INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees. The disease is characterized initially by episodes of reversible neurologic deficits. In most patients, these episodes are followed by progressive neurologic deterioration over time. The cause of the disease is not known, but it likely involves a combination of genetic susceptibility and a nongenetic trigger, such as a virus, low vitamin D levels, or environmental factors, that together result in a self-sustaining inflammatory, demyelinating disease of the CNS.1,2

Worldwide, approximately 2.1 million people are affected by MS. The disease is seen in all parts of the world and in all races, but rates vary widely. In general, the prevalence of MS tends to increase with latitude (e.g., lower rates in the tropics, higher rates in northern Europe), but there are many exceptions to this gradient (e.g., low rates among Chinese, Japanese, and African blacks; high rates among Sardinians, Parsis, and Palestinians), which implies that racial and ethnic differences affect risk. In addition, a substantial increase in MS incidence has been reported from different regions, suggesting that environmental factors, as well as geographic and genetic ones, play an important role in MS.

In India, crude prevalence of approximately 1.33/100,000 was reported by Singhal in the mid eighties from the west coast of India. Hospital-based studies in India have shown that over the last decade, the total proportion of MS-related neurology department admissions increased from 1.58% to 2.54%. This data is supported by the Multiple Sclerosis International Federation World MS Atlas, which projects a prevalence of 3/100,000, which is nearly triple the estimate of previous reports. Geographically north west India (above 15° N latitude) saw 4.15 new cases of MS per year as compared to 3.2 cases per year from south India (below 15° N latitude). The one exception is the Parsi population of India in whom Wadia and Bhatia observed a prevalence of 26/100,000. The Parsis (Zoroastrians) originated from the Pars province of Iran. Recent epidemiological studies have shown a high prevalence of MS in Iran especially in Isfahan province that adjoins Pars.3-7

PATHOPHYSIOLOGY

Examination of the demyelinating lesions in the spinal cord and brain of patients with MS shows myelin loss, destruction of oligodendrocytes, and reactive astrogliosis, often with relative sparing of the axon cylinder. In some MS patients, however, the axon is also aggressively destroyed. The location of lesions in the CNS dictates the type of deficit that results.

MS is characterized by perivenular infiltration of lymphocytes and macrophages in the parenchyma of the brain, brain stem, optic nerves, and spinal cord

Expression of adhesion molecules on the surface seems to underlie the ability of these inflammatory cells to penetrate the blood-brain barrier. The elevated immunoglobulin G (IgG) level in the cerebrospinal fluid (CSF), which can be demonstrated by an oligoclonal band pattern on electrophoresis, suggests an important humoral (i.e., B-cell activation) component to MS. In fact, variable degrees of antibody-producing plasma cell infiltration have been demonstrated in MS lesions. The image below provides an overview of demyelination.
The mechanism of demyelination in multiple sclerosis may be activation of myelin-reactive T cells in the periphery, which then express adhesion molecules, allowing their entry through the blood-brain barrier (BBB). T cells are activated following antigen presentation by antigen-presenting cells such as macrophages and microglia, or B cells. Perivascular T cells can secrete proinflammatory cytokines, including interferon gamma and tumor necrosis factor alpha. Antibodies against myelin also may be generated in the periphery or intrathecally. Ongoing inflammation leads to epitope spread and recruitment of other inflammatory cells (i.e., bystander activation). The T cell receptor recognizes antigen in the context of human leukocyte antigen molecule presentation and also requires a second event (i.e., co-stimulatory signal via the B7-CD28 pathway, not shown) for T cell activation to occur. Activated microglia may release free radicals, nitric oxide, and proteases that may contribute to tissue damage.

**IMMUNE CELLS IN MS**

Molecular studies of the white matter plaque tissue have shown that interleukin (IL)-12, a potent promoter of inflammation, is expressed at high levels in lesions that form early. A molecule required to stimulate lymphocytes to release proinflammatory cytokines, B7-1, is also expressed at high levels in early MS plaques. Evidence exists of higher frequencies of activated myelin-reactive T-cell clones in the circulation of patients with RRMS and higher IL-12 production in immune cells of patients with progressive MS, when compared with healthy controls.

