

SCIENTIFIC COMMENTARY**Acute disseminated encephalomyelitis and multiple sclerosis**

The differential diagnosis between multiple sclerosis and acute disseminated encephalomyelitis has major prognostic and therapeutic implications for the patient. As originally defined, acute disseminated encephalomyelitis is an acute monophasic disease that requires early anti-inflammatory treatment, whereas long-term immunomodulatory therapies are considered unnecessary due to the self-limiting nature of the disease. In contrast, multiple sclerosis in most patients is a long-lasting chronic disease, characterized by relapses and remissions, which may finally transform into a progressive disease. Thus, long-term immunomodulatory or immunosuppressive treatment must be considered. The distinction between these two entities is particularly important in patients presenting with severe or fulminant disease onset. In recent years, new diagnostic criteria have been developed for acute disseminated encephalomyelitis (DeSeze *et al.*, 2007; Krupp *et al.*, 2007; Tenenbaum *et al.*, 2007) and multiple sclerosis (McDonald *et al.*, 2001; Polman *et al.*, 2005), which may help the neurologist to differentiate these diseases at their initial presentation. Although these criteria in overall are useful, they are far from perfect. Major problems appear in patients with a very aggressive disease onset and widespread brain lesions, in whom the distinction between acute disseminated encephalomyelitis and early multiple sclerosis may become apparent only after prolonged follow-up of the individual patient. Furthermore, although recurrent or even relapsing forms of acute disseminated encephalomyelitis have been described in recent years, these disease entities are, as yet, poorly defined from the perspective of neuropathology (Tenenbaum *et al.*, 2007).

Pathology is generally regarded as the gold standard in defining different forms of inflammatory demyelinating diseases (Adams and Kubik, 1952; Alvord, 1985; Wegner, 2005). Classical acute disseminated encephalomyelitis is predominantly an inflammatory disease, in which demyelination is sparse and restricted to narrow perivenous sleeves. This pathological process is widespread throughout the nervous system, giving rise to large and diffuse or multifocal lesions in magnetic resonance imaging. In contrast, inflammation in multiple sclerosis is associated with focal confluent plaques of primary demyelination showing variable degrees of axonal injury and loss (Callen *et al.*, 2009). Thus, the distinctive pathological criterion distinguishing acute disseminated

encephalomyelitis and multiple sclerosis is the presence, or not, of confluent versus perivenous demyelination.

A study reported in the current issue (Young *et al.*, page 333), aims at validating clinical diagnostic criteria, including magnetic resonance imaging and cerebrospinal fluid parameters, against the pathological gold standard described above. The authors make use of a large collection of biopsy and autopsy material from patients with inflammatory demyelinating diseases, which have been collected at the Mayo Clinic during the last decades, together with very detailed clinical information on these patients. Individuals with disorders subsumed under the spectrum of neuromyelitis optica were excluded. The main result from this study is that, when taken as a whole, the diagnostic criteria for acute disseminated encephalomyelitis, defined by the International Paediatric Multiple Sclerosis Study Group (Krupp *et al.*, 2007; Tenenbaum *et al.*, 2007), matched the pathological diagnosis of acute disseminated encephalomyelitis with a sensitivity of 80% and a specificity of 91%. Three patients manifested pathological features of both perivenous and confluent demyelination. When these patients were included, sensitivity dropped to 77%. However, when individual criteria for acute disseminated encephalomyelitis were applied to the cohort with multiple sclerosis-like confluent demyelination, the overlap was higher. Multifocal brain MRI lesions were seen in 61%, polysymptomatic presentation in 75% and encephalopathy in 22% of the patients with multiple sclerosis-like confluent demyelination. Despite this overlap in initial clinical presentation, the disease remained monophasic in all patients with pure perivenous demyelination, whereas most of those with confluent demyelination subsequently developed further disease exacerbations and/or fulfilled the McDonald criteria for the diagnosis of multiple sclerosis at follow-up. In conclusion, this study shows that the clinical criteria for differentiation of acute disseminated encephalomyelitis and multiple sclerosis are imperfect, and it reveals considerable overlap in the clinical presentation between these two disorders. There are several possible explanations for this situation.

