Multiple Sclerosis: Indian Perspective

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ABSTRACT

Multiple sclerosis (MS) was earlier believed to be nonexistent in India. Over the years with the advent of magnetic resonance imaging (MRI) and modification in diagnostic criteria it is now commonly diagnosed in clinical practice. The earlier belief that MS in India was vastly different from that seen in the western world has given way to the fact that they are more or less the same with minor differences. This review revisits some of Indian studies especially pertaining to prevalence of MS in India, genetic studies, clinical presentation, cerebrospinal fluid (CSF) and MRI findings, treatment and finally suggesting an algorithmic approach to a given patient.

INTRODUCTION

Multiple Sclerosis is an autoimmune condition causing inflammatory demyelination of the central nervous system. It is a common cause for disability in adults. MS exerts a considerable socioeconomic burden on society by affecting the adult in the prime of their productive life.

Multiple Sclerosis was believed to be rare in India earlier. However with the advent of the MRI and its penetration into the interiors of India over the last two decades there are increasing number of cases being diagnosed now even in smaller cities. Other reasons for the increase in number of cases being diagnosed in India are an increase in awareness about the disease and also the changing criteria of MS. There is no doubt that MS not only exists in India but is a significant cause for disability. Considering that the present demographic profile of India has a large number of young people we will be seeing an increasing number of MS patients in the coming years. This is especially ominous considering that the majority of Indian patients cannot afford the disease modifying therapy.

This review aims to revisit the studies in MS from India and follow the evolution of MS over the past few decades with special attention to the prevalence, genetic studies, clinical presentation, differences from the west if any, MRI, CSF findings and treatment options. Finally the review ends with an algorithm for treatment of MS patients.

PREVALENCE OF MULTIPLE SCLEROSIS IN INDIA

There are only a few epidemiological studies from India, some of them being from the pre-MRI era. Singhal et al. in the mid 80s reported a prevalence of approximately 1.33/100,000 from Bombay region. Their conclusion was based on hospital data collected from 1957 to 1983. Jain et al. reported 4.15 new cases per year from north India (above 15°N latitude) while the figure from south India (below 15°N latitude) was 3.2. MS was found to constitute 2.54% of neurology admission between January 1993 and December 1997 in data from northwest India. It was higher as compared to previous data from the same institute (1.58%) possibly reflecting better diagnostic facilities and changing diagnostic criteria. A study by Bharucha et al. used a door-to-door survey of the Parsi community in Bombay to arrive at the conclusion that the prevalence of clinically definite MS in the Parsi community living in Bombay was 21/100,000. Wadia et al. also arrived at a similar figure of 26/100,000 for the same community. The Parsi community is a close-knit community believed to have migrated from the Pars province of Iran. A more recent epidemiological study from Isfahan, a province adjoining Pars showed a high prevalence rate of MS. It is likely that the prevalence in the Parsi community reflects the rates found in this area. Multiple Sclerosis International federation quotes a prevalence of 3/100,000 for India which may be an under estimation but it certainly is not as high as the rates found in high prevalence temperate zones (60–100/100,000) or higher.

Genetic Susceptibility in Indians

One of the earliest studies done by Wadia et al. found that 77.7% of their patients with MS had Class I HLA antigen association with HLA-B12 antigen (and not B7) compared to 13.8% of controls. Further studies of the Class II HLA genes, DRB1, DQA1, and DQB1 was done in a limited number of patients and revealed the known association with the European susceptibility haplotype DRB1*1501—DQB1*0602. A recent study by Pandit et al. has focused on evaluating the role of established non-MHC disease susceptibility loci in Indian population. It was found that a commonality exists in disease susceptibility gene in the Indian and western population.

Clinical Presentation of Multiple Sclerosis in India

Onset of MS is varied. It may start with an abrupt disabling symptom like paraplegia or less disabling, insidious, innocuous symptom like tingling over a portion of the trunk. The patient may have minor unilateral symptom but the findings may be more florid and bilateral. Sometimes a MRI scan done for an unrelated reason may show evidence of MS.

Much has been written about the perceived difference in the presentation of MS in India and the west. Earlier studies from India before the MRI era lay stress on the fact that Indian patients had more involvement of optic nerves and spinal cord. In 1985, Singhal found that optico-spinal MS was seen in 71.4% of their cases. In the same study sensory level occurred in a large number of patients and cerebellar involvement was less frequent. Jain and Maheshwari analyzed data of 354 cases of MS from nine different centers in India. Optic neuritis (OPN) as the initial presentation was seen in 22.2–58% of cases. However, more recent studies done in the MRI era from...
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different parts of India have shown a variable visual involvement when compared to west. Syal’s study from northwest showed 23.6%,3 44% was reported from south,12 Gangopadhyay from the east reported 33.3%,13 Bhatia et al. from New Delhi found 26% of their patients presenting with optic neuritis.14 These studies reflect more closely the figures seen in western studies.

