October 2019 Newsletter

Accelerated Cure project for multiple sclerosis

Accelerating research towards a cure for multiple sclerosis

iConquerMS™

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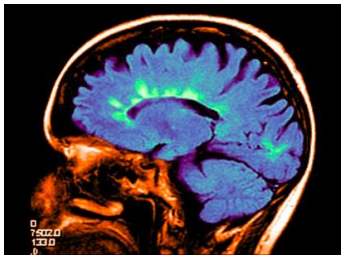
Understanding Progressive MS



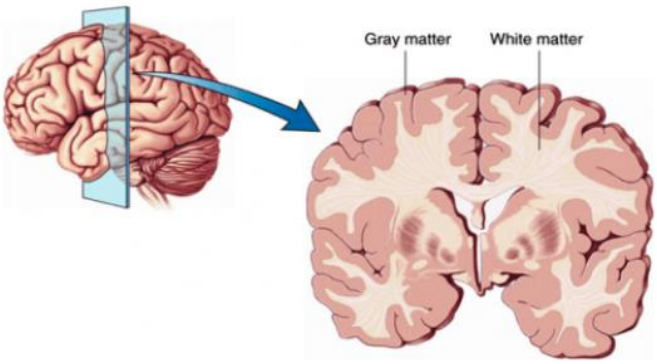
More than 2.3 million people worldwide currently live with MS, with more than 1 million of those living with progressive MS. Generally speaking, there are two progressive forms of the disease – secondary progressive MS (SPMS) and primary progressive MS (PPMS). SPMS is common, occurring as a second phase of the disease for most individuals with relapsing remitting MS (RRMS). In these cases, relapses and periods of remission change into symptoms that steadily get worse. This shift typically begins 15 to 20 years after an individual is first diagnosed.

Relapses can still occur in people with SPMS, however they tend to be less well defined and recovery is not as complete. SPMS can be classified further as being active or non-active, with or without progression, or stable. An individual with active SPMS experiences relapses or evidence of new disease activity on MRI. Non-active SPMS means there is no evidence of current disease activity. In a case of SPMS with progression, a person experiences worsening symptoms over time. SPMS without progression means there is no evidence of the condition getting worse. Stable SPMS is when neither disease activity nor progression is seen.

Once MS advances to the secondary-progressive stage, symptoms often become more challenging. These symptoms may include common symptoms of RRMS, such as numbness or tingling, bladder control problems, changes in vision, walking difficulties, and excessive fatigue. Other symptoms that may indicate a transition to SPMS include increased weakness and more difficulty with coordination, stiff or tight leg muscles, and increased depression or problems thinking. As with all types of MS, symptoms vary widely from one person to another and not everyone will have all of them. Which symptoms are experienced depends on where lesions are located in the brain and spinal cord. Most people with SPMS experience their symptoms regularly, with more or less intensity (depending on if they are having a relapse).

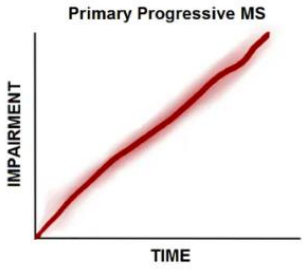
Secondary progressive MS can be hard to diagnose because the transition happens gradually. At least six months of progression must be observed before RRMS can be considered secondary progressive. Therefore, it's important for people with MS to keep track of their symptoms and communicate any changes to their healthcare team. A careful history of these changes, repeat brain MRI scans and a neurologic examination can help determine if the disease has actually progressed to SPMS.

MS researchers are working to better understand the secondary progressive phase of MS. Studies show men tend to progress to SPMS faster than women. Researchers in South Africa suggest that consumption of saturated fats (found in such foods as red meat and full-fat dairy products) not only increases the risk of developing MS, but is also linked to disease progression. The brain is divided into two types of tissue – white matter and gray matter. White matter is found in the deeper tissues of the brain (subcortical), and gray matter is found on the surface of the brain (cortical). Investigators in Japan suggest injury to the gray matter of the brain (specifically the cerebral cortex) plays a major role in the accumulation of long-term disability in people with MS. Results show lesions or atrophy in this area of the brain may play a significant



role in the transition to SPMS. A 2018 study also found subjects with a larger number of cortical (surface) lesions at disease onset had a higher risk of developing SPMS and the transition occurred sooner. Specifically, data showed subjects with two cortical lesions had more than double the risk of developing SPMS, those with five cortical lesions were almost 5 times more likely to develop SPMS, and those with seven or more cortical lesions had a more than 12-fold higher risk of developing SPMS. In addition, data showed other factors, such as older age at disease onset and three or more relapses early in the course of the disease also predicted a higher probability of developing SPMS.