Pathological studies have long since shown that perivenous and confluent demyelination may overlap in patients with the Marburg type of acute multiple sclerosis (Adams and Kubik, 1952). This combination is also clearly seen in the present study, which

identified three cases where both perivenous and confluent demyelination were present side-by-side in the biopsy or autopsy specimens. This is a problem with neuropathological diagnosis, in particular when only small (e.g. needle biopsy) specimens are available. The second caveat related to this study is that clinical presentation in the cohort of patients with confluent demyelination is not typical of multiple sclerosis. Biopsy or autopsy tissue from patients with multiple sclerosis is only available in situations where the clinical course has been very aggressive, justifying or necessitating tissue diagnosis, and the brain lesions often tend to be atypical. This may explain why such a large proportion of patients with confluent demyelination in this study showed at least some clinical features of acute disseminated encephalomyelitis. It is, however, exactly this population of patients, where the problems of differential diagnosis are most urgent.

Furthermore, the spectrum of acute disseminated encephalomyelitis and acute multiple sclerosis may harbour more than two different disease entities. Classical post-infectious or post-vaccinal acute disseminated encephalomyelitis as a monophasic inflammatory disease with sparse perivenous demyelination resembles, in many respects, experimental autoimmune encephalomyelitis (Alvord, 1985). However, considering the multiplicity of different agents that can trigger this condition, it is not clear whether post-infectious acute disseminated encephalomyelitis can be subsumed under a single disease entity. Furthermore, experimental autoimmune encephalomyelitis can present pathologically, not only with perivenous but also with confluent demyelination, depending upon the immunological mechanisms of disease (Lassmann, 1983). In Japanese patients exposed to rabies vaccine that contained neural tissue, the clinical presentation of this form of human experimental autoimmune encephalomyelitis resembled and reflected acute disseminated encephalomyelitis more than multiple sclerosis; however, brain lesions showed inflammatory demyelination that was typical for acute multiple sclerosis (Uchimura and Shiraki, 1957). A similar disease with extensive multiple sclerosis-like demyelination was subsequently described in a Caucasian patient, who received—as misguided treatment for presumed Parkinson's disease—seven injections of calf brain homogenate (Seitelberger *et al.*, 1958). Regardless of a multiple sclerosis or acute disseminated encephalomyelitis like clinical and pathological presentation, experimental autoimmune encephalomyelitis in humans strictly depends upon peripheral sensitization with brain tissue and ceases when that stimulus ceases.

Although excluded from the present study from the Mayo Clinic, neuromyelitis optica must still be considered in this context, since it too may present with a syndrome resembling acute disseminated encephalomyelitis or, more typically, with transverse myelitis (Saiki *et al.*, 2009). For a long time, this disease was considered to follow only an acute or subacute monophasic course; but with the availability of antibodies against aquaporin 4 as a biomarker for this condition (Lennon *et al.*, 2004), it has become clear that most patients do in fact have a relapsing disease course, and the spectrum of the disease is now much broader than previously assumed.

A particularly illustrative example of the problems of classifying acute disseminated encephalomyelitis and multiple sclerosis comes from the experience of paediatric neurology. A substantial number

of children with inflammatory demyelinating disease present with very high antibody titres against a conformational epitope of myelin oligodendrocyte glycoprotein, which is the target of demyelinating antibodies (O'Connor *et al.*, 2007; Brillot *et al.*, 2009). Such antibodies are particularly prevalent in children who develop inflammatory demyelinating disease under the age of 10 years; and the incidence of patients with such autoantibodies decreases with age. These patients present with an acute disseminated encephalomyelitis or multiple sclerosis-like clinical disease. However, the pathology shows widespread primary demyelination, as seen in multiple sclerosis, and experimental studies indicate that such antibodies can indeed induce demyelination *in vitro* and *in vivo* (Zhou *et al.*, 2006; Brillot *et al.*, 2009). Within the short follow-up period covered by the study, about half of the patients experienced a relapse of the disease, suggesting conversion to multiple sclerosis (Brillot *et al.*, 2009). Whether this myelin oligodendrocyte glycoprotein-related inflammatory demyelinating disease is part of the spectrum of multiple sclerosis or—similar to neuromyelitis optica—a different disease entity, is currently unresolved.

For all these reasons, acute inflammatory demyelinating disorders, such as acute disseminated encephalomyelitis and acute multiple sclerosis may be triggered and propagated by quite diverse disease mechanisms and it is therefore not surprising that diagnostic criteria, based only on clinical presentation and MRI findings, are imperfect. It is hoped that, as in neuromyelitis optica, knowledge of the underlying mechanisms and the development of disease-specific paraclinical markers will lead to accurate clinical diagnostic criteria and pave the way towards effective therapeutic strategies in affected patients.

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