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# Pediatric multiple sclerosis is similar to adult-onset form in Asia

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### *Abstract*

Pediatric-onset multiple sclerosis is underreported because of difficulty in diagnosis and assessment. In Western series, pediatric-onset disease showed significant differences from adult-onset disease with higher female preponderance, polysymptomatic in onset, frequent systemic manifestation in relapses, higher relapse rate, but less disability, and fewer lesions in brain magnetic resonance imaging. Multiple sclerosis manifests differently in Asians, yet there was no large series of pediatric-onset multiple sclerosis reported. We found that pediatric-onset disease in Asians showed greater similarity with adult-onset disease without the reported differences in female preponderance, relapse rate, and magnetic resonance imaging findings. There were also similar proportion and clinical features in optico-spinal form, and long spinal cord lesions were common in both groups. The significant difference was less disability among the pediatric-onset group. Thus, although multiple sclerosis in Asia is different from Western countries, there is greater similarity between the pediatric-onset and adult-onset group in Asia.

## INTRODUCTION

The first recorded patient with multiple sclerosis was believed to be a teenage girl in the 14th century.[1] However, the existence of multiple sclerosis in pediatric and adolescent patients was hotly debated until a series of case reports in the late 1950's; it was probably after a report of some 40 patients by Gall *et al* that the existence of multiple sclerosis in children was no longer doubted.[2] Pediatric multiple sclerosis, as defined as onset before the 18th birthday, represents some 2.7 – 5% of all multiple sclerosis, and occurs worldwide.[3] It is probably underreported, because subjective and transitory symptoms are easily overlooked, difficult to assess, and may be attributed to non-organic causes[1], and diagnosis is often delayed, by up to 2-5.4 years.[4] There is a female preponderance of 61-75%[3], though in actual fact, in children under the age of 10, there is a male preponderance, and in adolescents, the female preponderance is more marked than in adults (2-4 : 1 versus 1.5-2.1 : 1).[1] The clinical onset is more likely to be polysymptomatic (49%, versus 12% in adults), with systemic manifestation in up to 29%, such as headache, nausea, vomiting, seizure, fever and drowsiness.[4] Seizure occurs in up to 22% of children under 6 years old.[4] Children have higher relapse rate, with a mean annual relapse rate of about 0.54 $\pm$ 0.05, but it can be up to 1.9-2.8 relapses a year[3] and shorter inter-relapse interval. However, they recover faster than adults, taking an average of 4.3 weeks, compared with 6-8 weeks in adults.[1] They also make better recovery, and progression of disability takes longer. Children take twice as long to reach an Expanded Disability Scale Score (EDSS) of 3 to 4 compared with adults; on average they take 16-20 years compared with 7-10 years in adults. Over 10 years, only 16-23% of children reach an EDSS of 6.[3] Progressive disease is only a third of that in adults (7% versus 20%).[1,5] Though suffer from less physical disabilities, children are more susceptible to cognitive impairment; and it was estimated that 59% of children with multiple sclerosis had at least one major area of cognitive impairment, and 35% had at least two.[3,6] Magnetic resonance imaging (MRI) findings are similar to adults, though they have lower lesion load, and more likely to have tumefective lesions, and thus

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less likely to satisfy the Modified McDonald dissemination in space criteria.[3,7-9] There is however, as yet, no study of Asian pediatric multiple sclerosis, though it is well known that Asians with multiple sclerosis have different clinical manifestation, such as more severe visual and spinal cord lesions, lower incidence of oligoclonal bands, fewer brain lesions on MRI but longer and more severe spinal cord lesions.[10,11] We undertook two cross sectional surveys across the Asia Pacific region, the first to described the clinical features and the second the MRI findings of multiple sclerosis. We present here the clinical and MRI findings of pediatric multiple sclerosis compared with adults.

## METHODS

The methodology is as previously described.[10,11] Briefly, patients with definite multiple sclerosis according to the Poser's criteria were recruited from 22 centres in 7 regions in Asia (Hong Kong, India, Korea, Malaysia, Taiwan, Thailand and Singapore). Acute transverse myelitis was defined as an acute illness with onset of less than 4 weeks, with both sensory and motor involvement, the motor involvement being severe and bilateral. Recurrent opticospinal form of multiple sclerosis (OSMS) was defined in patients whose clinical relapses were limited to the optic nerve and spinal cord. The classical ("Western") form of multiple sclerosis (CMS) was defined as patients whose clinical involvement was beyond the optic nerve and the spinal cord. The results were collated and analyzed centrally. Parametric variables were analysed with ANOVA while non-parametric variables with $\chi^2$, Fisher's exact test or Mann-Whitney statistics. $\chi^2$ for trend was used to analyze trends of non-parametric variables. All p values of less than 0.05 were considered significant.

