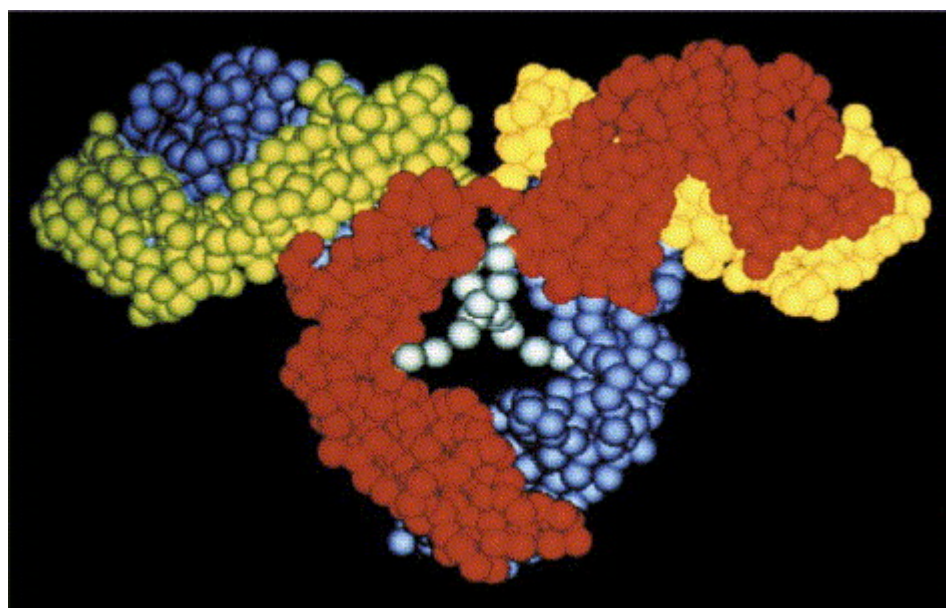


CSF Testing for Multiple Sclerosis

Michael P. Pender

Neuroimmunology Research Centre, School of Medicine, The University of Queensland, and Department of Neurology, Royal Brisbane & Women's Hospital, Herston, Queensland, Australia

New diagnostic criteria for multiple sclerosis (MS) were published in 2001 by McDonald and colleagues.¹ These criteria take account of the clinical features, brain and spinal-cord MRI findings, CSF findings, and visual evoked-potential studies. The McDonald criteria define rigorous MRI requirements but do not define an optimum CSF test for the diagnosis of MS. CSF testing should be optimised, because, in the McDonald criteria, a positive CSF study is an essential diagnostic criterion in patients who have objective clinical evidence of only one lesion and only a few MRI lesions, and it is a mandatory criterion for the diagnosis of primary progressive MS.¹ The rationale underpinning the use of CSF testing is the determination of whether there is synthesis of immunoglobulin G (IgG) in the CNS compartment (intrathecal synthesis). This indicates expansion of B cells in the CNS and is a characteristic feature of MS. In the McDonald criteria, a positive CSF study is defined as one showing either oligoclonal IgG bands or a high IgG index, which are two different indicators of intrathecal IgG synthesis. These indicators differ in sensitivity and specificity, and there are also differences in the techniques of CSF analysis.



Oligoclonal IgG in the CSF is a diagnostic feature of multiple sclerosis.

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To assess and recommend the type of CSF analysis that is optimum for a diagnosis of MS, the Consortium of Multiple Sclerosis Clinics commissioned a study group that included individuals who had considerable expertise in CSF analysis, the diagnosis and management of patients with MS, or both. The result is a recently published helpful consensus statement recommending a standard of CSF analysis in the diagnosis of MS.² The consensus group recommend that the gold standard should be qualitative assessment of paired CSF and serum samples for the detection of oligoclonal IgG bands that are present in the CSF but not the serum by use of isoelectric focusing and some form of immunodetection (immunoblotting or immunofixation). The recommendation is based on their conclusion that this method is more

sensitive and specific than quantitative IgG analytic methods, such as the IgG index. This difference results from fundamental differences in the way the two techniques distinguish normal from abnormal. In quantitative analysis, each patient is compared with a large population and, hence, a wide reference range of blood-derived proteins in CSF, whereas in qualitative analysis each patient's CSF IgG pattern is compared with his or her own serum sample.

Freedman and coauthors² recommend that consideration be given to repeating the lumbar puncture and CSF analysis if the clinical suspicion is high and if the CSF results are equivocal, negative, or show only a single band.² They also recommend that other components of the CSF analysis, such as the cell count, protein, glucose and lactate concentrations, should also be considered in the diagnosis of MS. One area worthy of further study is the usefulness of a high CSF leucocyte count and of leucocyte phenotyping in the diagnosis of MS. High CSF leucocyte counts, which are indicative of CNS inflammation and can occur in the absence of detectable oligoclonal IgG bands, have become undervalued in the differentiation of MS from non-inflammatory CNS disorders.

Whereas the sensitivity for detecting oligoclonal IgG banding with isoelectric focusing and immunodetection is high (~90%) in relapsing-remitting MS, it seems to be substantially lower in primary-progressive MS. Furthermore, it is often difficult to be sure about the diagnosis of primary-progressive MS unless the CSF shows intrathecal synthesis of IgG, a fact recognised by the mandatory requirement of the McDonald criteria for a positive CSF study for this diagnosis.¹ There have been no large studies with isoelectric focusing and immunodetection to compare relapsing-remitting MS and clinically diagnosed primary-progressive MS, but one small study found a sensitivity of 85% in relapsing-remitting MS and only 58% in chronic-progressive MS, although the researchers did not clarify whether the progressive group comprised only patients with primary-progressive disease or whether it also included those with secondary-progressive MS.³

A fundamental topic of debate is the pathogenetic significance of the oligoclonal IgG bands in the CSF: whether each individual band is monoclonal or not is unknown. However, analysis of immunoglobulin heavy-chain variable-region genes has shown monoclonal B-cell expansion in the CSF of patients with MS.⁴ The monoclonal expansion of B cells in the CNS in MS and in the target organs of other chronic autoimmune diseases, such as Sjögren's syndrome and autoimmune thyroiditis, may be due to infection of these B cells by the Epstein-Barr virus, and the infected B cells might produce pathogenic autoantibodies and promote survival of autoreactive T cells in the target organ.⁵ The new consensus statement on CSF analysis² is a step forward in optimising and standardising the diagnosis of MS.

I have no conflicts of interest.

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