Symptoms at onset were compared in patients admitted to a national hospital in south India before and after the mid 80s (after the mid 80s MRI was increasingly used for diagnosis). There was an obvious reduction in number of patients presenting with spinal cord dysfunction by as much as 50%. The authors attributed it to better awareness, early investigations including MRI and earlier diagnosis when patients presented with milder symptoms.12 More recent study done in the MRI era by Bansil et al.,15 compared the presentation of MS patients in India and United States and found it to be the same with respect to rate of disease progression and frequency of involvement of the cerebral hemispheres, cerebellum, spinal cord and brainstem were similar in the two populations. The visual system was more frequently involved in Indian patients. A similar study by Bhatia et al. from All India Institute of Medical Sciences (AIIMS), New Delhi found there to be no difference.14 Most Indian neurologists believe that the presentation of Indian patients with MS is similar to that seen in the west and any difference is more apparent than real. Average age of presentation is similar to the west with female predominance.1,3,13 An earlier study by Singh1 suggested that MS may be more common in higher socioeconomic group in India, however this too has not stood the test of time with MRI being available to nearly all now.

Susceptibility to Multiple Sclerosis of the Immigrant Population from India to the West

There is data from immigrant population to the West (including Indian) to suggest that if the child has migrated before puberty then the risk of MS increases significantly.16,17 However if the immigration has taken place after puberty then the risk continues to be same as that of the parent country. The risk of MS in children born in the United Kingdom to Asian immigrant parents including Indians (who migrated in adulthood) is also higher.

Diagnostic Criteria for Multiple Sclerosis

Over the years the diagnostic criteria have evolved to the present revised McDonald’s criteria with greater reliance on imaging and laboratory to diagnose early cases. The common theme in all the diagnostic criteria (Schumacher, Poser and now McDonald) has been the requirement to show dissemination in time and space. The revised McDonald criteria (2005) are given in the Table 1.

These diagnostic criteria are MRI based and simple to follow and should be used to diagnose MS including in India.

Course of Multiple Sclerosis

There are four categories of disease described: relapsing remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), primary progressive multiple sclerosis (PPMS) and progressive relapsing multiple sclerosis (PRMS). The commonest type of MS in India as in the rest of the world is RRMS.3,13

Cerebrospinal Fluid for Oligoclonal Band Studies from India

Oligoclonal bands may be positive in as many as 75-90% of patients as per data from west. Positivity for oligoclonal bands (OCB) is variable in different series from India. Syal et al. from northwest India reported 30.4%, Gangopadhyay et al. 31% from east, Pandit from the south reported 50% in conventional MS and 80% of patients from the series by Mani had OCB positive in the CSF.3,13,19,20 Our own series had 85% of the CSF samples positive for OCB.21

Magnetic Resonance Imaging Findings

Magnetic resonance imaging has revolutionized the diagnosis of MS and its differentiation from conditions like acute disseminated encephalomyelitis (ADEM) and acute transverse myelitis (ATM). The MRI criteria which help in the diagnosis of MS are given in Table 2.

Magnetic resonance imaging based studies from India are few and more recent. Transverse myelitis (post- or parainfectious) is a common condition seen in India. It can mimic MS as the initial presentation. MRI features which suggest MS as compared to transverse myelitis due to different etiology are:

- Localized myelitis extending less than three spinal segments
- High-intensity signals located peripherally
- Occupying less than half the cross-sectional area of the cord.

Transverse myelitis rather than MS is likely to have the central dot sign described by Murthy.22

Magnetic resonance imaging studies from India in patients with MS by Syal et al. showed positive findings in 86.9% of cases.3 Gangopadhyay et al. found 69.56% of their patient to have a positive MRI in either the brain or spinal cord.13 These figures are lower than that described from west where figures as high as 99% are reported.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Revised McDonald criteria18</th>
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<tbody>
<tr>
<td><strong>Clinical attacks</strong></td>
<td><strong>Objective lesions</strong></td>
</tr>
<tr>
<td>2 or more</td>
<td>2 or more</td>
</tr>
<tr>
<td>2 or more</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2 or more</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0 (progression from onset)</td>
<td>1 or more</td>
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Abbreviations: CSF, Cerebrospinal fluid; MRI, Magnetic resonance imaging; MS, Multiple sclerosis; VEP, Visual evoked potentials
and is more due to lack of complete screening of the neuraxis rather than an actual difference. Another study by Mani et al. showed an abnormal brain MRI in 24 of 25 patients and an abnormal spine MRI in 15 of 16 patients. The site of involvement in these studies is no different from those reported from the west.

**TREATMENT (FLOW CHART 1)**

The treatment of patients with MS involves treatment of acute relapses, disease modifying drugs and symptomatic therapy.