Decreased function of immune cells with a regulatory role (Tregs) has been implicated in MS. These Tregs are CD4+ CD25+ T cells that can be identified by their high expression of the transcription factor known as Foxp3. Conversely, the cytokine IL-23 has been shown to drive cells to commit to a pathogenic phenotype in autoimmune diseases, including MS. These pathogenic CD4+ T cells act reciprocally to counteract Treg function and can be identified by their high expression of the proinflammatory cytokine IL-17; they are therefore referred to as Th17 cells.

Tregs and Th17 cells are not the only critical immune cells in the pathogenesis of MS. Immune cells such as microglia (resident macrophages of the CNS), dendritic cells, natural killer (NK) cells, and B cells are gaining increased attention by MS researchers. In addition, nonimmune cells (i.e., endothelial cells) have also been implicated in mechanisms that lead to CNS inflammation.

**SPINAL MS**

In 1988, MS was first described in the upper cervical spine using MRI. Spinal MS is often associated with concomitant brain lesions; however, as many as 20% of patients with spinal lesions do not have intracranial plaques. No strong correlation has been established between the extent of the plaques and the degree of clinical disability.

Spinal MS has a predilection for the cervical spinal cord (67% of cases), with preferential, eccentric involvement of the dorsal and lateral areas of the spinal cord abutting the subarachnoid space around the cord. The gray matter may be involved. Approximately 55-75% of patients with MS have spinal lesions at some point during the coattacks or exacerbations of MS are characterized by symptoms that reflect CNS involvement. The sine qua non of MS is that symptomatic episodes are “separated in time and space”—that is, episodes occur months or years apart and affect different anatomical locations. As an example, a patient may present with paresthesias of a hand that resolve, followed a few months later by weakness in a leg or visual disturbances (e.g., diplopia). In addition, the attack clinically must be compatible with the pattern of impairment found in patients with MS, which typically means that the duration of deficit is days to weeks.

However, it is important to recognize that the progression of physical and cognitive disability in MS may occur in the absence of clinical exacerbations.

**CLINICAL FEATURES OF MS**

Presentation of MS may vary. Some patients have a predominance of cognitive changes, while others present with prominent ataxia, hemiparesis or paraparesis, depression, or visual symptoms.

Classic MS symptoms are as follows:

- Sensory loss (i.e., paresthesias) - Usually an early complaint
- **Spinal cord symptoms : Weakness, spasticity and sensory symptoms**
- Spinal cord symptoms (motor) - Spinal cord symptoms (autonomic) - Bladder, bowel, and sexual dysfunction
- Cerebellar symptoms - Charcot triad of dysarthria, ataxia, tremor
- Constitutional symptoms - especially fatigue (which occurs in 70% of cases) and dizziness; fatigue must be differentiated from depression (which may, however, coexist), lack of sleep, and exertional exhaustion due to disability
- Pain - Occurs in 30-50% of patients at some point in their illness
- Optic neuritis
- Subjective difficulties - With regard to attention span, concentration, memory, and judgment
- Depression - A common symptom
• Euphoria - Less common than depression
• Bipolar disorder or frank dementia - May appear late in the disease course but is sometimes found at the time of initial diagnosis.
• Trigeminal neuralgia - Bilateral facial weakness or trigeminal neuralgia
• Facial myokymia (irregular twitching of the facial muscles) - May also be a presenting symptom
• Eye symptoms - Including diplopia on lateral gaze; these occur in 33% of patients
• Heat intolerance (Uthopp's phenomenon)

Patients with MS may present with many other manifestations, including the following:
• Aphasia or dysphasia
• Seizures (5% of patients with MS)
• Significant motor complaints without sensory deficits or dysautonomia

OPTIC NEURITIS (ON)
As previously mentioned, approximately 20% of patients with MS present with ON as a first demyelinating event, although 40% of patients may present with ON during the course of their disease. Patients with ON may describe phosphenes (transient flashes of light or black squares) lasting from hours to months; movement or sound may induce them. Phosphenes may occur before or during an ON event or even several months following recovery.

