The Definition of Multiple Sclerosis: Implications for Research

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Editorial

The original McDonald criteria for the diagnosis of MS were intended for the use of practicing physicians [1]. These criteria, and subsequent revisions [1-3], regard MS as a clinical problem, diagnosed by both clinical and paraclinical criteria. Emphasis is placed on the importance of obtaining objective evidence of dissemination of lesions in space and time, and the exclusion of better explanations of the clinical findings. In opposition to what might be considered a clinical ‘definition’ of MS, is a pathological definition, as it could be argued that tissue studies are the only way to prove an MS diagnosis and to exclude alternative diagnostic possibilities [1,4,5]. What are the relative merits of a clinical vs. pathological definition of MS? A clinical definition of MS has several difficulties. Firstly, the original criteria had low sensitivity and specificity for the diagnosis of MS in non-Western populations: the 2010 revision of the McDonald criteria addressed this issue [3]. Secondly, a clinical definition of MS excludes subclinical cases of MS that are identifiable by pathological studies, e.g. at autopsy [4]. The real merit of using a clinical definition of MS is obviously in decision trees. That is, the division of patients in the clinical setting into MS or not-MS categories facilitates decisions about treatment options and other aspects of patient management [1-3]. As a practicing pathologist, I am tempted to argue for a pathological definition of MS, as I would expect that identification of inflammatory and demyelinating lesions typical of MS will more readily exclude Non-MS Pathologies than will clinical and paraclinical criteria. Also, a pathological definition will have optimal value in answering research questions about tissue changes in MS. However, a pathological definition of MS has several difficulties. Firstly, every pathologist is aware of both intra-observer and inter-observer variability in interpreting tissue pathology: an influential study more than 20 years ago showed that even expert pathologists, reviewing identical slides from the same breast biopsy material and applying known diagnostic criteria, often make different diagnoses [6]. Secondly, a pathological definition has minimal utility as a clinical tool, as CNS biopsies are not performed routinely in patients with putative MS and are unlikely to become part of routine assessment in the future. Thus, we are left with the clinical definition of MS. I cannot comment on the extent of intra-observer or inter-observer error among neurologists expert in MS, but expect that there must be some: the original McDonald criteria identified a subjective component to the diagnosis of MS [1]. Moreover, the clinical definition of MS is heuristic. By this, I mean that the clinical definition is a practical definition, which is neither perfect nor optimal but provides an approximation that is sufficient for its main purpose, namely to make clinical decisions.

Most MS researchers are either clinicians who treat patients with MS or basic scientists who collaborate with these clinicians. Obviously, selection of patients with MS for research into basic disease mechanisms involves these clinicians. By implication, if the clinical definition is heuristic, then patient studies will necessarily produce results that are only approximations of ‘truth’. Thus, the well-recognized heterogeneity in MS in terms of pathology, immunology and genetics [7] may occur because MS is a single disease entity, which is the result of different disease mechanisms, or a set of diseases or conditions with shared clinical features. Part of this heterogeneity could reflect minor differences in the application of the clinical definition of MS between expert neurologists and between MS clinics. I suggest that one needs to be aware of this latter possibility in interpreting the results of research studies in MS. For example, several groups studied T-cell homeostasis in MS, in view of the evidence in animal models that homeostatic T-cell proliferation can initiate autoimmune disease [8,9]. Although we reported increased homeostatic naïve T-cell proliferation in MS, others found no such evidence [reviewed in ref. 10]. Explanations for these different findings include experimental error or differences in methodology between laboratories, but also include differences in the application of the clinical definition of MS between centres. One way to exclude this latter possibility is demonstrated by large genome-wide association studies (GWAS) [11]. By combining data from multiple centres and including a validation cohort, this research strategy reduces the potential impact of minor differences in the application of the clinical definition of MS between centres.

References
