

The Registry of Asia Pacific Inflammatory Demyelination (RAPID Study)

Allan G Kermodé

Australian Neuromuscular Research Institute, Sir Charles Gairdner Hospital; Centre for Neuromuscular and Neurological Disorders, University of Western Australia, Queen Elizabeth II Medical Centre, Perth, Australia

Abstract

The diversity and heterogeneity of idiopathic central nervous system demyelinating disease in Asia has long been recognised, but there is a dearth of epidemiological work looking at this specific question. Existing data on demyelinating diseases from both the East and the West has been confounded by differences in case ascertainment, selection bias, differing study methodologies and the exclusion of so-called “atypical” cases. This is particularly so in Asia where the application of Western diagnostic criteria may not be appropriate. The RAPID Study is designed to identify the full spectrum of demyelinating disease presentations, including atypical forms, and those associated with other systemic diseases or other disease markers and it is not linked to any form of therapy or medical intervention. The time interval for data collection is finite at twelve months, at which stage the epidemiological data collected will be collated and analysed by the Central Steering Committee. The efforts of all contributors will be recognised in the planned publication derived from this study. Moreover, the data collected will be capable of forming the framework of subsequent clinically isolated syndrome follow up studies and may also form the basis of subsequent sub-studies such as in those centres which are in a position to perform serological and immunogenetic testing. Diagnostic criteria can only be established when a scientific evidence base has been established, and the criteria then tested prospectively. The RAPID data will be pivotal in helping to resolve current controversies surrounding immunological and radiological markers of demyelinating disease.

It is well known that demyelinating disease is heterogeneous in its array of clinical presentations and clinical behaviour. This is particularly so in the context of demyelinating presentations in the Asian region. Despite this there is a dearth of epidemiological work looking at this specific question in Asia, and indeed comparing presentations in both the West and Asia. Many publications have emphasised the reported clinical differences between multiple sclerosis (MS) in Asia and the West, but no study has attempted to collect data from different regions using the same clinical format. There are also many similarities of MS presenting in Asia and in the West, and there is no unique clinical presentation that occurs in Asia that does not occur in the West and vice versa. There is a very broad spectrum of clinical presentations in every country, and the current clinical classification systems that we impose on the heterogeneity of disease are manifestly inadequate. Overall, it appears the major differences between demyelinating presentations

in the East and the West are secondary to a relative difference in the reported proportions of the various clinical presentations rather than different disease phenotypes per se. Recent epidemiological and clinical studies in countries such as Japan, Taiwan and Hong Kong have shown significant variations in the clinical pattern of disease when compared with studies of 30 years and more.¹

MS in patients of European descent has been characterised by a high frequency of oligoclonal bands (OCB) in the CSF, typical periventricular distribution of cerebral and cerebellar lesions, and the relative rarity of longitudinally extensive spinal cord lesions.^{1,2} The term “OSMS” (optic-spinal MS) has been coined to describe clinical presentations in Asia involving clinically selective involvement of the optic nerves and spinal cord, with relative absence of clinical manifestations of clinical disease outside these areas.³ These patients have a higher female to male sex ratio than cases in the West, and have a tendency towards a greater degree of inflammation in the CSF and a lower

Address Correspondence to: Dr Allan G Kermodé, Australian Neuromuscular Research Institute, Sir Charles Gairdner Hospital; Centre for Neuromuscular and Neurological Disorders, University of Western Australia Queen Elizabeth II Medical Centre, 6009, Perth, WA, Australia Tel: +61 8 93881865, Fax: +61 8 93882149, Email: kermodé@mac.com

frequency of oligoclonal band positivity. In the West the term OSMS is not used, and perhaps in part as a direct consequence of this a diagnosis of OSMS in the West is uncommon and in the main is probably restricted to those patients classified as Devic's disease or neuromyelitis optica (NMO). NMO has been described as a variant of MS with sequential or simultaneous acute myelitis and optic neuritis without clinical disease outside the optic nerve or spinal cord.⁴ This area of classification however has become considerably more controversial with the recognition that brain lesions are in fact common in NMO.⁵ It has been suggested by a number of authors that OSMS and NMO have a number of similarities.⁶ Despite a very large number of publications on the subject, the diversity and nosology of MS such as recurrent optic neuritis, recurrent acute myelitis, OSMS and NMO have been controversial and are as yet unresolved.⁷ Notwithstanding the controversies surrounding aquaporin-4 IgG serology, the differences in clinical presentations between demyelinating disease in Asia and the West remains unclear.

It is also recognised that the McDonald criteria⁸ for the diagnosis of MS may be somewhat restrictive for the diagnosis of MS in Asia, and subsequently a number of proposed modifications to the criteria have been made for the diagnosis of MS in Asia.⁹ The great difficulty is that the McDonald criteria were retrospectively derived from the analysis of a number of Western cohorts of MS, and inclusion of the full spectrum of demyelinating disease in these cohorts was highly improbable as the number of presentations of MS do not meet these Western criteria.¹⁰ Moreover it is also known that anti-idiotypic antibodies occur in a much higher frequency in an Asian demyelinating disease population than those in the West, and a number of parasitic and infectious agents are reported to be much more frequent in oriental populations than in the West. Such associated laboratory findings add further complications when diagnosing these patients.

