Kappa Free Light Chain Index in the Diagnosis of Multiple Sclerosis

Adoption of the kappa free light chain index can enhance diagnostic accuracy and reduce latency in multiple sclerosis diagnosis, complementing MRI and expert assessment in clinical decision-making.

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Early and accurate diagnosis is essential for optimizing outcomes in individuals with multiple sclerosis (MS).[1] Since 1965, diagnostic criteria have guided clinicians in identifying MS.[2] The Schumacher criteria (1965) established the fundamental requirement of demonstrating dissemination of attacks in space and time, but relied solely on clinical evidence. At that time, advanced imaging techniques (eg, MRI), laboratory-based paraclinical tests to supplement clinical assessment, and cerebrospinal fluid (CSF) biomarker tests were either undeveloped or unavailable. This historical reliance on clinical criteria highlights the ongoing need for objective biomarkers to improve diagnostic accuracy and reduce diagnostic delays in MS.

Subsequent revisions of MS diagnostic criteria incorporated validated advances in imaging and laboratory biomarkers, enabling earlier and more accurate diagnosis by improving sensitivity without compromising specificity. As the Schumacher criteria evolved through the Poser criteria (1983) to the McDonald criteria (2001 onwards), objective paraclinical measures, particularly MRI, were progressively integrated. Key benchmarks included the incorporation of MRI findings into the 2001 McDonald criteria,[3] and the 2017 McDonald criteria updates which allowed CSF-specific oligoclonal bands (OCBs) to satisfy the dissemination in time criterion for individuals with a typical clinically isolated syndrome (CIS) and clinical or MRI demonstration of dissemination in space.[4]

Current Diagnostic Criteria

In 2024, the International Advisory Committee on Clinical Trials in Multiple Sclerosis (IACCTMS) established revised McDonald diagnostic criteria for MS.[5] Key revisions included recognizing the optic nerve as a qualifying site of central nervous system (CNS) involvement in the assessment of dissemination in space and incorporating advanced MRI radiomarkers—such as the central vein sign (CVS) (a feature seen on MRI that helps distinguish MS lesions) and paramagnetic rim lesions (PRLs) (chronic active lesions with a characteristic MRI appearance)—to support diagnostic confidence. The IACCTMS also recognized the CSF kappa free light chain (κFLC) index as an alternative marker of intrathecal inflammation to satisfy the "*positive CSF*" criterion (ie, evidence of immune activity within the CNS) in the demonstration of dissemination in time. The 2024 McDonald criteria state that advanced MRI and laboratory markers should augment, rather than replace, expert clinical assessment.

Practicing neurologists should be aware of these newly established criteria to enhance diagnostic accuracy and reduce the time between MS disease onset and diagnosis. This article focuses on the 2024 McDonald criteria's affirmation of the κFLC index as a substitute for OCBs in supporting an MS diagnosis. The κFLC index offers comparable sensitivity and specificity with improved automation and quantitative objectivity. Although OCBs are a well-established biomarker in the field of neurology, κFLCs and the κFLC index are newer metrics in neurology, with limited literature and little formal training available. This overview introduces and reviews κFLCs and the κFLC index, highlighting their mechanisms, diagnostic performance, and clinical applicability in the diagnosis of MS. For a review of novel MRI radiomarkers, see the article in this issue by Elfasi and Fagundo.

CSF-Restricted OCBs

CSF-restricted OCBs have served as the gold standard laboratory marker of intrathecal humoral immune activa-

TABLE. COMPARISON OF CSF BIOMARKERS FOR MS DIAGNOSIS

Biomarker	What it Measures	Advantages	Limitations	Diagnostic Performance
OCBs	Presence of CSF-restricted IgG bands showing intrathecal synthesis	Historical gold standard; widely available; high specificity	Manual interpretation; interlaboratory variability; labor-intensive; limited automation	Sensitivity and specificity ~85% to ~95% depending on cohort
κFLC (absolute CSF concentration)	Quantitative κ light chains reflecting intrathecal immunoglobulin production	Rapid, automated, objective; reproducible across platforms	Must be interpreted relative to serum κFLC and albumin when used diagnostically	Sensitivity ~85% to ~90%, specificity ~85% to ~95%
κFLC index	Ratio adjusting CSF κFLC for serum κFLC and CSF/serum albumin	Best-validated quantitative κFLC measure; strong correlation with OCB; incorporated into 2024 McDonald criteria	Requires paired serum sample; optimal cutoffs vary slightly by assay	Noninferior to OCBs; AUC ~0.90 to ~0.95 across cohorts