## RESULTS

We recruited 263 patients, 79 (30%) from Hong Kong, 58 (22%) from Malaysia, 34 (13%) from Singapore, 31 (12%) from Korea, 27 (10%) from Taiwan, 19 (7%) from India and 15 (6%) from Thailand. Two hundred and eight (79%) were female, 33 (12.5%) have their disease onset before 18 years of age and were thus defined as having pediatric-onset multiple sclerosis. The mean onset age for the pediatric patients was $15.7 \pm 2.26$ years, while that of the adults was $33.8 \pm 10.2$ years. There was only one patient whose onset was before the age of 10. Among the pediatric-onset patients, there were 21 Chinese, 3 Korean, 8 Indian and 1 Thai. The overall female to male ratio is 3.8: 1; and ratios in both the adult-onset and pediatric-onset patients are the same (Table 1).

Two hundred and seven patients were relapsing remitting, 19 were secondary progressive, 30 were relapsing progressive and 7 were primary progressive. Among the adult-onset patients, 73 (31.7%) were optic-spinal form of multiple sclerosis (OSMS), while among the pediatric-onset patients 14 (42%) were OSMS. The duration

**Table 1: Demography of the study patients**

| Parameters | Adult-onset, N=230 | Pediatric-onset, N=33 | P value |
|---|---|---|---|
| Country | | | 0.17 |
| Hong Kong | 72 (91%) | 7 (9%) | |
| Malaysia | 49 (84%) | 9 (16%) | |
| Singapore | 31 (91%) | 3 (9%) | |
| Korea | 28 (90%) | 3 (10%) | |
| Taiwan | 23 (85%) | 4 (15%) | |
| India | 13 (68%) | 6 (32%) | |
| Thailand | 14 (93%) | 1 (7%) | |
| Female | 182 (79%) | 26 (79%) | 0.85 |
| Race | | | 0.10 |
| Chinese | 161 (88%) | 21 (12%) | |
| Korean | 28 (90%) | 3 (10%) | |
| Indian | 17 (68%) | 8 (32%) | |
| Thai | 14 (93%) | 1 (7%) | |
| Malay | 9 (100%) | 0 (0%) | |
| Caucasian | 1 (100%) | 0 (0%) | |

of illness was significantly longer among the pediatric patients (13.8 ± 10.0 years, versus 8.8 ± 7.0 years in adults, p=0.004). The relapse rate was similar between the adult-onset and the pediatric-onset patients (0.830 ± 0.646 versus 0.760 ± 0.852 per-annum, p=0.06). Pediatric-onset patients had more attacks of optic neuritis compared with adult-onset patients (1.73 ± 1.76 versus 0.74 ± 1.06, p<0.001), but this probably was due to longer duration of illness among the pediatric patients, as the rate of optic neuritis attack (number of attack divided by duration of illness) was not significantly higher than adults (Table 2). There was no difference in the clinical features and the number of attacks in other sites. There was also no difference in the clinical features of pediatric optic-spinal form compared with adult-onset optic-spinal form of multiple sclerosis (Table 2).

Out of the 140 adult-onset patients with EDSS available, the median score was 4 (interquartile range 2.0 - 6.0), while that of the 27 pediatric-onset, the median was 2.5 (interquartile range 1.0 – 6.5, p=0.67). Out of the 133 patients with brain magnetic resonance imaging (MRI) done (20 pediatric-onset), the mean number of brain lesions were similar (adult-onset 3.47 ± 4.72 versus pediatric-onset 2.40 ± 2.30, p=0.57). Out of the 115 patients with spinal cord MRI (18 pediatric-onset), the mean length of spinal cord lesions were similar (adult-onset 3.56 ± 2.65, pediatric-onset 3.00 ± 1.94 vertebral bodies, p=0.85); the number of long spinal cord lesions (defined as longer than 2 vertebral bodies) was also the same among the adult-onset and the pediatric-onset (54/97 or 56% versus 10/18 or

