Epidemiological studies reveal that Multiple Sclerosis (MS)—the chronic inflammatory disorder of the CNS—is most commonly diagnosed in young Caucasian women of Northern European ancestry. Incidence of MS may be increasing worldwide, however, and this could reflect true increased prevalence of the illness or better ascertainment through more widespread use of paraclinical tools, such as magnetic resonance imaging. In this article, we describe three atypical patients with typical MS, and follow each case with a discussion of relevant points from the literature.

Case 1: Late Onset MS (LOMS) with Positive Family History
An 82-year-old right-handed woman began experiencing weakness and difficulty standing upright for long periods of time. She then developed a right hemiparesis that progressed over the course of several months noted by balance problems, difficulty writing, and tripping frequently. Three years later, her primary care physician ordered an MRI of the brain and cervical spinal cord. The scans were abnormal, showing two cord lesions at C1 and C2-3, multiple T2 hyperintensities scattered throughout the cerebral white matter, right pons, bilateral cerebellum, and corpus callosum—the latter noted to have corresponding T1 holes. She was then referred to our MS clinic.

Deeper probing revealed a remarkable family history for multiple sclerosis: two of four children and one granddaughter. One of the daughters died of MS complications at the age of 51, as did her daughter (granddaughter of proband) at age 40, while the other has maintained a benign clinical course. The current patient’s social history was significant for tobacco use, and she also complained of urinary urgency and frequency as well as heat induced fatigue. Neurological examination was remarkable for mild hypometric saccades, quadripareisis of 4+/5 strength in an upper motor neuron distribution, mildly spastic and wide based gait, and target dysmetria bilaterally. She had diminished vibration in the distal lower extremities, while all other sensory modalities were intact. Reflexes were increased symmetrically but not pathologic, and toes were down-going.


Discussion. LOMS may be defined as having first symptoms after age 50, and it accounts for five to 10 percent of all diagnosed cases.\(^1\)\(^2\) In a retrospective study of 52 LOMS compared to 52 patients with MS symptom onset under the age of 40 years old, Kis et al.\(^1\) noted LOMS was more likely to be heralded by motor symptoms (p= 0.014) and tended to follow a primary progressive course (83 percent). Radiographic lesions on MRI were more commonly observed in the spinal cord (81 percent versus 48 percent, p=0.024), less commonly in the cerebellum (11 percent versus 44 percent, p=0.001), and revealed less contrast enhancement (15 percent versus 63 percent, p <0.001). Cerebrospinal fluid examination was less likely to have pleocytosis (mean cell count 5 cells/µL versus 14 cells/µL, p=0.002); there was no difference in reporting of oligoclonal bands. Overall, the LOMS cohort was found to be less responsive to corticosteroids, p= 0.004.\(^1\)

The clinical course of 132 LOMS compared to typical adult onset MS was studied among patients in British Columbia.\(^2\) Researchers found no difference in time from disease onset to EDSS score of 6 between the groups categorized as PPMS or RRMS. When they controlled for risk factors, only MS subtype affected progression in both LOMS and typical MS. The authors concluded that LOMS is not associated with a worse outcome; however, the MS subtype—RRMS versus PPMS—has greater implications in disease prognosis.\(^2\)

The specificity of MRI for LOMS is lowered by other etiologies for non-specific white matter disease among this patient population. Seze et al.\(^3\) compared different radiographic criteria for LOMS and found that the Barkhof criteria\(^4\) were the best compromise of sensitivity and specificity for the diagnosis: 85 percent and 65 percent, respectively. The authors suggested the use of spinal cord MRI and CSF analysis to increase the specificity of diagnostic criteria for LOMS.\(^3\)

An intriguing element of this case is the extensive family history of MS. Genetic analyses in Canada suggested the presence of “susceptibility genes” and identified a higher genetic load among individuals with earlier onset MS and an affected parent.\(^2\) For instance, the lifetime risk to develop MS for a woman with an affected parent ranges from 7.26 percent (disease onset in the fourth decade) to 15.29 percent (onset in third decade). Relative risk among family members of a patient with MS ranges from no increased risk (adopted sibling/child) to 190-fold increased risk (monozygotic twin).\(^2\)

Among those of Northern European ancestry, the MHC haplotype HLA-DRB1*1501 has been identified as the key susceptibility gene in overall risk for MS. Recently, a study of 7,334 individuals with MS or related to someone with MS looked at the transmission of the MHC haplotype. When stratified by transmitting parent, maternal transmission was more likely than paternal transmission (OR 2.89 versus 2.07, p=0.0054).\(^5\) In addition to confirming the maternal parent origin effect, Chao et al.\(^6\) found a differential transmission of HLA-DRB1*15 haplotype among first- and second-degree family type. Over transmission of this haplotype was seen in affected sibling pairs and aunt/uncle/niece/nephew pairs; however, the risk carried was greater in families with second degree relatives affected (OR 4.07 versus 2.17, p=0.0085). The authors believe this observation may be due to gene-environment interactions and epigenetic modifications. Although our proband’s MHC haplotype is unknown, the family history suggests susceptibility gene transmissibility.

