

# MS in Asian Countries

**M Wasay<sup>1</sup>, IA Khatri<sup>2</sup>, B Khealani<sup>1</sup>, M Sheerani<sup>1</sup>**

<sup>1</sup>The Aga Khan University, Karachi, Pakistan; <sup>2</sup>University of Medicine and Dentistry of New Jersey, New Jersey, USA

## Summary

This paper reviews all available English language literature on MS from Asian countries published between 1970 and 2005. Although limited data are available, the review reveals that western Asia – including the Middle East – has the highest prevalence of MS across the continent, and that MS in Asia largely resembles

conventional MS in western countries. Opticospinal MS (a distinct clinical entity from conventional MS) is more common in eastern Asian regions. Larger epidemiological and genetic studies, with more complete ascertainment in various Asian populations, are needed so that we can understand the diversity of Asian MS.

### KEY WORDS:

MULTIPLE SCLEROSIS; OPTICOSPINAL MULTIPLE SCLEROSIS; ASIA; MIDDLE EAST; LITERATURE REVIEW

## Introduction

The diversity of MS in Asia has been a topic of debate for years. Although the prevalence of MS varies in different parts of this region (with Israel, the Middle East and west-Asian countries having the highest reported MS prevalences), nationwide MS surveys have rarely been undertaken, and differences in the availability of advanced medical care for MS patients may confound cross-border comparisons.

We believe that there are wide variations in the clinical presentation, male to female ratio and human leucocyte antigen (HLA) typing among MS patients throughout Asia. In addition, it is a matter of debate whether clinical and immunological features of Asian MS patients as a group are distinct from European or North American MS patients. For example, although opticospinal MS (OSMS) is reported to be common in Japanese literature and is sometimes referred to as Asian-type MS, this term may be misleading. Neuromyelitis optica – which is similar to OSMS in many respects – is found globally. It may be that historical variations in diagnostic criteria may be a major factor in the perceived excess of opticospinal-type MS cases in Asia. Moreover, in some Asian countries, OSMS is reported to be rare.

An extensive and systematic review of how MS is reported in Asia has not previously been undertaken. In the present study, therefore, we reviewed published MS-related literature (in the English language) from 22 Asian countries.

## Methods

A MEDLINE® search using the key words ‘multiple sclerosis’ and names of countries was performed, covering the period from 1970 to 2005. In total, 432 articles were identified, and papers published in English were included. Only epidemiological studies or case series larger than 15 patients were included. As a result, we reviewed 105 articles. Asian countries were divided into four geographical regions – eastern, southern, western, and central – to identify regional or racial differences in MS across the continent. We compared data from countries within each region in tabulated form. Data were input onto a pre-specified questionnaire that focused on prevalence, male to female ratio, clinical presentation (particularly opticospinal cord involvement) and HLA typing.

## Results

### Eastern Asia

There is relatively limited literature in the English language on MS from this region. We reviewed papers from Japan,<sup>1–7</sup> China,<sup>8,9</sup> Hong Kong,<sup>10–12</sup> Taiwan,<sup>13</sup> Singapore,<sup>14</sup> Thailand,<sup>15,16</sup> Korea<sup>17</sup> and Malaysia.<sup>18</sup> No papers were available from Vietnam, Cambodia or Indonesia.

In this region, the MS prevalence is estimated to be between 0.8 and 2 cases per 100 000 (Table 1),

although not all countries have prevalence data. A recent paper from northern Japan,<sup>6</sup> however, reported a higher prevalence of 8.57 cases per 100 000 population. An increase in the incidence, change in the diagnostic criteria, and the role of magnetic resonance imaging (MRI) in the diagnosis of MS may explain this apparent rise.

Female preponderance is reported by all series except Kurtzke *et al.*<sup>17</sup> The male to female ratio ranges from 1:1.3 to approximately 1.5. An unusually lower male to female ratio of 1:9.6 was reported from Hong Kong<sup>10</sup> in a 2002 article. The mean age of MS onset across Asia ranges from 25 to 33 years.

