PRIMARY PROGRESSIVE MS (PPMS) AND SECONDARY PROGRESSIVE MS (SPMS) ARE DIFFERENT MANIFESTATIONS OF A SINGLE DISEASE

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Multiple Sclerosis has several phenotypes which are actually phases of the same disease rather than different phenotypes. Earliest phase of MS is the radiologically isolated syndrome (RIS) which represents sub-clinical or preclinical relapses and remissions. Clinically isolated syndrome (CIS) occurs when one of the pre-clinical lesions somehow reach a threshold of enough neurological injury or a limited amount of recovery that leads to an acute clinical manifestation associated with the location of the lesion with or without recovery. If multiple lesions are identified within the CNS at different stages (e.g enhancing versus not) than we call this type of CIS, single-attack MS (SAMS). This is an operational term to differentiate CIS with limited evidence for dissemination in time and space from CIS with subclinical evidence of dissemination in time and space. If multiple lesions surface as relapses and remission with clinical evidence of dissemination in time and space this is known as relapsing-remitting MS (RRMS). Up to this point all of the above phenotypes represent one way or another, clinical or subclinical relapsing-remitting forms of MS characterized by acute episodes of variable amounts of, inflammatory demyelination, acute axonal injury and following remyelination and repair.

When a patient rather than acute neurological symptoms presents with slowly progressive chronic (at least one year long) worsening neurological symptoms mostly characterized by long-tract signs, they are known to have progressive MS. Currently accepted norm of progression mecahnism is one of slow axonal degeneration with or without additional acute inflammatory demyelinating activity interspaced along the course of progressive disease course. Progressive disease course should not be confused with disability progression. A patient may have progressive increase in disability due to either partial recovery from acute relapses with cumulative effect of residual neurological deficits after each relapse or a slowly progressive disease course. We refer to progressive disease course not disability progression when defining progressive MS.

If progressive MS follows no clinical relapses (or follows RIS) it is known as primary progressive MS. When Progressive MS follows CIS or SAMS it is known as single-attack progressive MS (SAPMS). When progressive MS follows at least 2 or more clinical relapses (RRMS) than it is known as secondary-progressive MS (SPMS). We argue that the actual mechanism of progression between these forms is similar while the difference lies in if more of the sub-clinical relapses surfaced as clinical relapses before the progressive disease course starts. The proof to that comes from several observations: 1) all definitions of progressive disease course (PPMS, SAPMS, SPMS) start at the same mean age with almost identical age distribution; 2) Many patients with SAPMS and PPMS at the onset of their progressive disease course already have lesions indistinguishable from secondary progressive cases; 3)Pathology studies indicate that when patients are matched for the total number of brain and spinal cord lesions, SPMS and PPMS differ by the presence of previous and ongoing inflammatory demyelination and recovery potential of individual lesions but share a similar spectrum of slowly expanding demyelination and axonal injury.

SPMS, SAPMS and PPMS likely share a common neurodegenerative mechanism of progression but differ by the extent to which inflammatory-demyelinating activity manifests as preceding clinical relapse(s). Therefore these definition refer to previous relapsing-remitting period but not differentiate the actual mechanism of progression between these phenotypes which are similar.