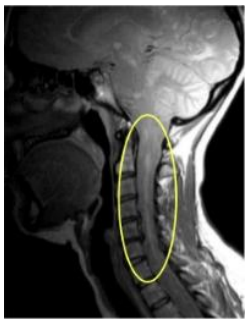
Studies suggest long-term treatment with disease modifying therapy (DMT) may influence the likelihood or timing of the transition to SPMS. Swedish investigators studied a cohort of RRMS subjects from the Swedish National MS Registry. Their findings suggest subjects on DMT for an extended period of time (12 years) took longer to transition to SPMS. A recent Spanish study demonstrated long-term treatment with DMT (13 years) lowers the likelihood of RRMS progressing to SPMS, as well. Interestingly, their results showed DMT does not appear to benefit those subjects that have already progressed to SPMS. Data suggest factors that may also increase the risk of disease progression in subjects with RRMS include multifocal relapses (experiencing more than one symptom during a relapse), being older than age 34 at disease onset (older subjects had a four times greater risk of progressing to SPMS), and failure to respond to one's first disease-modifying therapy.



Approximately 10 to 15 percent of people with MS have PPMS, where neurologic functions steadily worsen from the beginning. There are no flares in disease activity and there is no recovery, or remission. How fast the disease progresses may vary. This type of MS affects men and women equally and the average age of onset is approximately 10 years later than in relapsing forms of the disease. On average, people with PPMS start having symptoms between ages 35 and 39. In general, people with PPMS tend to require more assistance with their everyday activities and have more difficulty remaining in the workforce.

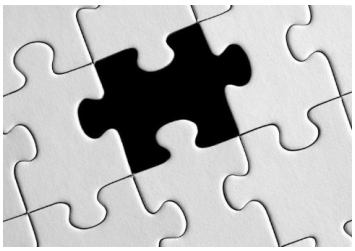
Some people with PPMS experience temporary plateaus and sometimes minor, temporary reductions in symptoms. This form of the disease can be further characterized at different

points in time as either active (MRI shows more lesions and disease activity) or not active (symptoms continue, but the disease is not causing further lesions), and with progression (levels of disability are increasing and symptoms are getting worse) or without progression (the disease is not causing further disability and symptoms are steady).



PPMS symptoms vary from person to person, both in type and severity. Because PPMS primarily affects the nerves in the spinal cord, the main symptoms often involve difficulty walking, weak or stiff legs and problems with balance. Other common symptoms include speech or swallowing issues, vision problems, fatigue, pain, Lhermitte sign (an electric shock sensation that runs down the back and limbs when the neck is bent), paralysis, numbness or tingling, dizziness, shakiness, trouble thinking clearly, mood changes or depression, sexual problems, as well as bladder and bowel dysfunction.

Symptoms commonly associated with PPMS may occur in all forms of MS. In order to determine a diagnosis of PPMS, a person must experience symptoms that consistently worsen over the course of 1 year. Given that diagnosis is based on an individual's symptom history, accurate tracking of MS symptoms is essential. In addition to having progressive symptoms, a person must exhibit at least two of the following criteria: (1) brain lesions on MRI that are typical of MS, (2) two or more MS lesions in the spinal cord, or (3) evidence of oligoclonal bands or an elevated IgG index in the spinal fluid, both of which are indicative of immune system activity in the central nervous system. Repeated diagnostic testing is necessary in order to obtain this information. It's important to keep in mind it may take time for a PPMS diagnosis to be made, particularly if a person has only recently begun to experience neurological symptoms.



A distinct type of damage to the brain and spinal cord occurs in PPMS. It involves much less inflammation, which is typical in relapsing forms of the disease. As a result, people with PPMS tend to have fewer brain lesions and the lesions tend to contain fewer inflammatory cells. As mentioned earlier, individuals with PPMS tend to have more lesions in the spinal cord. In 2014, Canadian researchers conducted a literature review to identify risk factors that may be associated with PPMS. They performed a search of six databases and included twenty

observational studies in their review. They found very few studies have reported findings by disease course (the majority focus on RRMS). For example, exposure to Epstein-Barr virus appeared to increase the risk of RRMS, but its association with PPMS was less clear. Other risk factors, such as cigarette smoking and other infections were not consistently associated with a specific disease course. This review exposes a need for further study to better understand the risk factors associated with the onset of PPMS.

The International Progressive MS Alliance (the Alliance) is a growing global initiative to end progressive MS. The Alliance, founded by a number of international MS organizations, awarded more than $2.7 million dollars in research grants in the last year to support promising MS research around the world. These studies are aimed at understanding progression, accelerating clinical trials, and improving the wellbeing of people living with progressive MS. A Scientific Steering Committee (a team of researchers, health professionals and people affected by progressive MS) provides expert perspective and strategic direction for the Alliance. This level of international participation and collaboration is unprecedented and holds great promise for groundbreaking discoveries toward better understanding, treating and, ultimately, ending progressive MS.

INTERNATIONAL
PROGRESSIVE MS ALLIANCE
CONNECT TO END PROGRESSIVE MS