Chiemchanya and Vishudhiphan<sup>16</sup> found MS in 17 paediatric patients from Thailand, six of whom developed the disease before 5 years of age. For most patients, disease onset was acute (<1 week) or subacute (1 week to 1 month), and optical symptoms and/or spinal cord involvement at onset and during the disease course were common (Table 1).

The prominence of opticospinal involvement in Asian populations has long been recognized. Many authors have divided MS into opticospinal and conventional forms, based on their differential clinical phenotypes. Kira *et al.*<sup>5</sup> consider these to be different clinical entities and have also shown immunogenetic differences between the types: they found an association between conventional MS and the DRB1\*1501 and DRB5\*0101 alleles in MS patients, but not those with opticospinal involvement. A subsequent paper<sup>4</sup> demonstrated a change in the clinical phenotype of MS in Japan over a 50-year period, identifying an increasing incidence of conventional MS and a concomitant decrease in the incidence of OSMS. Others have reported similar trends.<sup>19</sup>

High mortality rates (6–36%) have been described, with the mean duration of illness being between 20 months and 8 years before death in some countries.<sup>9,11,13,15,16,18</sup> The pathological findings from autopsies (which represent very few cases) show extensive opticospinal involvement. In addition to classic demyelinating lesions, destructive, necrotic lesions with hypercellularity have been found.<sup>11,13</sup>

**Table 1: Characteristics of MS in eastern Asian countries**

Lead author/ Reference No. Year of publication	Population	No. of patients	Prevalence per 100 000	Males:females with MS	Mean age of onset (years)	Opticospinal presentation (%)	
Kuroiwa <sup>1</sup> 1975	Japanese	1084	-	1:1.30	33±13	43	
Houzen <sup>6</sup> 2003	Japanese	31	8.57	1:2.90	29.1±14.2	16	
Fukazawa <sup>7</sup> 1992	Japanese	62	-	1:1.95	31	27	
Zhao <sup>9</sup> 1981	Chinese	70	-	1:1.80	30.6	30	
Lau <sup>10</sup> 2002	Hong Kong Chinese	53	0.77	1:9.60	29.4	45	
Yu <sup>11</sup> 1989	Hong Kong Chinese	47	0.88	1:1.80	29	33	
Hung <sup>13</sup> 1976	Taiwanese	25	0.80	1:3.20	32.1	56	
Das <sup>14</sup> 1998	Singaporean	21	-	1:3.20	-	43	
Jitpimolmard <sup>15</sup> 1994	Thai	50	-	1:4.00	30.4	68	
Kurtzke <sup>17</sup> 1968	Korean	22	2	2.1:1.0	25.8	64	
Tan <sup>18</sup> 1988	Malaysian	30	2	1:5	29.7	33	

-, not reported

### Southern Asia

Southern Asia (India, Pakistan, Bangladesh, Sri Lanka, Nepal, the Maldives and Bhutan), Iran, Myanmar and Afghanistan are considered to be areas of low MS prevalence (<5 per 100 000 population).<sup>20–23</sup> There are no published reports in English from Bangladesh, Nepal, the Maldives, Bhutan, Afghanistan and Myanmar. Literature on the subject is scarce from Pakistan,<sup>24</sup> Sri Lanka<sup>25</sup> and Iran,<sup>20,26</sup> although several reports are available from India,<sup>21,27–34</sup> the majority being hospital-based case series.

There are no nationwide prevalence reports from these countries, although two community-based prevalence studies from India, conducted in the late 1980s, revealed a prevalence of 21–58 per 100 000 population among the Parsi community.<sup>31,32</sup> MS diagnosis in both of these surveys was based on Schumacher's criteria. In a hospital-based study, Gangopadhyay *et al.*<sup>21</sup> reported an incidence of 0.62 per 100 000 population based on patients who visit neurology outpatient clinics. Although a population-based survey in Indian Kashmir, conducted in 1986, failed to detect any MS cases, another hospital-based study showed that, over time, the total proportion of MS-related neurology department admissions increased from 1.58% to 2.54%.<sup>28</sup> This apparent rise is likely to be multifactorial and has been linked to increased awareness (possibly because of a growing number of neurologists) and the availability of sophisticated diagnostic tools, especially MRI.

