

September 2019 Newsletter



When do MS symptoms start?

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For MS epidemiologists, we are interested in identifying factors influencing the natural history (progression/severity) of MS. Alternatively stated: determining factors contributing to the manifestation of MS. And defining *manifestation* is where things get really interesting. What is the appropriate definition: It is disease activity? Is disease activity measured by number of relapses? Or is time between relapses more relevant? What about the rate of disability, such time from onset to using a walking cane? How about the diversity in symptoms and the patterns of symptoms? Well, these are all important interpretations of the term. But to study the manifestation of MS, we must start at the beginning.

I teach an introductory class on epidemiology, and in one of my first lectures I introduce a conceptual framework of the natural course of a disease. **Figure 1** is a hypothetical timeline of the natural history of a chronic disease with a genetic and environmental/lifestyle risk component; such as in MS.

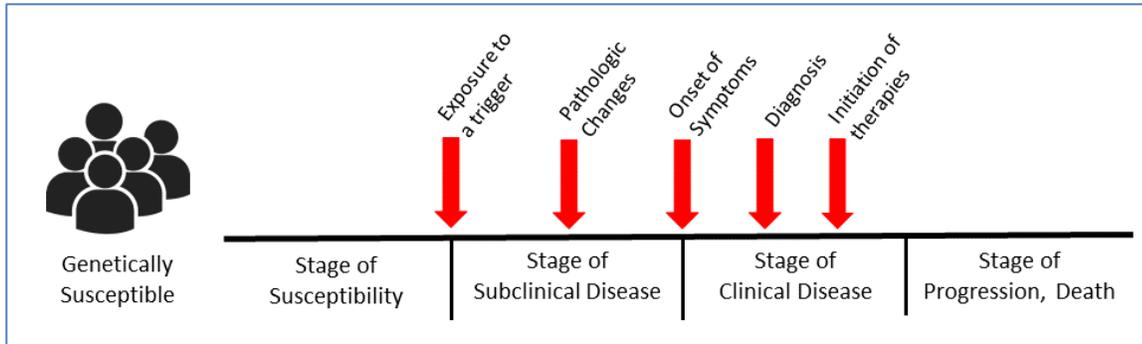


Figure 1: Natural history timeline of a chronic disease.

In studying the natural history of MS, and resultantly MS progression, we should start at the beginning of the disease. But when does the disease start? For most of us, researchers or not, we generally conceptualize the start of MS as the first episode of neurological dysfunction (the first clinically noticeable symptom). However, as shown in **Figure 1** there is the subclinical stage, where MS disease processes are ongoing but there has been no clinical event, therefore pre-clinical MS goes undetected. For some diseases, screening tests can be used to detect the disease while in the subclinical stage (i.e. mammography to detect breast cancer before symptoms even start). Developing screening tests for MS is an active research area, but in the meantime, are there other subtle symptoms and signs occurring during the subclinical stage to aid in detecting MS earlier?

In 2017, a Canadian research team reported there was a pre-clinical phase in MS¹. The study used health administration records from four Canadian provinces (British Columbia, Saskatchewan, Manitoba, and Nova Scotia). Due to the nature of the Canadian health-care system, these provinces have computerized health-care records on >99% of residents, including hospital discharges, physician billing, prescription records, and dates of all medical visits – all records can be linked by a unique health-care number assigned to individuals. Using these records, medical histories for 14,428 MS cases and 72,059 controls were included for this study. They compared health-care utilization in the same five years period prior MS diagnosis between cases and temporally matched controls. *Interestingly*, five years before a MS diagnosis, the number of hospital admissions for people who eventually developed MS was **26%** higher than controls, and this increased to **78%** higher a year before MS diagnosis. A similar pattern was observed for physician billing (5 years before diagnosis: **24%** higher in people with MS than controls; 1 year before diagnosis: **88%** higher in people with MS than controls). There was also a substantial

increase in the number of prescribed drug classes in people with MS compared to controls (5 years before diagnosis: **23%** higher; 1 year before diagnosis: **49%** higher). These results clearly demonstrated a pre-clinical stage for MS where subtle symptoms exist before clinically definitive symptoms (also known as a prodromal stage).

This same research group has since published a few more studies that aimed to add resolution to the 2017 findings. In a 2018 study², the researchers investigated which diagnostic codes were more common prior a confirmed diagnosis of MS in a similar Canadian study population. Individuals who eventually developed MS had a much greater occurrence of diagnosis codes related to spinal cord injury (e.g. **10-16x** more diagnoses for ICD-9 952: Spinal cord injury without evidence of spinal bone injury), cerebrovascular disease, visual disturbances, Parkinson's disease (e.g. **8-35x** more diagnoses), urinary conditions (e.g. **2x** more diagnoses for ICD-9 596: Other disorders of bladder), and muscular disorders 5 years *prior* to their diagnosis of MS compared to non-MS individuals. In a study from July of this year³, they saw similar results in a complementary analysis, including more health care encounters for nervous (130% increase), sensory (40% increase), musculoskeletal (20% increase), and genito-urinary systems (17% increase) 5 years prior a diagnosis of MS, including more visits to a psychiatrist and urologist (50% and 80% increase, respectively).

Collectively, these studies suggest that individuals who eventually develop MS are having a variety of health conditions in the years preceding onset of MS. It is possible that these early conditions reflect the earliest stages of MS, prior to the manifestation of classic neurological symptoms and MRI lesions. Thus, if we determine what combination of early diagnoses and symptoms might significantly predict MS, we can aim to start MS therapies much earlier and slow the accumulation of neurological disability.

1. <https://www.ncbi.nlm.nih.gov/pubmed/28434855>
2. <https://www.ncbi.nlm.nih.gov/pubmed/30121490>
3. <https://www.ncbi.nlm.nih.gov/pubmed/29979093>