ACUTE TRANSVERSE MYELITIS
Partial, rather than total, acute transverse myelitis usually is a manifestation of MS. Strongly consider mechanical compression in the differential diagnosis. Acute partial loss of motor, sensory, autonomic, reflex, and sphincter function below the level of the lesion indicates acute transverse myelitis.

FATIGUE
Fatigue is one of the most commonly reported symptoms of MS, being experienced in up to 90% of patients with the disease. Fatigue is described as an overwhelming feeling of lassitude or lack of physical or mental energy that interferes with activities. An estimated 50-60% of persons with MS describe it as one of their most bothersome symptoms, and it is a major reason for unemployment among MS patients. Rule out comorbid medical conditions, such as infections, anemia, or thyroid disease, before attributing fatigue to MS.

SPASTICITY
Spasticity in MS is characterized by increased muscle tone and resistance to movement; it occurs most frequently in muscles that function to maintain upright posture. As a result of increased stiffness, much more energy is expended to perform activities of daily living (ADL), which in turn contributes to fatigue.

COGNITIVE DYSFUNCTION
Estimates of the prevalence of cognitive dysfunction in MS range from 40-70%. No correlation exists with the degree of physical disability, and cognitive dysfunction may occur early in the course of disease. This complication of MS can be a significant problem, affecting family and social relationships, as well as employment. Areas of cognition affected include comprehension and use of speech, attention, memory, visual perception, planning, problem solving, and abstract reasoning.

PAIN
As previously mentioned, pain is a common occurrence in MS, with 30-50% of patients experiencing it at some time in the course of their illness. Pain typically is not associated with a less favorable prognosis, nor does it necessarily impair function; however, since it can have significant impact on quality of life, it needs to be treated appropriately. Pain in MS can be classified as primary or secondary. Primary pain is related to the demyelinating process itself. This neuropathic pain is often characterized as having a burning, gnawing, or shooting quality. Secondary pain in MS is primarily musculoskeletal in nature and possibly results from poor posture, poor balance, or abnormal use of muscles or joints as a result of spasticity.

URINARY SYMPTOMS
Urinary symptoms are common in MS, with most patients experiencing problems at some point in their disease. Bladder problems are a source of significant morbidity, affecting the person’s family, social, and work responsibilities. Bladder dysfunction can be classified as failure to store, failure to empty or combined dysfunction. Patients with failure to store difficulties have a small spastic bladder with hypercontractility of the detrusor muscle. Symptoms experienced may include urgency, frequency, incontinence, and nocturia.

CONSTIPATION
Constipation is the most frequent complaint concerning the bowels in patients with MS and is characterized as the infrequent or difficult passage of stools. Constipation may be the result of a neurogenic bowel or of immobility, which leads to slowed bowel activity. Finally, patients who have limited their fluid intake in an attempt to manage bladder symptoms or those with limited access to fluids due to immobility tend to have dry hard stools.

HEAT INTOLERANCE
MS is divided into the following categories on the basis of clinical and radiologic criteria, including the frequency of
clinical relapses, time to disease progression, and lesion development on MRI

CLINICAL TYPES OF MS

- Relapsing-remitting MS (RRMS)
- Secondary progressive MS (SPMS)
- Primary progressive MS (PPMS)
- Progressive-relapsing MS (PRMS)

RELAPSING-REMITTING MULTIPLE SCLEROSIS

RRMS is characterized by recurrent attacks in which neurologic deficits appear in different parts of the nervous system and resolve completely or almost completely over a short period of time, leaving little residual deficit. Patients with a relapsing-remitting pattern account for approximately 85% of MS cases.

