at home. The migration studies by Dean and Elian[15] have further supported the 'environmental' hypothesis where persons migrating before the age of 15 years carry the risk of the country of origin while persons migrating after the age of 15 years have the risk of their adopted country. The increase in MS prevalence with increasing latitude in Europe also supports the role of environmental factors. Differences in solar radiation and consequent differences in the levels of serum Vitamin D3 may play a role to account for this latitude difference.[16]

Although no definite virus as the trigger or cause of MS has yet been identified, a case control study by Bansil *et al.*,[17] in Indian patients noted a higher dog exposure in MS patients than in other neurological diseases, which suggested a possible role of canine distemper virus in MS patients. Recently Epstein-Barr virus (EBV) is believed to play a significant role in the pathogenesis of MS.[18] However, Pandit *et al.*,[19] in a study of 140 MS patients did not find evidence for a strong association with remote EBV infection. Vitamin D is believed to have a protective effect on developing MS[20] and its deficiency exposes an MS patient to a higher frequency of relapses. It is hard to clearly define the role of vitamin D deficiency in MS in India as vitamin D deficiency is very common in this country. However, the study by Pandit *et al.*,[21] does support the hypothesis that Vitamin D deficiency has an inverse relationship with MS with persons having low vitamin D levels carrying a higher risk of MS and a greater chance of relapse.

There is no single diagnostic test for MS. The diagnosis requires that there should be lesions in the white matter of the CNS, which should be disseminated in time and space and that there should be no other diagnostic possibility. Before the advent of MRI, the criteria used were clinical (Schumacher *et al.*,[22]) and later on also included laboratory data (Poser *et al.*,[23]) to define the categories of definite and possible MS. Today, well-defined McDonald criteria (revised in 2010)[24] are used, which have included MRI findings to diagnose MS. MRI is now available in most metropolitan cities in India and also in several smaller towns. The protocol followed and the reporting, however, is not always of a high standard and there is a need for improvement in this regard. The recent revised McDonald criteria[24] have used modified MRI criteria for early diagnosis of MS to enable early start of the treatment.

Although Poser criteria[23] used the laboratory data to define laboratory-supported definite MS, these are not relevant today. Also, the earlier Indian papers commented on the low yield of oligoclonal bands in CSF in the Indian subjects. Regrettably, this was due to the faulty technique of not using the standardized Iso-electric focusing which even today is being used by some but not all laboratories in India. The use of this technique has resulted in a higher yield of positive cases. It is not mandatory to do the CSF study and several patients opt for avoiding this study.

The first Indian paper using international criteria of Schumacher was published by Mathew *et al.*, from Vellore[25] followed by another paper by Singhal and Wadia[26] describing the clinical features in MS. These papers supported the occurrence of MS in India. For diagnosis of definite MS a histological confirmation was needed. It was provided by the paper by Dastur and Singhal[27] describing the pathology of two unusual cases of MS. Soon thereafter, several papers from the North West[28] and other parts of India were published, describing the clinical features and demographic data concerning MS in India. Few more autopsy proven cases were also reported. These were summed up in the paper by Singhal *et al.*,[5] Jain and Maheshwari[29] reviewed the published cases from India till 1985 and commented on the higher frequency of optic nerve involvement and low yield of oligoclonal bands in Indian MS patients.

The essential demographic features in the Indian subjects are similar to those seen in the West. The average age of onset is 25 to 35 years. Females are about two times more affected than men. In the Schumacher criteria, age at onset was defined to be from 15 to 50 years. Of late, it has been well recognized that MS also occurs in the pediatric age group. So far there have been no large publications on MS occurring in the pediatric age group, though one does see an occasional patient with MS starting in childhood.

To study the differences in the clinical presentations of MS in the Asian patients as compared to the patients in the West, the late Professor Kuroiwa organized meetings in Japan with delegates from diverse Asian regions. These discussions were summed up in the two publications titled Multiple Sclerosis in Asia[30] and Multiple Sclerosis East and West.[31] The essential differences noted were: More frequent initial clinical presentation with optic nerve or spinal cord involvement, often bilateral optic nerve affection, severe myelopathy with sensory level, less frequent clinical presentation to suggest cerebral or cerebellar involvement and more frequent painful tonic spasms.[32] These differences were believed to distinguish Asian MS from Western MS. The term optico-spinal MS (OS-MS) was used to emphasize the clinical features in Asian MS.[32] Even today the term OS-MS continues to be used, though many of these patients are cases of neuromyelitis optica (NMO). Several others will also show lesions in the brain MRI at the classical sites seen in MS patients.