In general, research undertaken since the 1990s indicates that MS affects more women than men,<sup>35</sup> although, an earlier Indian paper indicated a male preponderance.<sup>27</sup> The mean age of MS onset has been reported between 25 and 30 years (Table 2) (ranging from 4.5 years<sup>27</sup> to 55 years<sup>21</sup>). Kalanie *et al.*<sup>20</sup> found a higher age of onset for patients with progressive disease, especially primary-progressive MS, which is also recognized in Western countries.<sup>36</sup>

Visual symptoms were the most common presenting features (followed by motor symptoms) in Indian patients,<sup>27</sup> while in Iran, motor manifestations were the most common, followed by sensory and visual symptoms in that order.<sup>20</sup> Cerebellar involvement was both less common at onset and was relatively less frequent during the course of illness compared with expectations with western-type MS.

### Key Points

- The prevalence of MS is high in western Asia and the Middle East compared with eastern or south-eastern Asia
- Opticospinal MS is more common in eastern Asia; patients from western or south-eastern Asia predominantly suffer from western-type MS
- The genetic make-up of patients with MS in western Asia is probably closer to Caucasians than those from eastern Asia
- Large multicentre studies, involving all Asian countries, are needed to understand the epidemiology and course across the continent

The reported frequency of OSMS is 23–33% in the majority of Indian papers,<sup>21,27, 29</sup> but some studies report as high as 47–58%<sup>27,28</sup>, whereas OSMS is relatively less common in Iran.<sup>20</sup> Common presenting features in Sri Lankan patients were visual and pyramidal, which is consistent with reports of western-type MS.<sup>25</sup> No papers describing the clinical manifestations of MS in Pakistan have been published.

Few studies from India have identified an immunological or genetic basis for MS, although one case-control study found that measles infection and exposure to dogs were significantly more common in MS patients than in controls.<sup>37</sup> An Iranian study found that 5% of patients had a family history of MS in first-degree relatives,<sup>20</sup> but an Indian study failed to detect a single case with a positive MS history in a first-degree relative.<sup>30</sup> Various HLA antigens have been noted to be more common in MS patients compared with the general population, although the frequency of HLA markers from people born in this region differs from that reported in western literature. An Iranian study<sup>26</sup> found a higher occurrence of HLA DR2, DR15 and A24 in patients with definite MS, with a relative risk of 1.9 for each marker. Indian investigators<sup>33,34</sup> identified an association between HLA B12 and MS: this antigen was detected in about 80% of cases, compared with about 15% of controls.

There is little information on disability and prognosis in people with MS from this region, although the clinical course of MS tends to be more severe compared with patients from western

**Table 2: Characteristics of MS in India and Iran**

Lead author/ Reference No.	Jain <sup>27</sup>	Syal <sup>28</sup>	Mani <sup>29</sup>	Gangopadhyay <sup>21</sup>	Bansil <sup>30</sup>	Kalanie <sup>20</sup>
Years covered by study	1957–1980	1986–1998	1991–1996	1989–1999	1990s	1996–2001
Population	Indian	Indian	Indian	Indian	Indian	Iranian
No. of patients	354	100	31	45	81	200
Mean age of onset (years)	27	28.5	25.3	30.5	27.5	27.0
Males:females with MS	1:1.32	1:1.32	1:2.10	1:1.50	1:2.25	1:2.50
Optic-spinal presentation (%)	22–58	47	23	33	–	20

–, not reported

countries, with higher percentages of southern Asian patients being severely disabled or bedridden. Some papers have included Expanded Disability Status Scale (EDSS) scores of <5 in most patients,<sup>20,21</sup> and annual attack rates of 0.4 from Iran<sup>20</sup> and 0.63 from India,<sup>28</sup> in patients with relapsing–remitting MS. The median EDSS score for Indian patients was 3.7 (mean of 6 years from disease onset),<sup>21</sup> whereas it was 2.1 in Iran at 5.5 years post onset.<sup>20</sup> The Iranian investigators<sup>20</sup> also noted that 12% of their patients had EDSS scores <2 at 5 years and 14% had EDSS scores <3 at 10 years.

