36.1. Introduction

Summary:
- In patients with intrathecal immunoglobulin synthesis, κ FLC concentrations in cerebrospinal fluid are typically high, whilst λ FLC concentrations are only moderately elevated.
- It is preferable to calculate a κ FLC index by correcting for FLC diffusion into the CSF.
- An elevated κ FLC index can support a diagnosis of multiple sclerosis.
- An elevated κ FLC index has been found more diagnostically sensitive than oligoclonal band detection.

Inflammation of the central nervous system (CNS) may be caused by infections (e.g. viral encephalitis, cerebral malaria) or autoimmune disorders such as Guillain-Barré syndrome or, notably, multiple sclerosis (MS). When inflammation of the CNS occurs, there is usually synthesis of intrathecal immunoglobulins [1]. Since the blood-brain barrier largely prevents their escape into the blood, the immunoglobulins gradually accumulate in the cerebrospinal fluid (CSF). They are then detectable as oligoclonal bands (OCB) on electrophoretic gels or can be quantitated using protein assays.

When determining the clinical relevance of OCB, CSF samples should always be assessed alongside paired serum samples to determine whether the immunoglobulin was synthesised locally within the CSF or has diffused from the blood [2]. The presence of two or more additional OCB in the CSF that are not present in the serum reliably indicates intrathecal immunoglobulin synthesis [3]. However, if the patient’s serum contains monoclonal immunoglobulins produced in the bone marrow, some will cross the blood-brain barrier, making interpretation of intrathecal production difficult [2]. Similarly, if there is inflammation of the meninges, serum proteins will enter the CSF more readily. The gold standard for detection of OCB is isoelectric focusing (IEF), followed by immunoblotting [2]. However, this protocol is non-quantitative, time-consuming, and interpretation may be difficult; consequently, it is not always routinely available.

Alternatively, quantitative IgG analysis may be used as a measure of intrathecal immunoglobulin synthesis. To ensure that measurements represent local (intrathecal) synthesis and not IgG which has diffused from the blood, values are corrected using albumin measurements. This serves as a marker of the blood-CSF barrier function because albumin is never synthesised within the CNS. For
example, the IgG index is calculated using the IgG and Albumin quotients (Q) as follows: $Q_{IgG/Alb} = [IgG_{CSF}/IgG_{serum}]/[Albumin_{CSF}/Albumin_{serum}]$. Alternative non-linear formulae improve the diagnostic accuracy of IgG measurements and are recommended [2]. However, in general, quantitative IgG analysis will only identify around 75% of OCB positive patients [2]. Consequently, there is a need for alternative, sensitive tests to identify intrathecal immunoglobulin synthesis.

Immunoglobulin free light chains (FLCs) are typically secreted along with intact immunoglobulins from plasma cells (Section 3.4). If they are produced intrathecally, they should accumulate locally and significant diffusion from the blood is unlikely as serum concentrations are low due to rapid renal clearance (Section 3.5). For these reasons, the measurement of FLCs in CSF is a potentially sensitive marker of intrathecal immunoglobulin synthesis and it has been investigated a number of times using various assay techniques (Section 36.2).

36.1.1. Multiple sclerosis and intrathecal immunoglobulin synthesis

The majority of the studies exploring the measurement of FLCs as an alternative marker of intrathecal immunoglobulin synthesis have focused on MS.

MS is an autoimmune inflammatory disease of the CNS, characterised by myelin loss, axonal pathology, and progressive neurologic dysfunction [4]. The majority of patients will first present with what is termed a clinically isolated syndrome (CIS): a single episode of symptoms and objective findings, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, lasting at least 24 hours [3]. Over a period of 20 years, about 60% of CIS patients will suffer a second demyelinating event and progress to a diagnosis of clinically definite MS [5]. The diagnosis of MS relies on the integration of clinical, magnetic resonance imaging (MRI) and laboratory findings to demonstrate that damage to the CNS is disseminated in both time (DIT) and space (DIS) [3]. The latest revisions to international MS diagnostic guidelines (the 2017 McDonald criteria) place a strong emphasis on CSF examination, particularly when clinical and MRI evidence is insufficient to confirm a diagnosis of MS [3]. When patients present with a typical CIS, but clinical or MRI findings only demonstrate DIS, the detection of CSF-specific OCB allows a diagnosis of MS to be made. The impact of the 2017 McDonald criteria was assessed in a retrospective study by Beesley et al. [6]. They concluded that the revised criteria allow earlier diagnosis of MS, without affecting diagnostic accuracy. In another study by van der Vuurst de Vries et al. [7], it was reported that the 2017 McDonald criteria had greater sensitivity but lower specificity for a second attack than the 2010 criteria. The new MS diagnostic guidelines enable identification of more patients with less active disease course.

Next
36.2. CSF FLCs as a marker of intrathecal immunoglobulin synthesis
References