As mentioned above the frequency of OSMS in the West is likely to be significantly underestimated as these criteria are often applied retrospectively to patient cohorts, whereas in Japanese studies the classification is generally made prospectively at presentation.² As a significant number of OSMS cases, if not all, develop brain lesions in their later life such cases in the West are likely to be classified as classical MS. Indeed a study from Amsterdam applied OSMS criteria and found proportions of OSMS similar to those seen in

Japan.¹¹ Given that data has been collected using different methods, it is hardly surprising that prospective data from newly diagnosed definite MS in Amsterdam found that over one third did not meet the Barkhof MRI criteria, and that 13 of 104 had long spinal lesions with a mean length of 11.4 segments.¹⁰ The majority of Asian studies have shown similar low rates of meeting the Barkhof criteria.¹² It is therefore of some priority to obtain an appropriate evidence base for diagnosis of MS in Asia.

Diagnostic criteria can only be established when a scientific evidence base has been established, and the criteria may then be tested prospectively. As a result, a number of neurologists in the Asian region with an interest in demyelinating disease have agreed that a more inclusive epidemiological assessment of idiopathic demyelinating disease presentations in Asia was urgently needed. There are a number of issues that need to be resolved. This includes establishing the full clinical spectrum of idiopathic demyelinating disease presentations, and the significance of these presentations with subsequent prognosis. Regional differences in the clinical presentations also need to be established. The prevalence and characteristics of anti-idiotypic antibodies associated with demyelinating disease has not been adequately assessed. An evidence base from the Asian region is necessary in order to prospectively test the diagnostic criteria for the diagnosis of multiple sclerosis and other demyelinating syndromes. The prognostic significance of the clinically isolated syndrome needs to be established. Comparison of MRI findings in Asian patients with demyelinating disease presentations and Western patients is also required, using the same data collection methods. Finally a framework for ongoing prospective studies needs to be established.

A Steering Committee was established to oversee the design and implementation of a Registry which would be inclusive of all idiopathic demyelinating disease presentations. The composition of the Steering Committee is representative of the region as a whole. (Table 1)

The RAPID Study has been structured differently from previous Asian epidemiological studies, which have focused more on conventional forms of multiple sclerosis than the reported greater prevalence of spinal disease. The RAPID Registry by contrast includes all patients with inflammatory demyelinating disease presentations, including atypical forms and those that are associated with anti-idiotypic antibodies and other systemic diseases. The collection of data is not linked to

Table 1: RAPID Steering Committee Members

Victor HT Chong	- Malaysia
Allan G Kermode	- Australia
Qi Cheng	- China
Ho-Jin Kim	- Korea
Jun-ichi Kira	- Japan
Patrick CK Li	- Hong Kong
Benjamin KC Ong	- Singapore
Naraporn Prayoonwiwat	- Thailand
Ching-Piao Tsai	- Taiwan
Dessa Sadovnick (External consultant)	- Canada

any form of therapy or medical intervention. All regions will be collecting data using the same data acquisition form, hence allowing comparisons to be made. The time interval for initial analysis and data collection is finite at twelve months at which stage the data will be collated and analysed by the Central Steering Committee. The efforts of all contributors will be recognised as co-authors in the planned publication derived from this Study. Data collection in each region may form the basis of subsequent sub-studies, and a number of centres are in a position to perform serological and immunogenetic testing. In this fashion the RAPID Study will build further on data already obtained but more importantly obtain a cross-sectional view of the full spectrum of demyelinating disease presentations.

The key features of the RAPID Study proposal are as follows:

1. The Registry is inclusive and will accommodate patients with multiple sclerosis but also with all MS variants and other CNS demyelinating diseases of uncertain origin such as acute disseminated encephalomyelitis (ADEM).
2. Data entry will be performed using a standardised form as part of normal clinical practice.
3. Patient details will be de-identified during data collection analysis.
4. Data collected at each centre will remain the property of the local centre, but overall data collection analysis publication will be coordinated by an International Asian-based Steering Committee. This will ensure that the results publication and progress will remain in the best interests of the greater Asian community and Registry participants.

5. All participants will receive recognition for their contribution in addition to the knowledge that they are advancing neurological expertise in their region.

In conclusion, the urgent need for comprehensive clinical and epidemiological data in demyelinating disease in Asia is self evident, and it is recognised that only neurologists practising in Asia are in a position to contribute to world knowledge in this area. It is anticipated that most centres will have completed twelve months of patient registration by the first half of 2009. The establishment of the demyelinating disease registry is a crucial step in the advancement to our knowledge.

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