Abbreviations: AUC, area under the receiver operating characteristic curve; CSF, cerebrospinal fluid; IgG, immunoglobulin G; κFLC, kappa free light chain; MS, multiple sclerosis; OCB, oligoclonal band.

tion for decades and remain deeply familiar to practicing neurologists. Their value derives from the demonstration of compartmentalized CNS immunoglobulin synthesis of foundational relevance in demyelinating disease and their consistently demonstrated high sensitivity. CSF-restricted OCBs are present in ~85% to ~95% of individuals with clinically definite MS, with meta-analytic estimates of ~88% sensitivity and ~92% specificity for MS or CIS vs controls without inflammation. In CIS cohorts, the presence of ≥2 CSF-restricted OCBs yields a sensitivity of ~90%, specificity of ~94%, positive predictive value of ~97%, and negative predictive value of ~84% for subsequent development of MS, although estimates vary across studies and meta-analyses.[6,7]

Although widely used, traditional CSF OCBs have limitations in standardization, turnaround time, and interpretation. OCB detection requires isoelectric focusing coupled with immunoblotting, a method that is limited to laboratories with special expertise because it is technically complex, labor-intensive, and subject to interlaboratory variability.[8]

CSF-restricted OCBs result from intrathecal immunoglobulin synthesis by activated B cells and clonally expanded plasma cells that have migrated across the blood–brain barrier (BBB). Within the CNS, plasma cells produce both fully assembled immunoglobulins and free light chains (FLCs). During immunoglobulin G (IgG) synthesis, heavy and light chains are produced independently in the rough endoplasmic reticulum and then assembled to form a complete immunoglobulin molecule composed of 2 heavy chains and 2 light chains.[9] The assembled immunoglobulin molecules are transported out of the cell via secretory vesicles. Light chains are produced in an estimated 20% to 40% molar excess compared with heavy chains.[10] The surplus light chains that are not incorporated into complete immunoglobulin molecules remain unpaired and are secreted as FLCs. Among these, κFLCs are more abundant than lambda FLCs and are more easily measured. The key takeaway is that activated plasma cells act as antibody assembly factories, producing both fully assembled immunoglobulins and FLCs.

κFLC Measurement in CSF

Interest in measuring κFLCs in CSF emerged as researchers recognized that quantitative measurement of free immunoglobulin light chains could serve as an objective, scalable biomarker of intrathecal inflammation, analogous in significance to oligoclonal IgG detection. κFLC measurement uses automated platforms providing rapid quantification and improved interlaboratory standardization compared with the subjective interpretation of OCB gels.[11] κFLC measurement can be conducted in hospitals and institutions where OCB determinations are unavailable with cost-effective platforms that return quantifiable and rater-independent results.[5]

History

Early experimental work on FLC biology dates to the mid-20th century in the hematologic and immunopathologic literature. Application of FLC biology to neurologic disease evolved more gradually, gaining traction as analytical technology improved and clinical immunology assays matured. Early laboratory methods could not reliably distinguish κFLCs from κ-light chains that were part of a complete antibody because the 2 forms share almost all the same protein sequences. A breakthrough occurred when scientists used monoclonal antibody technology based on hybridoma methods to create laboratory antibodies that could bind only to κ-light chains that were not attached to heavy chains.[12] This gave researchers the ability to selectively measure free κ-light chains, which

are meaningful markers of active antibody production in the CSF of individuals with MS.