NMO was considered to be a variant of MS and a monophasic illness in India and several other countries with the distinctive features of involvement of optic nerves and spinal cord within a short span of time. With the discovery of Aquaporin 4 antibody by the Mayo group[33] it has now been well established as a distinct disease and frequently having a multiphasic course. The criteria for the diagnosis of NMO have been laid down by Wingerchuk *et al.*[34] Cases of NMO have now been described from India as well.[35] In the pediatric age group, the first presentation of MS may occasionally resemble Acute Disseminated Encephalomyelitis. Schilder's disease and Balo's concentric sclerosis are other rare primary demyelinating disorders. Eale's syndrome, well known to ophthalmologists with occasional myelopathy (Singhal and Dastur[36]) may sometimes mimic MS but it is a distinct syndrome.

In the diagnostic criteria of MS, it has been emphasized that other diagnostic possibilities must be excluded. Thus several conditions may result in T2 white matter lesions mimicking MS. Non-specific white matter lesions are frequently seen, especially in persons with migraine, hypertension and diabetes.

In particular, one should exclude vasculitis and conditions like CNS lupus, Sjogren's syndrome and Behçet's disease, which may result in such white matter lesions. Sarcoidosis may also have presentation like MS.

The course of MS in India is largely similar to that in the West though there has been no well-defined study reported from India on this subject. We see patients with 'Radiologically Isolated Syndrome', 'Clinically Isolated syndrome', with a large majority having 'Remitting Relapsing (RR) course'. As in the West, over time, in some RR MS patients, phase of 'Secondary Progressive MS' sets in. Though the precise figures are not known we also see patients with 'Primary Progressive MS' (PPMS).

Until the early 1980s, the treatment of MS was largely symptomatic and supportive along with the use of injection ACTH or corticosteroids in the acute phase. In the acute phase today, the majority of neurologists in India, as elsewhere in the world, use IV methylprednisolone Gm 1 daily for 3 to 5 days. If there is no significant benefit, one could also use plasma exchange or IV immunoglobulin.

The recent researches and large multinational trials (India has also been involved in few recent trials) have provided drugs (approved by agencies like FDA in USA) to delay the onset of relapse, reduce the number of relapses and also demonstrate significant benefit on MRIs (used as surrogate marker). The first ones were the β-interferons (three varieties) followed later by glatiramer acetate (all injectable preparations). The introduction of IV Natalizumab in severe cases and in those who do not respond to interferon or glatiramer acetate showed marked benefit. However, the occurrence of progressive multifocal leukoencephalopathy due to JC virus has resulted in a word of caution for its use. All these agents have been made available in India by their parent companies. More recently oral agents like Fingolimod, Teriflunomide and dimethyl fumarate have received approval by the drug supervising authorities. Only dimethyl fumarate has been approved and is available in India. It is recommended that the treatment should be initiated early in the phase of inflammation before the secondary progressive phase sets in. There is as yet no approved therapy for PPMS.

There is no large scale data of the usage of the above-mentioned disease modifying agents from India. The use of these agents is determined by interactive discussion regarding effectiveness, side effects and cost of the drug with the patient and the relatives. As there is limited support by the government (available mainly for defense personnel and other government employees) and large multinational companies, most patients have to bear the expenses themselves. There is as yet no insurance coverage. As a result, a large majority of patients are deprived of this therapy. We cannot as yet accurately predict the course of events in a given patient though there may be some who remain well. The search for biomarkers continues. The entity of benign MS is still a matter of debate. The patients in India who remain free of illness for two to three years enquire if they can discontinue the costly drugs but so far we do not have data to guide them.

For severe MS one could use Mitoxantrone, also approved by the agencies like FDA. It is available in India at an affordable cost. Singhal *et al*.,[37] published their experience with this drug in 21 patients. Other neurologists have used this drug as well. It not only showed benefit in reducing annualized relapse rate but also showed benefit in reducing disability. However, the use of this drug is restricted in view of the risk of cardiac toxicity and an increased risk of developing leukemia. Alemtuzumab, approved in UK and Europe, has not yet received approval from the US FDA in view of the side effects and is not available in India. There are also reports of benefit from agents like Rituximab but there are no large scale trials.

Although we are diagnosing more patients with MS today, much needs to be done in the Indian context. We need greater awareness, more infrastructure facilities especially for rehabilitation, specialized MS clinics in the institutions, MS registry, government support, insurance coverage and availability of effective and affordable disease modifying agents. Fortunately, MS Society has been in existence for over 25 years with several chapters to provide support for the patients and their caregivers.

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