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Review article

Analyses of cerebrospinal fluid in the diagnosis and monitoring of multiple sclerosis

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ABSTRACT

The laboratory evaluation of cerebrospinal fluid (CSF) has been routinely employed as a diagnostic test in the diagnosis of neuroimmunological disorders such as multiple sclerosis (MS). Recently, CSF analyses in MS have garnered renewed interest as a tool for monitoring disease activity and prognosis. With the identification of patients that are very early in their disease course, namely patients with a radiologically isolated (RIS) or a clinically isolated syndrome (CIS), the true value of these evaluations has yet to be fully explored. Ultimately, the hope is that biomarkers within this compartment will be identified that will identify etiologic factors of MS and other inflammatory disorders of the central nervous system.
In this review we discuss the history of CSF diagnostic tests and the most recent methodological advances. We also outline the potentially important diagnostic role and possible limitations of these tests.
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Contents

1. History and general considerations

In late nineteenth century, Heinrich Irenaüs Quincke and Heinrich Georg Queckenstedt developed methods of sampling and studying cerebrospinal fluid (CSF) (Murray, 2005). CSF sampling was initially developed for therapeutic purposes in the treatment of hydrocephalus, but shortly became a very useful diagnostic test for infections and other disorders.

The first to report a CSF abnormality in multiple sclerosis (MS) was Hinton (1922), when he noticed that patients with MS and syphilis had an abnormal protein precipitation. The most characteristic change was visible with colloidal gold test; however, the test was found to be variable and non-specific, and its applicability soon faded.

In 1939, Lange modified the Pandy colloidal gold gel test by controlling the pH and the size of the colloidal particles (Lange, 1946).

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The result of the new modification was the "Lange *D* curve", which provided a greater sensitivity and specificity for colloidal particles in the CSF of patients with MS. Using Pandy's method, Merritt (Friedman and Merritt, 1982) evaluated the CSF of a large MS cohort and found that the original colloidal gold gel test was abnormal in 33% of patients, the Lange *D* curves were abnormal in 73% of patients and gamma globulin was elevated in about 91% of affected individuals.

Kabat et al. (1942) introduced the new technique of electrophoresis. Kabat in 1954, and Melvin Yahr in 1957, established the diagnostic value of CSF quantitative studies of gamma globulins of MS and other diseases (Yahr and Kabat, 1957–1958). Oligoclonal bands (OCBs), immunoglobulins present in CSF but not the serum of MS patients, were first described by EC Laterre in 1964 using gel electrophoresis (Laterre et al., 1970). Agarose gel electrophoresis (AGE) to detect OCBs became widely utilized in the late 1970s (Link and Huang, 2006). Currently, the most sensitive method to detect IgG OCBs is isoelectric focusing (IEF) followed by immunoblotting (Keren, 2003; Fortini et al., 2003; Reiber et al., 1998).

OCBs were first incorporated as a paraclinical test in the diagnostic criteria for MS by Charles Poser in 1983 (Poser et al., 1983). While the presence of OCBs is not required to establish a diagnosis of MS, the diagnosis can be facilitated in certain circumstances (s. below) (Tumani et al., 2009). In addition, OCBs have been utilized for the purpose of enrolling patients with primary progressive MS (PPMS) into clinical trials (Wolinsky et al., 2007). Not surprisingly, they also included in the new diagnostic criteria, McDonald criteria, in 2001 (McDonald et al., 2001) and in the 2005 revision (Polman et al., 2005). In these criteria, a positive CSF refers to OCBs and IgG index.

In addition to establishing a diagnosis of MS, CSF has historically been a very attractive tissue source for neuroimmunologists. OCBs are immunoglobulins (IgG, IgM, or IgA) that are generated by plasmablasts and plasma cells in the CSF or CNS compartment. In chronic infections of the CNS, the OCBs are directed against the causative agent. Therefore, identifying the molecular target of OCBs in patients with MS may provide clues to the pathogenesis of this disorder. However, it is also conceivable that OCBs are a product of the disease that may not reflect on prognosis or therapeutic effect.

2. Oligoclonal banding: current methodology

AGE and IEF are two methodologies currently employed for the detection of CSF OCBs. The sensitivity of AGE for the detection of OCBs in MS CSF varies from 47% to 77% (Luque and Jaffe, 2007a). Paired CSF and serum are electrophoresed on high-resolution agarose and stained for protein to identify unique CSF protein bands in the γ region. A positive test is considered 2 or more bands in the γ region of the CSF that do not appear in the serum. Unfortunately, considerable inconsistencies in commercial agarose gel plates and the insensitivity of protein staining have limited the sensitivity of this technique for OCB detection.

