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Recruitment criteria for acute disseminated encephalomyelitis studies: the need for consensus

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Acute disseminated encephalomyelitis (ADEM) is classically defined as a monophasic disease of the central nervous system arising after an infection or vaccination [1]. ADEM, which is generally classified among the autoimmune demyelinating diseases, is a condition that may be regarded as a bridge linking neurology and the infectious diseases. However, many observations in the most recent literature demonstrate that this definition is incomplete and misleading, even though it continues to be a point of reference in clinical practice and applied research. Given the lack of specific biological markers for ADEM, its diagnosis is still based on a combination of clinical and neuroradiological features and on the exclusion of other diseases. The diagnostic process is difficult and often frustrating, both in the acute phase and during the evolution of the disease, which can show unexpected and unexplained complications. In the past few years, nine primary studies of ADEM have been published, involving samples ranging from 40 to 132 subjects [2–10]; five of these studies concerned children and adolescents, three dealt with adults, and in the other no age distinction was made. Only three were conducted prospectively. The inclusion criteria variably used in these studies (history: the presence of a previous infectious episode; clinical features: monophasic course, polysymptomatic onset, presence of encephalopathy and exclusion of isolated myelitis; MRI: presence of multiple demyelinating lesions) are poorly justified by the findings reported in the

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literature. Several Authors have suggested new classifications for the disease based on the distribution of the lesions, the temporal pattern, or both [11]. Since the manifestation of the disease does not correspond to the full clinical expression of disseminated encephalomyelitis in nearly half of the cases, the existence of "site-restricted" forms is accepted, even though it is not clear why some authors apply this label only to the "pure post-infectious encephalitis" and not to the "pure post-infectious myelitis" forms. A variant characterised by a recurrent course is widely recognised, as are chronic-progressive forms. Both raise serious problems of differential diagnosis versus multiple sclerosis, even though, in our experience [12], the age group to which a patient belongs, together with MRI and CSF features, can be useful criteria in this regard. Patients may also present associated damage of the peripheral nervous system (axonal, demyelinating or mixed). Such damage, highlighted both in case reports and in large studies (with a frequency of 5% to 43%), could be a risk factor for relapse and for an unfavourable outcome. Unfortunately, however, only one study has systematically conducted neurophysiological investigations suitable for highlighting a possible association with polyradiculoneuritis [7]. Although ADEM is rarely a life-threatening disease, its functional outcome can vary greatly: in 20%–25% of cases the damage is disabling, in 20% it is mild, and in the remaining cases it is entirely reversible. Therefore, it is not always clear what is the best choice of treatment. There is general agreement that high-dose steroids should be used during the acute phase, whereas the role of IVIgs has still not been clarified [13] and, in particular, no studies have been carried out to investigate the efficacy of immunosuppressive drugs for the prevention of relapses, or for the forms characterised by a progressive course.

Despite all this confused information, there are a few particularly interesting points that deserve prompt evaluation by the international scientific community: (a) the syndromic spectrum of ADEM is much more variable than the classical definition suggests, which means that this definition needs to be radically reviewed, with analysis all its fundamental aspects, i.e. the course of the disease, the extent of the damage, and the temporal relationship with an infectious episode or vaccination; (b) the suggestion, present in some studies, that possible prognostic factors can be identified needs to be confirmed and explored in greater depth through the definition of subgroups presenting different profiles of risk for relapse and poor long-term functional outcome; (c) the areas of overlap between ADEM and MS need to be defined with a view to the possible adoption of therapeutic measures to modify the disease course. In our view, these objectives can be achieved only through the reaching of consensus on these priority issues among the different clinical researchers operating in this field at international level. In short, what is needed is: (a) a common approach to the choice of inclusion criteria; and (b) the planning of multicentre prospective studies. The first of these points is, we think, is fundamental and calls for extensive debate and discussion among the experts. Various ADEM researchers agree with the general methodological rule that careful selection of a sample will lead to the production of more reliable results, but this rule is valid only if the fundamental features of the disease in question are well established and well known. When precise characteristics and an exhaustive definition are lacking, as they are in ADEM, the use of restrictive selection criteria runs the risk of producing a selection bias. The finding of peripheral damage, the occurrence of "site-restricted" forms, and the presence of a recurrent course are all clear examples of this. If these possible features of the disease, all widely documented in the literature, were to be considered exclusion criteria on the basis that they do not match the classical definition, then we would never arrive at a complete understanding of the full clinical spectrum of the disease and would simply go on affirming, wrongly, that ADEM is a monophasic disease of the central nervous system. We are still in an "exploratory" phase and we cannot afford to take, as essential points of reference, the features that were once but no longer considered typical of the disease. It has become essential to reach consensus on the best criterion for selecting samples: in short, to choose a common denominator. The current definition of ADEM corresponds to only one of the disease's possible variants. As we see it, the only feature that can be adopted as a reasonably representative selection criterion in the recruitment of patients is the post-infectious

condition, in view of the frequency with which it is observed. Because this is such an important issue, we urge the experts directly involved in demyelinating diseases to consider and debate these questions.

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