Global clinical deterioration in RRMS has traditionally been attributed to cumulative deficit due to incomplete recovery from repeated occurrences of individual relapses. However, evidence increasingly suggests an ongoing background neurologic deterioration that is independent of relapses. Although MS was previously thought to be silent between relapses, MRI studies have demonstrated that inflammatory events are occurring in the brain at 10-20 times the predicted rate indicated by the mean relapse rate. This silent disease activity is associated with cerebral atrophy, which in most patients is evident in volumetric studies even at diagnosis. 8,9,12

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Objective</th>
<th>Additional</th>
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<tr>
<td>2 or more</td>
<td>2 or more</td>
<td>None</td>
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<tr>
<td>2 or more</td>
<td>1</td>
<td>2 or more MRI lesions consistent with MS</td>
</tr>
<tr>
<td>1</td>
<td>2 or more</td>
<td>Dissemination in time by MRI or second clinical attack</td>
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<tr>
<td>1</td>
<td>1</td>
<td>Dissemination in space by MRI or positive CSF</td>
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**Table 1 : Diagnosis of MS**

Diagnostic criteria for MRI determination of dissemination in space (3 out of 4 of the following)

- At least one Gd enhancing lesion or 9 T2 hyperintense lesions
- At least one infratentorial lesion
- At least one juxtracortical lesion
- At least three periventricular lesions
- A spinal cord lesion can substitute any of the brain lesions
- *If CSF is positive for oligoclonal band then MRI criteria may be relaxed to presence of only two T2 lesions typical of MS

**Table 2 : Diagnostic criteria for MRI determination of dissemination in time**

- Gadolinium-enhancing lesion demonstrated on a scan performed at least 3 months after onset of a clinical attack at a site different from attack
- In the absence of gadolinium-enhancing lesions at the three month scan follow up scan after another three months showing Gd enhancing lesion or new T2 lesion

SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

Approximately 50% of patients with RRMS convert to a secondary progressive pattern within 10 years after disease onset. This pattern may or may not include relapses, but it is characterized by continued progression over years, with increasing disability. Unlike RRMS, SPMS does not seem to be responsive to currently available disease-modifying agents.

PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

In this pattern, which accounts for approximately 10% of MS cases, function declines steadily without relapses.

PROGRESSIVE-RELAPSING MULTIPLE SCLEROSIS

Persons with this PRMS (< 5% of patients with MS) have occasional relapses.

CLINICALLY ISOLATED SYNDROME (CIS)

Clinically isolated syndrome (CIS) is defined as an acute neurological disease suggesting demyelination of central nervous system but not fulfilling the criteria for clinically definite multiple sclerosis (CDMS). However studies have shown that left untreated a high percentage (70%) of these patients develop MS within next 15 years.16

MULTIPLE SCLEROSIS IN INDIA

In the mid seventies in Kurtzke’s MS world map India was included in the list of countries belonging to the low prevalence zone (<5/100,000). Even at that time, it was believed that in developing countries there was underestimation of disease prevalence for MS. Early literature on MS from different parts of India suggested that there was high prevalence of optic and spinal cord involvement. In 1985 Jain and Maheshwari published data on 354 cases of MS from 9 different centers in India. Optic neuritis (ON) as the initial presentation was seen in 22.2–58% of cases seen at 5 of these centers. Recent studies have shown a frequency of 23.6% from the North West 44% from the south of the country. And 53.3% from the east of the country which is significantly high as compared to western data. In patients of North American and European origin optic neuritis was noted to be the initial presentation in only 17.2% of patients. Acute onset of motor weakness was the next common initial presentation.16-20
Multiple Sclerosis – Indian Perspective

NEUROMYELITIS OPTICA (NMO)
NMO is characterized by recurrent and severe involvement of optic nerve and spinal cord, with longitudinal spinal cord lesions involving more than 3 segments and atypical brain lesions. NMO is associated with a highly specific serum antibody marker, NMO-IgG which targets the water channel aquaporin 4. Evidence suggests that NMO is distinct from MS and pathogenesis include humoral autoimmune mechanism.21