The sensitivity of IEF for the detection of OCBs in MS CSF exceeds 95% (Keren, 2003; Fortini et al., 2003; Reiber et al., 1998). IEF separates proteins according to their isoelectric point (Reiber et al., 1998). It is typically performed using polyacrylamide or agarose as a supporting medium. Agarose is preferred because it is non-toxic, and easy to store and handle. Following IEF, IgG is identified by immunostaining. The number of OCBs detected by IEF is usually higher than 10 and significantly greater than AGE. The visualization of OCBs is improved with IEF, since the OCBs are sharper and contrast easily from the background. Whichever procedure is used, standardization is very important and positive and negative control samples need to be run in parallel on every plate. Due to high sensitivity and reproducibility, IEF is now the preferred technique in detecting OCBs.

3. Oligoclonal bands in multiple sclerosis: roles in diagnosis, prognosis, and monitoring of disease activity

The diagnosis of MS is ultimately a clinical decision that does not require laboratory tests if neurologic dysfunction in time and space can be established, and alternative diagnoses excluded. However, CSF analysis is extremely helpful in patients with an atypical clinical presentation, age of onset, or magnetic resonance imaging (MRI) (Merra, 1984). It is also of paramount importance to exclude some infectious and inflammatory mimics (Herndon, 2006). For this particular purpose, CSF studies are undertaking routinely in some European countries.

Diagnostic CSF findings in MS patients include qualitative IgG oligoclonal banding and the quantitative IgG index (Mayringer et al., 2005). Two or more OCBs detected by separation of CSF proteins while not demonstrable in corresponding serum reflect a local B-cell response and define the positive IgG OCBs in MS (Link and Huang, 2006).

Despite its high sensitivity, IgG OCBs are not specific for MS. OCBs can be seen in a myriad of inflammatory and non-inflammatory disorders (Table 1) (Psimaras et al., 2009; West et al., 1995; Joseph and Scolding, 2009; Sharief et al., 1991; Delalande et al., 2004; Honnorat et al., 2001; Takahashi et al., 1994; Caudie et al., 2003; Hall et al., 1992; Hall et al., 1992; Sakuta et al., 1990; Mavra et al., 1999; Shi et al., 2007; Tsementzis et al., 1986; Cohen et al., 2000; Olsen et al., 1995; Thompson, 1995; O'Brien et al., 1996). Consequently, a positive laboratory test for OCBs has a high negative predictive value (NPP) and a low positive predictive value (PPV), making it a sensitive screening tool but not a diagnostic one (Kraemer, 1992). OCBs may also have a prognostic value in MS. Joseph et al. (2009) reported that patients with negative OCBs had a more benign prognosis than those that were OCB positive. However, their observation was recently challenged by Siritho and Freedman in April 2009 (Siritho and Freedman, 2009) who observed no difference between OCBs-positive and OCBs-negative patients. Perhaps the pattern and specificity of OCBs may provide additional clues with regard to the prognosis of individual patients. In a recent study, IgM against myelin lipids were

Table 1
Conditions associated with CSF OCBs other than MS.

Autoimmune
Paraneoplastic disorders (5–25%) (Psimaras et al., 2009)
Systemic lupus erythematosus (30–50%) (West et al., 1995)
Neurosarcoidosis (40–70%) (Joseph and Scolding, 2009)
Neuro-Behçet's disease (20–50%) (Sharief et al., 1991)
Neuro-Sjögren syndrome (75–90%) (Delalande et al., 2004)
Anti-glutamic acid decarboxylase antibody syndromes (40–70%) (Honnorat et al., 2001)
Steroid-responsive encephalopathy (Hashimoto encephalopathy) (25–35%) (Takahashi et al., 1994)
Vogt–Koyanagi–Harada syndrome (uveomeningoencephalitis) (30–60%) (Thompson, 1995)
Subacute sclerosing panencephalitis (100%) (Thompson, 1995)
Infectious
Neurosyphilis (90–95%) (Caudie et al., 2003)
Neuroborreliosis (80–90%) (Bednárova, 2006)
Human immunodeficiency virus (HIV) infection (60–80%) (Hall et al., 1992)
Meningitis (5–50%) (Sakuta et al., 1990)
Rubella encephalitis (100%) (Thompson, 1995)
Structural lesions
CNS masses and structural lesions (<5%) (Mavra et al., 1999)
CNS vascular disorders (5–25%) (Shi et al., 2007; Tsementzis et al., 1986; Cohen et al., 2000)
Hereditary
Ataxia telangiectasia (50–60%) (Thompson, 1995)
Adrenaoleukodystrophy(encephalitic) (100%) (O'Brien et al., 1996)
Leber's hereditary optic atrophy (5–15%) (Olsen et al., 1995)