### Western Asia and Middle East

This region can be considered as a medium-risk zone for MS, where the disease prevalence is 5–29 per 100 000 population, as opposed to a high-risk zone (prevalence rates >30 per 100 000 population), or low-risk zone (prevalence <5 per 100 000 population).<sup>38</sup> Surveys from the Middle East have demonstrated MS to be less common in this region compared with western Europe and North America, but the prevalence of MS in this region is higher than in any other part of Asia. A limited number of English language papers on MS from this region have been published. We reviewed papers from Kuwait,<sup>39,40</sup> Turkey,<sup>41</sup> Jordan,<sup>42</sup> Iraq,<sup>43,44</sup> Israel,<sup>45–47</sup> and Saudi Arabia.<sup>48–50</sup> No English language papers were available from Qatar, United Arab Emirates, Syria, Palestine, Yemen, Bahrain, Oman and Lebanon.

Excluding Israel and Turkey, most west-Asian countries have predominantly Arab populations. The

MS prevalence is approximately 10–20 per 100 000 population (Table 3), compared with 30–80 per 100 000 population in North America. One study, however, reported a higher extrapolated prevalence of 20 per 100 000 Jordanians and 42 per 100 000 Palestinians.<sup>42</sup> The prevalence of MS in Palestinians is reported to be the highest among Arab countries.<sup>39,40,42</sup> Palestinians living in Kuwait also have a higher incidence of MS than native Kuwaitis; reasons for this are unclear, but may be related to the admixture of northern European peoples who have settled in this area during migration or invasion. A similar explanation may apply for other non-Arab nations – including the Kurds who live in northern Iraq – who also have higher MS prevalence rates than others native to these regions.<sup>43,44</sup>

The MS prevalence was found to be 0.4/100 000 in Saudi Arabia.<sup>48</sup> Israel, however, is considered to be a high-risk zone for MS with a prevalence of more than 30 per 100 000 population,<sup>45</sup> with higher rates in native Jews of Asian/African origin (52/100 000) than immigrant Jews of Asian/African origin (22/100 000).<sup>47</sup> In Turkish people, the male to female ratio of MS ranged from 1:1.1 to 1:1.9.<sup>41</sup>

The mean age of MS disease onset in this Asian region ranges from 12 to 34 years, although local studies have rarely assessed the signs, symptoms and course of MS. The few that have done so have usually studied Arab populations, in whom the most common symptoms are visual loss and sensory symptoms. Daif *et al.*<sup>49</sup> reviewed 89 MS cases and Yaqub and Daif<sup>50</sup> reported 16 cases; both studies

**Table 3: Characteristics of MS in the Middle East**

Lead author/ Reference no.	Al-Din <sup>39</sup>	Al-Din <sup>40</sup>	Kantarci <sup>41</sup>	Karni <sup>47</sup>	Al-Din <sup>42</sup>
Year of publication	1990	1986	1998	2003	1995
Population	Kuwaitis and Palestinians	Kuwaitis	Turkish	Israel	Jordanians
No. of patients	201	89	1259	272	139
Prevalence per 100 000	10.2	8.33	–	46.2	20.0
Males:females with MS	1:1.7	1.11:1	1:1.19	1.64:1	1:1.9
Mean age of onset (years)	34.7	31.2	27.6±8.8	–	29.6±8.1
Opticospinal presentation (%)	–	27	25	–	28

–, not reported

were undertaken in Saudi Arabia and found the presentation and course of MS in these patients to be no different to western MS. A review of 300 Iraqi patients included clinical and demographic data similar to Caucasian populations.<sup>43</sup>