Case 2: MS and African Descent
A 21-year-old Nigerian woman presented to our clinic with a prior diagnosis of bilateral optic neuropathy and an episode of decreased sensation in her lower extremities during the prior year. Her optic neuropathy was characterized by visual acuity of 20/400 on the right, and 20/50 on the left. MRI of the brain revealed prominent optic nerves with subtle enhancement. Repeat MRI eight months later showed new non-enhancing lesions of the cerebellar peduncle, corpus callosum, and left parietal white matter. Approximately nine months later, she experienced two separate attacks of distal lower extremity paresthesias. Neurological examination was notable only for a chronic right-sided ptosis. Four months later, she complained of paresthesias over her chest—MRI of the cervical and thoracic spine showed a T2 hyerintense lesion from T3 to T4. A lumbar puncture was performed and showed: 19 WBC (100 percent mononuclear), 5 oligoclonal bands, and an IgG index of 1.3. After diagnosis of relapsing-remitting MS, she started glatiramer acetate. Over four years on treatment, two MRI scans showed two separate enhancing lesions. During this time period, she also suffered one demyelinating episode of bilateral lower extremity weakness and paresthesias. The exam confirmed paraparesis in an upper motor neuron distribution. After administering high dose corticosteroid she promptly improved to baseline.

Discussion. Prevalence of MS in sub-Saharan Africa is exceedingly rare—so rare, that before four autopsy cases of MS in Senegal, physicians claimed that MS did not exist in this region.\(^5\) In a population-based cohort study of 211 North African (NA-MS) patients with MS, Debouverie et al. determined that NA-MS is more severely disabling than MS among Europeans (E).\(^5\) In comparison, NA-MS population tended to have a higher proportion of men, a younger age at onset of symptoms, and higher rate of incomplete recovery from first relapse, p <0.0001. In addition, NA-MS was observed to have more relapses during the first five years of diagnosis, and shorter time to reach an EDSS score of 6 (13.0 versus 23.9 years, p <0.0001).\(^6\) Interestingly, this observed pattern of earlier disease onset and
more aggressive disease course among NA-MS is contradictory to the typically observed prognostic factor: older age at onset portends more disability and more rapid disease progression.4

Population studies have also documented a more severe disease course for African-Americans (AA) with MS than Caucasians.7 The North American Research Committee on Multiple Sclerosis (NARCOMS) database was studied for the effect of race on disability among four domains: mobility, hand function, vision, and cognitive function. After adjusting for all covariates, including socio-economic status, AA patients reported more disability in hand, vision, and mobility (OR 1.27-1.59); however, there was no reported difference among races in cognitive function. Overall, there was no difference found in disability progression between races; nor was there a disparity among use of disease modifying therapies (DMT) and immunosuppressive agents (IS).7

Response to DMT/IS among these cohorts is largely unknown. Two post hoc analyses disagree on this subject.6,8 Cree et al. found a trend for more exacerbations and lower proportion of relapse-free time among AA patients compared to Caucasians being treated with interferon β-1a over 48 weeks. The only statistically significant endpoint was a higher number of new brain lesions among AA patients over 48 weeks after initiation of therapy (2.00 versus 1.10, p=0.04).6 Lebrun et al. observed a beneficial effect of DMT/IS among NA-MS.6 Despite having a higher EDSS score at time of diagnosis, the EDSS evolution rates over three years among NA-MS and E-MS—regardless of MS subtype—were identical. The authors also reported that NA-MS patients tended to move toward IS therapy (mitoxantrone and cyclophosphamide) than E-MS patients. NA-MS patients also were more likely to be on combination therapy.

Case 3: MS in China and Eastern Asia

Our final case is a 26-year-old Chinese woman from Beijing with a previous diagnosis of MS. Five years prior, she suffered bilateral lower extremity weakness for approximately eight weeks followed months later by three weeks of left optic neuritis. Prior investigations included MRI scans of the brain that revealed several T2 hyperintensities with corresponding T1 “black holes” in the periventricular region, posterior corpus callosum, and white matter of the left temporal lobe consistent with the diagnosis of MS. Lumbar puncture was remarkable solely for mild vibratory loss and exquisitely sensitive neurological examination was remarkable solely for mild vibratory loss and break-up of smooth pursuits of extraocular movements.

Discussion. Due to the rarity of MS in Eastern Asia, epidemiologic studies are scarce. Estimated prevalence of MS in Japan ranges from 1.0 to 4.0 per 100,000.7 In the largest survey of Chinese MS to date, Cheng et al.11 studied various clinical features of 249 patients in Shanghai. The female: male ratio was 1:4; mean age of onset was 37.4 years. RRMS comprised 86.3 percent of those surveyed, while 8 percent represented progressive forms of MS. Peculiar to Chinese MS, lesion location has a predilection for the spinal cord: 61.4 percent with spinal cord involvement, followed by the cerebrum (55.4 percent) and optic nerves (40.6 percent). Combined optic nerve and spinal cord involvement is more common than cerebrum and spinal cord—35 percent versus 14 percent. Cerebrospinal fluid surprisingly showed that 52.2 percent of patients were positive for oligoclonal bands, while 34 percent demonstrated an elevated IgG Index. Moreover, mild disease course was reported—86 percent with little or no disability.11

