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Commentary

How long is the presymptomatic phase of multiple sclerosis?

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An emerging challenge in neurodegeneration is diagnosing disease in the preclinical phase prior to onset of irreversible damage (Dubois et al., 2010). The hypothesis is that if a relatively safe disease-modifying therapy could be given, or started, early enough in the course of a neurodegenerative disease we may be able to prevent, or delay, the onset of clinical disease or at least reduce the consequences of the disease. Multiple sclerosis (MS) is not too dissimilar to other neurodegenerative diseases in this regard with evidence demonstrating a presymptomatic phase. In this context the presymptomatic phase is distinct to the prodromal phase of MS, or period of latency (Kurtzke, 2000), which refer to the so called 'at risk' period prior to the onset of focal inflammatory pathology that defines MS pathologically (Ramagopalan et al., 2010). Migration studies suggest the period of latency from exposure to putative causal environmental risk factors and the onset of biological disease, i.e. presymptomatic or clinical disease, is between 10 and 20 years (Kurtzke, 2000). MS prevention strategies would need to target the periods prior to, and during, the period of latency. This has practical implications in that prevention strategies may only work in the prodromal phase of the disease, prior to the onset of biological disease, or focal inflammatory pathology, and hence the distinction between a pre-disease state and a disease state is not trivial. In comparison, disease-modifying therapies could potentially target the disease after of the onset of focal MS pathology and could be given in either the presymptomatic (radiologically isolated syndrome-RIS) or symptomatic phase (clinically isolated syndrome or multiple sclerosis).

How long is the MS presymptomatic phase? Pathological studies indicate this could potentially be decades; in a large Danish post-mortem study approximately 25% of people with pathological evidence of MS on post-mortem were never diagnosed as having MS in life. Either these subjects had asymptomatic MS or weren't diagnosed in life because their symptoms were either minor or ascribed to another pathology (Engell, 1989). We have been aware for decades that MS begins before the first clinical attack as the majority of patients presenting with a clinically isolated syndrome compatible with demyelination (CIS) have older lesions on MRI that do not account for the presenting syndrome (Miller et al., 2012). Familial and twin studies demonstrate that some siblings, including dizygotic and monozygotic twins, have lesions on MRI compatible with demyelination and/or the presence of oligoclonal IgG bands in their CSF when a proportion of them will never go onto to develop symptomatic MS (Haghighi et al., 2000; Thorpe et al., 1994; Tienari et al., 1992). Endophenotype is the term that is used to capture the 'at risk' or 'prodromal', 'presymptomatic' and 'symptomatic' phases of a disease and has been used in MS (Dobson et al., 2013; Ramagopalan et al., 2010).

Similarly, when patients with radiologically isolated syndromes (RIS) are monitored they can be shown to have asymptomatic focal inflammatory disease activity on MRI (Hutchinson, 2012; Lebrun et al., 2009), which is compatible with observations of subclinical MRI activity in patients with established MS (Giovannoni et al., 2000).

More recent studies have shed some light on the question of how long the presymptomatic phase of MS potentially is. An MRI study performed by the Canadian Pediatric Demyelinating Disease Network compared 36 patients with relapsing-remitting MS, with

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disease onset prior to 18 years of age, to 25 age- and sex-matched healthy normal controls (Aubert-Broche et al., 2014). They found significant differences between the groups in relation to brain and normalized thalamus volumes ($p < 10^{-4}$), indicating a failure of brain growth, and in particular, thalamic growth prior to the disease manifesting clinically (Aubert-Broche et al., 2014). In an Argentinian case-control study that evaluated the school performance in a group of patients, who would later develop the disease, and compared them to an age- and sex-matched control group, found that school performance was poorer in subjects destined to develop MS after leaving school (Sinay et al., 2015). The later the onset of the initial symptoms after leaving school the better their school performance. Although the numbers were relatively small a trend was noted up to 10 years after leaving school (Sinay et al., 2015), indicating compromised cognition years before the first clinical manifestation of MS. The Argentinian data is supported by findings in patients with radiologically isolated syndromes (RIS) or asymptomatic MS. An Italian consortium found that just over a quarter of patients with RIS have significant cognitive impairment with a profile similar to that found in patients with established MS. In this cohort cognitive impairment correlated with T1 lesion volume and low cortical volume on MRI (Amato et al., 2012). We shouldn't be surprised by these findings as we have known for decades that the majority of patients presenting with a clinically isolated syndrome (CIS) have pre-existing lesions on MRI that are non-contemporaneous with the presenting symptoms (Miller et al., 2012).

What is emerging is that MS has a variable presymptomatic period of at least years and possibly decades. Please note my use of the term presymptomatic to define this prodrome, rather than asymptomatic. A significant proportion of subjects in this phase of the disease have cognitive deficits, what keeps these people asymptomatic is the remarkable capacity of the brain to compensate for the damage. The big debate is whether, or not, we should extend the diagnosis of MS into this presymptomatic phase of the disease and offer DMTs to patients with RIS (Hutchinson, 2012). I have little doubt about both of these issues and predict the next rendition of the McDonald criteria (McDonald et al., 2001; Polman et al., 2005, 2011, n.d.) will extend the diagnosis of MS into the presymptomatic phase of the disease.

Conflicts of interest

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