When Does MS Start?

Neurologic health care providers generally are very good at identifying new disease activity in MS. They use three criteria:

1. The clinical history
2. The neurologic exam
3. Changes on central nervous system MRIs

But all too often, even at the first indication of the illness, there are changes either on exam or on MRIs that show the disease had been present “silently” for an unknown period of time.

Knowing when MS starts is important. It could allow scientists to discover events that trigger the disease process, possibly even preventing the illness. It also could lead to very early treatment of the disease if the changes noted suggest a higher risk for disability. But the challenge has been finding a marker that could predict the risk of developing MS. Recent research findings suggest this may now be possible.

First, some background on markers…

Many scientists have tried to find compounds in blood and cerebrospinal fluid (CSF) that indicate disease activity in MS. One of the most promising compounds is a group of proteins called **neurofilament light chains** (NfL). These proteins are found in the fibers (axons) of nerve cells. NfL are released when nerve cells are injured. This results in elevated levels of NfL in blood and CSF. As you may have already predicted, elevations of NfL are not specific for MS and can occur with any injury to nerve cells, and elevated levels are **found** in several central nervous system diseases. To complicate things further, neurofilament light chain

levels increase with age and are **higher as a group in men** than in women. As a result, it can be difficult to decide what level of NfL is truly “abnormal.”

Despite these issues, multiple studies showed that NfL levels are elevated in both blood and spinal fluid when MS is active, either clinically or when detected on central nervous system MRIs. Levels also decrease after someone has been on a **disease-modifying therapy**. With the availability of a new, very sensitive test called SIMOA (single molecule arrays), it is now possible to follow NfL levels in blood over time and possibly detect “silent” disease before it causes clinical changes. Testing NfL blood levels is not only less invasive and less expensive than obtaining central nervous system MRIs, it may also be more sensitive in terms of showing disease activity.

But how does this all relate to learning about when MS really starts?

Several recent studies suggested that persons with MS had ill-defined health issues years prior to the development of their **disease.** This was called “prodromal MS,” and was associated with more frequent visits to health care providers and greater utilization of particular medications. However, these observations did not directly indicate that there were already inflammatory changes in the brain.

This problem was overcome with observations described in an exciting **recent paper** that studied levels of NfL in the blood of people entering military service in the United States. Blood levels of NfL were measured years before the development of MS and when the disease was eventually diagnosed. Researchers showed that there were elevations of NfL years before onset of clinical illness. NfL levels rose even further when the disease caused neurologic symptoms. These observations indicate that low-grade brain injury can occur in persons subsequently diagnosed with MS long before the disease begins to cause neurologic difficulties, and that such low-grade inflammation can be detected with a relatively simple blood test.

But there are some shortcomings to this study. Most of the people studied were male, a sharp contrast to the usual population of persons with MS that is overwhelmingly female. In addition, since elevated NfL levels can occur for other reasons than MS, there were no data on the presence of other neurologic diseases that could raise NfL levels, such as **traumatic brain injury**, a condition for which persons in the military are at **higher risk**.

Despite these shortcomings, the results of the above study are important. There is now good reason to study NfL levels in persons at high risk for developing MS with the goal of identifying possible triggers for the development of clinical disease. Such studies may also offer an opportunity to initiate treatment prior to the development of neurologic symptoms. The challenges of identifying triggers of MS, and what treatments may be of value will be the subject of intense research in the next several years.