**Relapses**

Disabling relapses are best treated with IV methylprednisolone 1 gram for a period of 3–5 days. This may be followed by a tapering course of oral steroids. However, this largely depends on the individual experience of the treating neurologist. In case of partial recovery from relapse methylprednisolone pulse can be repeated. During infusion transient hyperglycemia, hypertension and hypokalemia may occur. GI bleed and flare up of pre-existing infection may also occur.
Disease Modifying Drugs

The currently available US FDA approved disease modifying drugs are shown in Table 3.

Treating the Indian Patient with Multiple Sclerosis

Patient with an acute relapse can be treated with methylprednisolone. All the disease modifying drugs mentioned in the table are available in India except fingolimod presently. There are only two original published studies on the use of disease modifying drugs in MS in humans available from India. Singhal et al. studied the use of mitoxantrone in 23 patients with clinically definite MS and found it to be efficacious.24 Our own study found that β interferon was effective in reducing the relapse rate with good safety profile.21 Almost all the United States Food and Drug Administration (FDA) approved disease modifying drug therapies for MS are beyond the financial reach of most Indian patients. Mitoxantrone is a good cheap option for such a patient who is relapsing frequently. However, this drug may be toxic and can be associated with cardiac toxicity or acute leukemias which may appear even 5 years after cessation of drug therapy.25 Mitoxantrone may be given till the cumulative ceiling dose of 140 mg is reached (2–3 years) followed by an approved cheaper disease modifying drug such as glatiramer acetate (approximate monthly cost ₹20,000/-) or Avonex (β interferon 1a 30 µg IM once a week, monthly cost of approximately ₹30,000/-). However, for patients who are unable to afford even these follow-up drugs then cheaper therapy which are not proven or FDA approved may be tried like azathioprine or methotrexate. To tailor the requirements of Indian patients’ drug trials using cheaper drugs need to be conducted.

Symptomatic Therapy

Great symptomatic relief can be provided to the patient by addressing issues like bladder and sexual dysfunction, spasticity, weakness, fatigue, tonic spasms, paroxysmal symptoms, depression and cognitive changes.26

### Table 3: Disease modifying drugs for multiple sclerosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Type of MS</th>
<th>Reduction in relapse rate</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon Beta 1b</td>
<td>250 µg sc every other day</td>
<td>RRMS, SPMS with superimposed relapses</td>
<td>34% red in relapse rate at 2 years, MRI load reduced</td>
<td>Flu-like symptoms, depression, injection site reaction, leukopenia, elevated transaminases, neutralizing antibody</td>
</tr>
<tr>
<td>Interferon Beta 1a</td>
<td>30 µg IM once a week</td>
<td>RRMS, SPMS with superimposed relapses</td>
<td>29% red in relapse rate at 2 years, MRI load reduced</td>
<td>As above</td>
</tr>
<tr>
<td>Interferon Beta 1a</td>
<td>44 µg sc thrice weekly</td>
<td>RRMS, SPMS with superimposed relapses</td>
<td>33% red in relapse rate at 2 years, MRI load red</td>
<td>As above</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>20 mg sc once a day</td>
<td>RRMS</td>
<td>29% red in relapse rate at 2 years</td>
<td>Injection site reaction transient flushing</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>300 mg IV once monthly</td>
<td>RRMS/SPMS who relapse while on IFN</td>
<td>68% reduction in relapse rate</td>
<td>PML initially for which drug withdrawn now reintroduced</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12 mg/m²/2 IV in every 3 month</td>
<td>As above</td>
<td>66% reduction</td>
<td>Cardio toxic &gt; 140 mg/m², acute leukemia</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>0.5 mg orally every other day</td>
<td>RRMS</td>
<td>55% reduction</td>
<td>Cardiac toxicity, AV blocks</td>
</tr>
</tbody>
</table>

Abbreviations: Av, Atrioventricular; IFN, Interferon; IM, Intramuscular; MRI, Magnetic resonance imaging; PML, Progressive multifocal leukoencephalopathy; RRMS, Relapsing remitting multiple sclerosis; sc, Subcutaneously; SPMS, Secondary progressive multiple sclerosis

CONCLUSION

Multiple sclerosis exists in India but at a lower prevalence than that seen in the Caucasian population. It is increasingly believed that some of the genes carried in the Indian patient suffering from MS are similar to that seen in the western patient. The phenotypic presentation of MS in India may be similar to that in the west and more studies in the present era may be required to support this view. CSF for oligoclonal bands have been found in variable proportions in different studies. MRI is the most useful tool in making the diagnosis and should include brain and whole spine. In RRMS disease modifying drugs should be initiated where possible. Multiple sclerosis in India needs well-planned epidemiological studies and studies to explore cheaper disease modifying drugs since the present lot are beyond the reach of most patients.

REFERENCES

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