Relapses do not matter in relation to long-term disability: Commentary

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Although there is no strong evidence base, there are a number of reasons to believe that effective anti-inflammatory treatment in relapsing–remitting multiple sclerosis (MS) delays the time course to the onset of the progressive course and prevents long-term disability.

The more you look the more you will see

An important concept is that a relapse is an infrequent clinical signal of ongoing inflammatory disease. A ratio of 8–10 new brain (T2 lesions) to every clinical relapse is widely quoted. However, in patients who had active disease of the type seen in those entered in the clinical trials of first-line disease-modifying therapies (DMTs) and who had monthly gadolinium-enhanced MRI scans, the ratio of new asymptomatic gadolinium-enhanced lesions to relapses was 30:1. In another small study of frequent monthly scanning the ratio was 60:1. When one considers the MS pathology that the routine MRI scan does not see (such as cortical lesions [only 5% seen on FLAIR], diffuse white matter disease, small spinal lesions and meningeal inflammation), then the neurologist is blind to most of the inflammatory disease in the relapsing phase of the illness. When a patient on a DMT describes a relapse event to their neurologist, this is an important marker of inadequate disease control and requires thorough reassessment of the treatment strategy.

A number of natural history studies, importantly those from George Ebers’ group, have shown a relationship between relapse activity in the first few years of illness and time to hard outcomes (death). Thus, even with advanced MRI techniques we can only partially ascertain the extent of inflammatory disease in relapsing MS. Neurologists need a serological biomarker for inflammatory induced neuroaxonal injury which has the sensitivity of cerebrospinal fluid (CSF) neurofilaments.

Despite their low sensitivity in the detection of MS inflammatory disease activity, relapses are highly specific and indicate imperfect disease suppression that results in eventual progressive disability.

One might end by quoting from a recent paper from the Ebers’ group: ‘Early disease stages, especially during young ages, represent a window of opportunity for future treatments that should be focused on preventing or delaying the onset of the secondary progression, the major determinant of permanent disability development.’

References