**Table 2: Clinical features of study patients**

| Parameters | Adult-onset | Pediatric-onset | P value |
|---|---|---|---|
| Course | | | 0.11 |
| Relapsing remitting | 182 / 230 (88%) | 25 / 33(12%) | 0.83 |
| Secondary progressive | 19 / 230 (100%) | 0 / 33 (0%) | 0.18 |
| Relapsing progressive | 23 / 230 (77%) | 7 / 33 (23%) | 0.11 |
| Primary progressive | 6 / 230 (86%) | 1 / 33 (14%) | 0.66 |
| Type | | | |
| Classical | 157 / 230 (89%) | 19 / 33 (11%) | 0.31 |
| Optic-spinal | 73 / 230 (84%) | 14 / 33 (16%) | |
| Paroxysmal tonic spasm | 54 / 194 (27.8%) | 9 / 30 (30%) | 0.98 |
| Transverse myelitis | 85 / 189 (45.0%) | 13 / 30 (43.3%) | 0.98 |
| Oligoclonal bands | 94 / 191 (49.2%) | 9 / 27 (33.3%) | 0.18 |
| Relapses rate (no. per year) | (Total 230 patients) | (Total 33 patients) | |
| Cerebral | 0.072 ± 0.17 | 0.064 ± 0.19 | 0.85 |
| Optic nerve | 0.13 ± 0.21 | 0.21 ± 0.40 | 0.062 |
| Brainstem | 0.11 ± 0.24 | 0.077 ± 0.21 | 0.29 |
| Cerebellum | 0.015 ± 0.071 | 0.025 ± 0.076 | 0.33 |
| Spinal cord | 0.30 ± 0.39 | 0.31 ± 0.45 | 0.70 |
| Optic-spinal multiple sclerosis | | | |
| Female | 56 / 73 (77%) | 13 / 14 (93%) | 0.31 |
| Chinese | 49 / 73 (67%) | 8 / 14 (57%) | 0.68 |
| Secondary progressive | 7 / 73 (10%) | 0 / 14 (0%) | 0.59 |
| Paroxysmal tonic spasm | 34 / 73 (47%) | 6 / 14 (43%) | 0.97 |
| Transverse myelitis | 50 / 69 (72%) | 6 / 14 (43%) | 0.065 |
| Optic neuritis relapse per year | 0.17 ± 0.26 | 0.37 ± 0.56 | 0.080 |
| Spinal relapse per year | 0.49 ± 0.47 | 0.34 ± 0.45 | 0.12 |

56%, p=0.8). The mean number of spinal cord lesions was also the same (adult-onset 1.39 ± 1.16 versus pediatric-onset 1.15 ± 0.67, p=0.66). Of the 99 patients who had cerebrospinal fluid oligoclonal bands done, 22 out of 91 adult-onset and 5 out of 8 pediatric-onset patients had positive oligoclonal bands (p=0.033).

## DISCUSSION

To our knowledge, this is the first systematic survey of pediatric-onset multiple sclerosis in this region. Pediatric-onset multiple sclerosis is seen among various ethnic groups in Asia Pacific; the absence of pediatric-onset disease among the Malay was probably due to the small number of patients recruited. There was little difference between adult-onset and pediatric-onset disease; both had similar relapse rate, similar proportion of classical and optic-spinal forms, similar attacks in various parts of the central nervous system except the optic nerve, similar brain and spinal cord MRI findings. In the optic-spinal form, pediatric patients had similar clinical features as the adult-onset optic-spinal multiple sclerosis. The significant differences, however, were that the pediatric-onset patients had similar degree of disability in spite of longer duration of illness and more likely to have positive cerebrospinal fluid oligoclonal bands.

Compared with reported series of Western patients, pediatric-onset multiple sclerosis is not uncommon in this region; and very young onset of multiple sclerosis, defined by disease onset before 10 years of age, was rare. However, the percentage pediatric-onset of 12.5% was higher in our series than what is reported among Western patients of 2.7-5%. The female to male ratio of 3.8:1 in pediatric-onset patients was similar to adult-onset patients, and this ratio is similar to the Western pediatric-onset disease (2-4:1), and was significantly higher than Western adult-onset disease. Although secondary progressive disease was uncommon among pediatric-onset patients, similar to reported series, pediatric relapsing progressive and primary progressive disease were seen. Also unlike Western patients, relapse rate was not significantly higher than adult-onset patients. However, similar to reports among Western patients, pediatric-onset patients had similar degree of disability despite longer duration of disease. This probably reflects the better healing capacity in children compared with adults. On spinal cord MRI, the mean length of lesions among both pediatric-onset and adult-onset patients was significantly longer than Western patients, and in both groups of patients, 56% had lesions longer than 2 vertebral bodies. In summary, unlike the reported series from Western patients, there were far fewer differences between pediatric- and adult-onset multiple sclerosis in this region.

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