In Eastern Asia, MS is categorized as either classic MS (CMS) or optico-spinal MS (OSMS). OSMS is defined by MRI findings and symptoms confined to the optic nerves and spinal cord.11 There is a striking resemblance between OSMS and Western neuromyelitis optica (NMO)—prevalent disease activity of the spinal cord and optic nerves, higher female: male ratio, CSF with polymorphonuclear pleocytosis and low frequency of oligoclonal bands, and longitudinally extensive spinal cord lesions with necrotic pathologic features.12 Wingerchuk and colleagues recently revised diagnostic criteria for definite NMO given the discovery of antibodies against aquaporin-4 (NMO-IgG) and the observation that 60 percent of one case series demonstrated brain lesions in NMO.13,14

Tanaka et al. studied 128 Japanese patients with clinically definite MS and examined their serum for the presence of NMO-IgG (12). Twenty-five of 45 patients with longitudinally extensive (≥3 segments) cord lesions or atrophy were seropositive; while all those without longitudinally extensive lesions were seronegative. Seropositive status was associated with more annual relapses, p=0.0004. Moreover, there was a strong relationship between blindness and NMO-IgG seropositivity, p=0.0005. The authors concluded that NMO seropositivity is a good biomarker for Japanese MS with longitudinally extensive cord lesions. However, they fell short of diagnosing these patients with NMO, and rather categorized those with longitudinally extensive cord lesions with NMO-IgG seropositivity and OSMS as diseases in “the same clinical spectrum.”12

Follow-up MRI scans showed several new lesions in the medulla, cerebellar peduncles, and junction of the thalamus and globus pallidus without enhancement. Spinal cord imaging revealed two enhancing lesions at C3 to C4 and left aspect of T6 to T7. She responded promptly to high dose corticosteroids—neurological examination was remarkable solely for mild vibratory loss and break-up of smooth pursuits of extraocular movements.
It has been hotly debated in recent years whether OSMS represents a variant of MS, or is, in fact, NMO, as has been postulated.\textsuperscript{1} Japanese researchers acknowledge that OSMS and NMO share clinical and pathologic characteristics, that OSMS clinical course and NMO-IgG status are largely dependent on cord lesion length, and that the definition of OSMS is more inclusive than NMO criteria—particularly for length of cord lesion.\textsuperscript{25} They appear to view the revised NMO criteria—with acceptance of brain lesions—as an evolution of NMO towards the MS end of the clinical spectrum.\textsuperscript{21} Those arguing against OSMS being on the same continuum as MS point out that Japanese OSMS does not carry the DRB1*1501 haplotype seen in Western MS, but rather the DPB1*0501 allele.\textsuperscript{16} Others argue that NMO more closely resembles disseminated encephalomyelitis and that continued reference of OSMS as a form of MS is “pointless” and adds confusion to epidemiological studies of MS prevalence.\textsuperscript{17} This is not a trivial argument as the clinical course and treatment of MS and NMO differ significantly.\textsuperscript{10} To date, a causal relationship of the NMO-IgG antibody in NMO has not been established, although evidence for association is mounting.\textsuperscript{16} It seems unlikely that there will be a consensus on this issue until the pathogenesis of NMO is elucidated.

**Conclusion**

These three cases represent typical MS in atypical patients. Several points may be reinforced from their stories. First, typical MS can be found throughout the world among populations with different genetic backgrounds. Second, there is an unambiguous genetic component in the cause of MS, where first degree relatives have a 15 to 25-fold relative risk of developing MS in their lifetime.\textsuperscript{29} There are likely complex gene-environment and epigenetic interactions that may affect disease manifestation in different populations. Third, it is unclear how potential putative “environmental agents” play a causative role in MS, especially in these relatively understudied and genetically diverse populations. For example, vitamin D deficiency appears to be a clear risk in Caucasians but not African-Americans.\textsuperscript{22} Other potential agents for future study in these populations include tobacco, diet, sunlight and Epstein-Barr virus exposure.\textsuperscript{20,21} Fourth, MRI is a powerful tool that allows easy identification of CNS demyelination. As citizens in industrialized nations live longer, we may be more likely to see and diagnose individuals with common conditions manifesting later in life. Clinicians must recognize that MRI is nonspecific—particularly among aging populations with additional comorbidities—and should never be used alone to make the diagnosis of MS. Fifth, we live in a world where individuals travel great distances, and it will not be unusual in the future to be confronted with patients from different parts of the world. They may have common or uncommon problems compared to the “typical” patients we see in clinic. 

A. Scott Nielsen, MD is senior neurology resident at the University of Colorado, Denver.

John R. Corboy, MD is Professor in the Department of Neurology at University of Colorado, Denver and is on staff at Denver Veteran’s Affairs Medical Center and the Rocky Mountain Multiple Sclerosis Center at Anschutz Medical Campus.