PRIMARY PROGRESSIVE MS AND SECONDARY PROGRESSIVE MS ARE COMMON MANIFESTATIONS OF DIFFERENT DISEASES

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A disease is conventionally defined as disorder of structure or function that either produces specific symptoms, or affects a specific location of human body. In this definition, specific symptoms are sufficient to characterise a distinct disease. There are many medical disorders that share a final common pathogenic pathway, but are distinct in terms of genetic predisposition or environmental risks, onset and nature of symptoms, clinical progression, morbidity and response to treatment. Diabetes mellitus, spinocerebellar ataxia, lymphoid or myeloid lukaemia are common examples where subtypes of a common pathway disorder have sufficient molecular, clinical or biochemical specificity to merit classification as separate diseases. Despite sharing a common neurodegenerative process that leads to cumulative disability and loss of function at a similar rate, the epidemiological and clinical features, disease evolution and MRI findings of primary and secondary progressive multiple sclerosis (PPMS and SPMS) are sufficiently distinct to be considered as separate disease entities.

The similarity of PPMS and SPMS is in the pattern of progressive accumulation of disability and neurodegeneration sharing a common pathway of self-perpetuating tissue injury involving myelin units, axons and neurons and identical longitudinal disease activity. The key differences, however, are in the potential trigger and biological response to this process of tissue injury. SPMS follows a variable period of relapsing and remitting disease (RRMS) in younger and predominantly female patient population in contrast to PPMS that presents around 40 years of age with equal ratio of adult men and women, but with a higher male preponderance in early onset PPMS (<30 years). The peak age of onset of PPMS is almost a decade earlier than women (30-35 years as compared to 40-45 years). This contrasts sharply with RRMS population progressing to SPMS. Pathologically, there are larger, confluent and active areas of demyelination in the brain of SPMS patients as compared to more focal and inactive demyelinating brain lesions in PPMS and the difference in morphology is significant. Conversely, the proportion of remyelinated shadow plaques and overall remyelination capacity is higher in the brain of PPMS than SPMS patients (Bramow et al, 2010). This observation correlates well with a much higher clinical prevalence of cognitive impairment and pseudobulbar affect in SPMS. The most common clinical presentation of PPMS-seen over 80% of patients at presentation-is spastic paraparesis due to myelopathy unlike the frequently overlapping and combined clinical features of optic neuropathy, brain stem-cerebellar and asymmetric spastic-ataxic myelopathy seen in SPMS. In the spinal cord, both forms of progressive MS is associated with diffuse abnormality but PPMS typically presents clinically because of myelopathy due to walking impairment that worsens more steeply than SPMS (Weinshenker et al, 1989). Despite similar structural damage, over-recruitment and overactivity of cervical spinal cord is more pronounced in SPMS than PPMS possibly because of loss of cortical inhibition and release of spinal interneurons (Valsasina et al, 2012), contributing to more commonly prevalent problem of bladder and bowel incontinence in SPMS patients.

PPMS constitutes about 15% of total MS population and is a distinctive clinical phenotype. Early life relapses are retrospectively reported by a minority (less than 1 in 10) of PPMS patients and it would be inappropriate to make an assumption on this basis that the entire cohort of PPMS represents SPMS population with clinically inapparent relapses in early life. The constellation of clinical features from multi-focal cerebral demyelination in predominantly female and younger population with mobility deterioration in SPMS can be clearly segregated clinically from PPMS. The similar course of disability progression to EDSS end points (6 and 8) and survival outcome reflect the course of degenerative process rather than the disease. As a similarity, one could use the example of vascular complications from diabetes mellitus, such as heart disease or peripheral neuropathy, that largely reflect the duration of impaired glycemic control rather than the disease type (early onset, type 1 or late onset, type 2 diabetes mellitus).

When restrictively defined as a disease of impaired glucose metabolism due to relative insulin insufficiency, the distinction between type 1 and type 2 diabetes mellitus blurs, but in terms of pathogenesis and management of these types, as well as genetics, the two types of diabetes mellitus stand as different diseases. Similarly, if interpreted from the point of longitudinal progression of disability and neurodegeneration, PPMS and SPMS would appear similar. However, what separates the two is RRMS- and the metabolic influence that predetermines the risk of disease relapses and progression in SPMS. There is a clear role of a developmental and metabolic process underpinning the disease pathogenesis in the relapsing onset disease phenotype leading to SPMS that is potentially modifiable and worthy of attention. The differential morphological patterns and reparative response to demyelination in brain between SPMS and PPMS patients suggest an inherent difference in vulnerability and tissue repair that may hold the key to the understanding of neurobiology of multiple sclerosis.

Reference
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