Role of MRI criteria and OB for diagnosing multiple sclerosis in patients presenting with clinically isolated syndromes

It has now become evident through the work of several authors that the presence of oligoclonal bands (OBs) in patients with clinically isolated syndromes (CIS) increases the risk of having a second attack and is therefore useful in identifying patients at risk for developing multiple sclerosis (MS) [1,2]. However, as magnetic resonance imaging (MRI) is invariably recommended to establish a diagnosis of MS, to rule out other conditions, the relevant question is whether the results of a cerebrospinal fluid (CSF) tap (which is an unpleasant examination for patients, sometimes associated with transient, side effects) add valuable information to baseline MRI in predicting further attacks and for differential diagnosis. In the present issue of *Multiple Sclerosis*, Zipoli et al. presented a study in which they have assessed the contribution of CSF examination to the diagnosis of MS in current clinical practice in a cohort of consecutive patients, suspected of MS, who underwent diagnostic work-up [3]. The precise value of OBs in the context of the two definitions for dissemination in space (DIS) proposed by the McDonald criteria are compared in terms of sensitivity, specificity, and accuracy to predict a second attack, this is, clinically definite MS (CDMS) at 1 year or CDMS at the end of follow-up in the total cohort (all patients referred with a suspicion of MS) and in the CIS subgroup (after exclusion of patients with alternative diagnoses) [4–6]. Given that these two groups have not been followed for a similar period and that we are considering a time-dependent endpoint, such as CDMS, it may be suggested that it would be fairer to draw such comparisons at a predefined and similar time point (1 year in the study). It is also important to point out that, as shown in a meta-analysis evaluating the use of MRI in the diagnosis of MS, short follow-up studies tend to produce higher estimates of sensitivity and lower estimates of specificity compared with longer-term studies [7]. Therefore, using 1-year endpoints, the present study may underestimate the specificity of the different options tested.

The paper by Zipoli and coworkers could provide clinically relevant information for the assessment of patients referred with a suspicion of MS in three different clinical scenarios:

1) Patients presenting with CIS typical of MS and MRI fulfilling 3–4 Barkhof MRI criteria: In terms of predicting conversion to CDMS, it has recently been shown that OBs are an independent risk factor resulting in an almost two-fold increased risk of having a second attack in all patients, independent of MRI [8]. However, in patients with CIS and a MRI and a clinical picture typical of MS, the added value of OBs may be trivial from the clinical standpoint as patients already have a high risk of conversion. In the current cohort, 58 of 90 patients fulfilled this condition. Using data from Zipoli and coworkers, specificity of OBs in such patients already fulfilling 3–4 Barkhof criteria and with a clinical picture typical of MS (CIS cohort) is only 20%, while sensitivity values are up to 79%. However, this data should be interpreted with caution as they might be heavily influenced by the short follow-up of this cohort, as this is clearly responsible for the low values of specificity encountered.

2) Patients presenting with CIS typical of MS and MRI not fulfilling 3–4 Barkhof criteria: It is mainly in those patients with a normal baseline MRI or with an MRI not fulfilling Barkhof criteria for DIS, where the added value of CSF examination can be clinically meaningful. Thirty-two of 90 patients fulfilled this situation in the present paper. In this group of patients, presence of OBs is associated with a specificity of 50% and a sensitivity of 62% reinforcing the practice of a lumbar tap when 3–4 Barkhof criteria are not met.

3) Patients presenting with an atypical clinical picture but with an MRI fulfilling 3–4 Barkhof criteria: In this setting, the paper presented by Zipoli, et al. adds an important piece of information. In 28 subjects an alternative diagnosis was assumed, whereas DIS using MRI only was confirmed in 12 out of 28 (43%) of such patients, OBs were not detected in any of them. When including such patients in the analysis (total cohort), DIS using CSF is the preferred test with a specificity of 72%. Therefore, this study highlights the importance of a CSF examination in patients with atypical presentations, even if they fulfill the Barkhof criteria. However, several issues...
need to be considered. First, the median follow-up of the group of patients with an alternative diagnosis is less than 2 years, and this group includes, for example, five patients diagnosed as Neuromyelitis optica (NMO) or Acute disseminated encephalomyelitis (ADEM). It is important to point out the difficulties in excluding MS in patients presenting with a clinical picture of ADEM when the follow-up is so short. It is also difficult to discard MS in patients with an optico-spinal presentation and an MRI fulfilling DIS using MRI only, even if anti-NMO antibodies are present. In fact in the current Wingerchuk diagnostic criteria for NMO, MRI needs to be normal or with nonspecific white matter lesions [9]. Second, even though there are other conditions that may mimic MS radiologically and even meet 3–4 Barkhof criteria [10], at least some of these patients may have what has been labeled as “clinically asymptomatic syndromes” or “radiologically isolated syndromes.” In fact, in a recent paper, 37% of such patients presented with a clinical attack in a follow-up period of 5 years and up to 77% presented with new lesions in the follow-up scans [11]. In another cohort of 44 patients who exhibited incidental imaging findings highly suggestive of MS (3–4 Barkhof criteria), radiological progression was identified in 59% of cases over a median period of 2.7 years and 10 patients developed CIS or CDMS after a median of 5.4 years [12]. All the above considerations are essential when considering what can be considered true positive, true negative, false positive, and false negative. Finally, it is important to bear in mind that test validity results in this last clinical scenario are heavily dependent on referral biases, as such a high percentage of “incorrect” suspicions may not be present in other clinical settings (e.g. up to five patients with a final diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) were referred to an MS clinic in a period of 5 years).

Overall, this study adds important information on the role of OBs for diagnosing MS early in the disease course. Although some caution may be exercised in the interpretation given the short follow-up (CDMS at 1 year) and the possibility that some of the excluded patients may later on turn to be MS, the paper by Zipoli, et al., serves to emphasize the importance of performing a CSF examination, especially when the clinical or MRI assessments reveal atypical features for MS. Therefore, this work supports the well-established common sense approach: when there are doubts about diagnosis, please perform a CSF tap.

References