Diagnostic criteria for neuromyelitis optica (NMO)
- Optic neuritis
- Transverse myelitis (longitudinally extensive)
- At least two of the following supporting criteria
  1. Brain MRI normal or showing nonspecific lesions not characteristic of MS
  2. Spinal cord MRI showing myelitis involving more than 3 consecutive segments
  3. NMO-IgG seropositivity

SPINAL-OPTIC MS AND NMO
Therein lies the dilemma in understanding how common it is among Indian CNS demyelinating disorders, wherein optic spinal presentations are common. Winger chuck et al have compiled available literature on NMO in India which included 59 cases reported between 1950 and 2006. They constituted roughly 9–24% of all demyelinating disorders seen in each series. There is not enough data available nor long-term followup on these patients to suggest there was severe visual loss or disproportionate spinal cord dysfunction in the subset with optic spinal presentation. In studies backed by MRI data MRI morphological data including length of spinal cord segments involved is not available. The high frequency of optic and spinal involvement cannot be therefore loosely translated into a possible high prevalence of NMO. Jain and Maheshwari compilation of 59 cases reported between 1950 and 2006. They constituted roughly 9–24% of all demyelinating disorders seen in each series. There is not enough data available nor long-term followup on these patients to suggest there was severe visual loss or disproportionate spinal cord dysfunction in the subset with optic spinal presentation. In studies backed by MRI data MRI morphological data including length of spinal cord segments involved is not available.

Neuromyelitis optica Immunoglobulin G (NMO IgG) seropositivity in Indian patients has been reported Pandit et al. analyzed NMO-IgG status in 78 consecutive cases obtained from their demyelination registry. In this study 62/78 (80%) patients belonged to the NMO spectrum. Longitudinally extensive transverse myelitis was seen in 39/78 (50%) and included all cases of NMO, ATM, and recurrent ATM. Neuromyelitis optica-IgG was positive in 3/78 patients (3.8%), one each of NMO, optic spinal MS and recurrent acute transverse myelitis. The current data appears to indicate that althoughoptic and spinal cord presentations of CNS demyelinating diseases may be common in India, NMO meeting current diagnostic criteria may be no more common in India than in the west.

DISABILITY PROGRESSION OF MS

KRUTZKE EXPANDED DISABILITY STATUS SCALE (EDSS)
The most widely accepted of these is the 10-point Krutzke Expanded Disability Status Scale (EDSS), which was developed originally in 1955 as the Disability Status Scale and has been revised over the years. The EDSS assigns a severity score to the patient’s clinical status that ranges from 0-10 in increments of 0.5. The scores from grades 0-4 are determined using functional systems (FS) scales that evaluate dysfunction in 8 neurologic systems, including pyramidal, cerebellar, brainstem, sensory, bladder and bowel, vision, cerebral, and “other.” EDSS grades are as follows.10

- 0 - Normal neurologic examination (all grade 0 in functional systems [FS], cerebral grade 1 acceptable)
- 1.0 - No disability, minimal signs in 1 FS (i.e., grade 1 excluding cerebral grade 1)
- 1.5 - No disability, minimal signs in more than 1 FS (more than 1 grade 1 excluding cerebral grade 1)
- 2.0 - Minimal disability in 1 FS (1 FS grade 2, others 0 or 1)
- 2.5 - Minimal disability in 2 FS (2 FS grade 2, others 0 or 1)
- 3.0 - Moderate disability in 1 FS (1 FS grade 3, others 0 or 1) or mild disability in 3 or 4 FS (3/4 FS grade 2, others 0 or 1) though fully ambulatory
- 3.5 -Fully ambulatory but with moderate disability in 1
FS (1 grade 3) and 1 or 2 FS grade 2, or 2 FS grade 3, or 5 FS grade 2 (others 0 or 1)

- 4.0 - Fully ambulatory without aid; self-sufficient; up and about some 12 h/d despite relatively severe disability, consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest approximately 500 m

