Truly benign multiple sclerosis is rare: let’s stop fooling ourselves – No

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Over the last 60 years the natural history of multiple sclerosis (MS) has received considerable attention. Mild MS is very common early in the course of the disease. Charcot and those who first described MS encountered cases with low levels of disability after a course of many years. Cases of MS with good levels of function occur frequently in many recent series, but there is no universally agreed definition of benign MS. As with the first two versions, the third iteration of the McDonald criteria ‘Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria’, by Polman and colleagues,1 does not address the topic of benign MS. The novel term ‘truly benign MS’ has no status whatsoever.

The clinical presentation of MS is very variable at the time of first diagnosis, and in an individual case the course is unpredictable. MS has a very wide spectrum. At one extreme, cases of demyelinating disease can progress rapidly to death, as in Marburg’s disease. At the other extreme is so-called subclinical MS when, unexpectedly at autopsy, brains have been found to have pathological findings of MS but no symptoms or signs of MS were reported during life. Other examples of extremely mild, asymptomatic MS have been identified in clinically unaffected co-twins subjected to magnetic resonance imaging (MRI) scans. Thorpe et al.2 found scans that met the Fazekas criteria in 13% of monozygotic and 9% of dizygotic asymptomatic co-twins. Also, asymptomatic individuals have been found to have typical MRI scans for MS where there were family members with typical MS. An MRI diagnosis without symptoms or signs does not constitute what has been thought of as benign MS. No systematic follow-up has been performed in the cases of subclinical MS identified by MRI that have been described to date. It could be that the cases reported in the literature have gone on to develop typical forms of MS. Cases of clinically isolated symptoms (CIS) have been subjected to long-term sequential MRI examination. As in the highly informative series of publications on CIS from Queen Square, none of these MRI studies is population based.

Estimates of the frequency of benign MS vary from 6–60%.3 Most studies are clinic based, the definitions vary considerably in stringency, and the length of the studies is not uniform. Most studies have published the results of serial cross-sectional follow-up. Few are truly prospective. Few are population based. The definitions of ‘benign MS’ quoted in the literature vary considerably. Before the days of the Kurtzke Disability Status Scale (DSS), it was recognized that some cases of MS presented with typical mild or indeed severe relapses. The relapses recovered and the patients remained with minimal disability, not progressing even over several decades. After the introduction of the Kurtzke DSS and later the Expanded Disability Status Scale (EDSS), more precise definitions of benign MS were formulated. In 1996 Lublin and Reingold4 suggested a consensus definition of benign MS as being ‘fully functional in all neurological systems 15 years after disease onset’. Despite that, the most common definition was EDSS 3.0 or less, 10 or more years after the first symptoms of MS.5 Patients who reach EDSS 3.0 are more likely to progress than those who remain at EDSS 2.0. Pittock et al.6 from the Mayo Clinic, and Sayao and colleagues7 using the University of British Columbia database, have proposed this. The lower the EDSS and the longer the duration of the qualifying period for EDSS, the less likely patients were to progress. Recently, EDSS of 2.0 or less at 15 years has been suggested as being the appropriate criteria for benign MS. Even these mild cases, if followed-up for long periods of time, can convert to secondary progressive MS.

Within the last 10 years reports of long-term follow-up of clinic-based cohorts have been published from Dublin,8 Cardiff,9 and the University of British Columbia.7 These have been cross-sectional studies with follow-up at 20 years. All these studies have found that after long periods of mild disability, patients can enter the secondary progressive phase. Patients who have progressive disease from the onset – primary progressive and progressive relapsing MS – are unlikely ever to meet any criteria for benign MS. Of relevance to the present debate is the observation that if

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patients remain at EDSS 2.0 or better, they are much less likely to enter the progressive phase.\textsuperscript{6}

So much for the background. Now let us consider the motion: ‘truly benign MS is rare’. The struggle to define benign MS has been summarized above. There is a lack of consensus. Now let us consider what might be ‘truly benign’. Portaccio et al.\textsuperscript{10} have suggested that since the EDSS is biased towards ambulation, cognitive function is relatively ignored. They performed systematic studies of cognition and neuropsychological function in benign cases (EDSS 3.0 or better 15 years or more from onset) and found that many apparently benign cases have cognitive impairments. Cognitive impairment in apparently benign cases was related to an observed increased risk of becoming ‘no longer benign’. Could it be the extra restriction of good cognition should be added to a very low EDSS?

What should be considered to be the definition of ‘rare’? I propose that a definition of rare is that the value should be less than 1%. A value of 10% of a cohort is not rare, and is within the 95% confidence limit of the least stringent level of conventional statistical significance. I propose that the distinction between benign MS and ‘truly benign MS’ is arcane, metaphysical and without clinical relevance.

Andersen\textsuperscript{11} recently reported the results of 50 years of prospective follow-up of a prospectively observed series of cases in Gothenburg. He reported that five decades after the onset of MS, when reaching the normal life expectancy of the population, approximately 10% of MS patients from an essentially unbiased cohort had minimal neurological and neuropsychiatric disability, although they often had neurological signs of MS and MRI abnormalities typical of MS. The Pittock study was also population based and prospective. Their data were also more benign than most published series. Benign cases are more likely to escape regular review in clinic-based series. This suggests that ‘truly benign MS’ is not rare.

\textbf{References}