A significant association between MS and HLA-DR2 and HLA-DQW1 was found in Palestinians,<sup>39</sup> and a population-based cohort of clinically definite MS patients showed a significant association between HLA class II alleles (DRB1, DQA1, DQB1) and MS, in Ashkenazi and non-Ashkenazi Jewish populations.<sup>45</sup> These data also suggested that DRB1\*1501 is the susceptibility allele for MS in the Jewish population.<sup>45</sup> An Israeli MS study showed that Ashkenazi Jews originating from Northern Europe had the highest  $\Delta 32\text{CCR5}$  allele frequency, and that the  $\Delta 32\text{CCR5}$  mutation, correlated with slower MS disease progression.<sup>51</sup>

### Central Asia

Literature from this region published in the English language is limited. We reviewed four papers from Uzbekistan and Tajikistan.<sup>52–55</sup> The Tajikistani study reviewed 182 patients with conventional MS and suggested climatic factors for pathogenesis.<sup>52</sup> Three studies by Alaev *et al.*<sup>53–55</sup> reviewed over 100 MS cases from Uzbekistan, concluding that MS was more common in people of Russian descent compared with those of Uzbeki origin. OSMS was not specifically mentioned in these studies.

## Discussion

The present study presents a systematic and comprehensive review of the prevalence and clinical presentation of MS throughout Asia. Our findings are greatly limited by the weakness of available data and the extreme variability of ascertainment bias, which could influence prevalence, gender ratio, disease subtypes, clinical course and genetic associations. The data are also limited by the variable quality of the different studies, small sample sizes, diagnostic difficulties, and incomplete and variable reporting methods. Most studies were hospital-based case series rather than population-based studies, which limited the scope of our review. Although reports or case series from many Asian countries have not been published, we believe that MS exists throughout the Asian region. The MS diagnosis is closely related to the availability of neurologists and diagnostic tools, therefore the prevalence of MS in developing countries may increase when access to these services is more widespread.

The overall prevalence of MS in Asia is lower than in Europe or North America, which may in part be related to genetic factors. In support of this conclusion, the prevalence of MS in Asians born in western countries is lower than that of the native population.<sup>56,57</sup> Large epidemiological studies are needed to study MS incidence and prevalence, and its natural disease course, in developing Asian countries.

Although OSMS is perceived to be more common in Asia than elsewhere, such findings mostly emerge from research undertaken in eastern Asia rather than across the continent.<sup>58</sup> Reports from India, Iran, the Middle East and Iraq show OSMS to be rarer in these countries than in eastern Asia. OSMS is uncommon – although it may be more correct to say under-recognized – in North America, because the disease has traditionally been diagnosed only in those with classic features of Devic's disease. This form of MS is more common in African-Americans compared with Caucasian Americans.<sup>59</sup> Various reports suggest that OSMS is clinically, radiologically and immunologically distinct from conventional MS,<sup>60–70</sup> although another study suggests that OSMS and neuromyelitis optica may be the same condition.<sup>71</sup> Our literature review is unable to differentiate the true prevalence of neuromyelitis optica or OSMS from cases of western MS with optic and spinal involvement, primarily because the criteria that allow these entities to be differentiated have only recently emerged.

It is generally felt that neuromyelitis optica or OSMS do not respond to interferon therapy. Recent research, however, indicates a trend in favour of high-dose beta interferon therapy for reducing relapses in people with opticospinal MS, although the results were not statistically significant.<sup>72</sup> Further studies are needed to establish whether patients with opticospinal MS do respond to beta interferon therapy.

Finally, one should note that it is extremely difficult to compare genetic characteristics of western and Asian MS: the Asian subcontinent comprises racially and geographically diverse populations, and few studies from Asian countries have reported HLA typing in MS patients. Available data, however, suggest that the genetic make-up of MS patients from western Asia is probably closer to that of Caucasians than of those from eastern Asia.<sup>73</sup>

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## Conflicts of Interest

No conflicts of interest were declared in relation to this article.

## Address for Correspondence

M Wasay, Department of Neurology, The Aga Khan University, Stadium Road, Karachi 74800, Pakistan  
E-mail: mohammad.wasay@aku.edu;  
mohammadwasay@hotmail.com

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