- 4.5 - Fully ambulatory without aid; up and about much of the day; able to work a full day; may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest for approximately 300 m

- 5.0 - Ambulatory without aid or rest for approximately 200 m; disability severe enough to impair full daily activities (e.g., to work full day without special provisions; usual FS equivalents are 1 grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)

- 5.5 - Ambulatory without aid or rest for approximately 100 m; disability severe enough to preclude full daily activities (usual FS equivalents are 1 grade 5 alone; others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0)

- 6.0 - Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk approximately 100 m with or without resting (usual FS equivalents are combinations with more than 2 FS grade 3+)

- 6.5 - Constant bilateral assistance (canes, crutches, or braces) required to walk approximately 20 m without resting (usual FS equivalents are combinations with more than 2 FS grade 3+)

- 7.0 - Unable to walk beyond approximately 5 m even with aid; essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about approximately 12 h/d (usual FS equivalents are combinations with more than 1 FS grade 4+; very rarely, pyramidal grade 5 alone)

- 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair (usual FS equivalents are combinations with more than 1 FS grade 4+)

- 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms (usual FS equivalents are combinations, generally grade 4+ in several systems)

- 8.5 - Essentially restricted to bed much of the day; has some effective use of arms; retains some self-care functions (usual FS equivalents are combinations, generally 4+ in several systems)

- 9.0 - Helpless bed patient; can communicate and eat (usual FS equivalents are combinations, mostly grade 4+)

- 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow (usual FS equivalents are combinations, almost all grade 4+)

- 10.0 - Death due to MS

**TREATMENT OF MULTIPLE SCLEROSIS**

**TREATMENT OF “ACUTE ATTACK”**

**PREVENTION OF RELAPSE**

**TREATMENT OF SECONDARY PROGRESSIVE MS**

Treatment of acute attacks consists of intravenous methylprednisolone. In adult the dose consists of 1 gram I/V daily for 5 days.

Treatment of relapse in RRMS consists of using “Disease modifying agents” (DMT)

At present following DMT are approved in RRMS.

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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side effects</th>
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<tr>
<td>Interferon beta 1A (Avonex)</td>
<td>30 ug I.M every week</td>
<td>Injection site reaction, flu like symptoms, hepatic dysfunction</td>
</tr>
<tr>
<td>Interferon beta 1A (Betaseron)</td>
<td>44 ug S.C alternate day</td>
<td>DO</td>
</tr>
<tr>
<td>Glatirimar acetate</td>
<td>20 mg S.C daily</td>
<td>Injection site reaction, lipoatrophy, chest pain</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>300mg I.V every 4 weeks</td>
<td>Headache, fatigue, PML</td>
</tr>
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For secondary progressive MS only drug approved is Mitoxantrone. Dose in adult is 12mg/m.sq body surface every 3 months. Serious side effects like cardiotoxicity and incidence of leukaemia have been reported. Total cumulative dose should not exceed 140mg/sq meter.

**SUMMARY**

Multiple sclerosis is an inflammatory demyelinating disease of central nervous system which typically relapses and recurs leading to progressive neurological dysfunction. Unless treated early the disease carries a high degree of morbidity
and mortality. Currently a number of disease modifying agents (DMT) have been approved for treatment of RRMS. To achieve maximum benefit from these DMTs they should be started early. The use of DMT in clinically isolated syndrome is controversial. Based on several studies, the recommendation is to start DMT in CIS cases with high risk. Contrary to earlier belief, there is a changing view that MS is not uncommon in India, though the incidence may be lower than in western countries. The predominance of spinal and optic involvement in Asia provoked the debate whether the “spino-optic MS” is a variant of MS or NMO. NMO is now established as an entity distinct from MS. Studies from India have shown low positivity for NMO IgG. The future of MS research is targeted towards development of more effective disease modifying drugs and agents capable of repair of damaged neurons. It should be understood that MS is an important disease in India and all cases presenting with symptoms suggestive of demyelinating disease (clinically isolated syndrome) to be evaluated for MS.

REFERENCES