

CSF analysis in the 2010 revised McDonald's MS diagnostic criteria

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Review

CSF analysis in the 2010 revised McDonald's MS diagnostic criteria

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The 2010 revised McDonald criteria for the diagnosis of multiple sclerosis (MS)¹ have altered the place of cerebrospinal fluid (CSF) analysis in relapsing cases. In the 2005 criteria it was possible to reduce magnetic resonance imaging (MRI) requirements if CSF was positive. By incorporating the MAGNIMS data, MRI requirements have now been liberalised, and so further reduction of imaging criteria using CSF analysis is, quite rightly, no longer appropriate. However, CSF analysis remains important in the diagnosis of primary progressive multiple sclerosis, or further investigation of atypical neuroinflammatory disease.

With respect to CSF analysis, we would like to point out that an essential revision to the McDonald criteria has been inadvertently omitted. The 2005 McDonald criteria had equated the presence of oligoclonal bands to an elevated immunoglobulin (IgG) index.² Subsequently, a widely accepted "gold standard" for CSF analysis was set out by Freedman et al, 2005, an International Consensus of CSF experts in MS and CSF diagnostic techniques.³ In summary, it was recognized that quantitative IgG analysis is an informative complementary test but should not be considered a substitute for qualitative IgG assessment, which has the highest sensitivity and specificity. Moreover, amongst the measures of intrathecal IgG synthesis, the IgG index is notoriously unreliable in view of its linearity. The IgG index is calculated by dividing the IgG CSF/serum quotient by the albumin CSF/serum quotient, and thus incorrectly assumes a linear relationship between the two quotients. Estimations of intrathecal IgG synthesis which take into account the nonlinear relationship between the IgG and albumin CSF/serum quotients, such as the Reiber-Felgenhauer hyperbolic equation⁴, are more accurate^{3,5}. Indeed, it is frequent to encounter cases of elevated IgG index in the absence of oligoclonal bands, which "correct" on applying hyperbolic equations. Thus application of the IgG index as a marker of "positive CSF" can result in an erroneous diagnosis of primary progressive MS.

The incorporation of the 2005 consensus on CSF analysis into the 2010 revision of the McDonald criteria is natural. Although its omission would be considered as an unintended error by many MS experts, this may not be the case for all neurologists and neurology trainees. Moreover, the message to diagnostic laboratories around the world needs to remain unchanged: (1) oligoclonal bands are the mainstay of diagnosis (2) quantitative measures of intrathecal IgG synthesis are only complementary, and when performed, should be reported using nonlinear equations as opposed to the linear IgG index. Hence, if the authors agree, we strongly recommend the timely publication of an addendum.

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References:

1. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol* 2011;69(2):292-302.
2. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005;58(6):840-6.
3. Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. *Arch Neurol* 2005;62(6):865-70.
4. Reiber H. Cerebrospinal fluid--physiology, analysis and interpretation of protein patterns for diagnosis of neurological diseases. *Mult Scler* 1998;4(3):99-107.
5. Andersson M, Alvarez-Cermeño J, Bernardi G, et al. Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. *J Neurol Neurosurg Psychiatry* 1994;57(8):897-902.