Laboratory Studies

Once these specific monoclonal antibodies were developed, they could be used in automated laboratory instruments to measure κFLCs quantitatively in both serum and CSF. The principle is straightforward. The monoclonal antibodies are mixed with the sample. If κFLCs are present, the antibodies bind to them and form tiny immune complexes. These complexes cause the liquid specimen sample to become slightly cloudy, or to scatter light, measured as turbidimetry or nephelometry, respectively.

Turbidimetry and Nephelometry

Turbidimetry measures how much light transmission is blocked by cloudiness caused by the antigen–antibody complexes that have formed in the specimen under study. The degree of turbidity is associated with κFLC concentration. Nephelometry measures how much light is scattered by the immune complexes, with the amount of scatter proportional to the κFLC concentration in solution. Both technologies enable standardized, high-throughput, clinical-grade testing, making κFLCs suitable for integration into routine diagnostic workflows. Both methods allow κFLC levels to be obtained quickly, automatically, and reproducibly. This allows more reliable quantification of FLCs than earlier qualitative electrophoretic methods.

With these innovations, κFLC assays transitioned from research settings into clinical immunology laboratories. Turbidimetry and nephelometry technologies are now well established and widely available in clinical laboratories and larger hospital laboratories. For the fortunate clinician whose laboratory offers both technologies, nephelometry may be better suited for CSF antibody measurement due to higher sensitivity, lower detection limits, and better analytic performance at clinically relevant concentrations.[13] Measuring turbidimetry is easier and less expensive with easy automation in high-throughput clinical laboratories. Turbidimetry is more commonly used for higher-concentration immunoglobulins and serum testing.[14] However, the 2024 McDonald criteria updates do not specify a preferred technology for the assessment of CSF κFLC index.

Diagnostic Accuracy of κFLCs vs OCBs

Intrathecal synthesis of κFLC can yield different readouts. These include raw CSF κFLC concentration, κFLC index, intrathecal κFLC fraction, and κFLC quotient. A more robust body of evidence supports the use of absolute CSF κFLC concentration and the κFLC index, demonstrating diagnostic accuracy that is comparable in sensitivity and specificity to oligoclonal bands (OCBs).

κFLC Concentration

κFLCs in CSF measured as raw CSF κFLC concentration are typically reported in units of mg/dL. Advantages to measuring a fixed CSF κFLC concentration value include obviating the need for concurrent serum testing, standardizing quantitative measurement, eliminating human error, and reducing cost and turnaround time compared with standard OCB testing. A simple CSF κFLC cutoff of 0.1 mg/dL has performed moderately well as a practical OCB alternative in some small studies.[15] Saadeh and colleagues[16] compared CSF κFLCs and OCBs in a validating prospective cohort that used a cutoff κFLC value of 0.1 mg/dL. Study results provided Class 1 evidence that a κFLC value >0.1 mg/dL was a valid alternative to OCB testing, with sensitivities ~79% and specificities of 87% to 89%, somewhat lower than the sensitivity and specificity associated with the κFLC index.

Although an elevated CSF κFLC concentration can be caused by intrathecal immunoglobulin synthesis, it can also be caused by passive diffusion from serum in cases where the BBB is leaky. Measuring CSF κFLC concentration alone cannot differentiate between these 2 potential sources. This introduces the risk of false-positive elevations in cases of disrupted BBB integrity.

κFLC Index

The κFLC index, analogous to the CSF IgG index for detecting intrathecal immunoglobulin synthesis, adjusts the CSF κFLC value by comparing it with both serum κFLC levels and the albumin quotient (QAlb), which reflects the permeability of the blood–CSF barrier. The CSF κFLC index accounts for CSF κFLC concentration, serum κFLC concentration (estimating how much might be entering from blood), and the QAlb, which acts as a surrogate marker of blood–CSF barrier permeability because albumin is not produced in the CNS. This assessment helps distinguish true antibody production inside the CNS (intrathecal synthesis) from κFLC molecules that have passively leaked in from the blood, making it a more accurate marker for MS-related immune activity. The κFLC index normalizes the CSF value and provides a measurement that more accurately reflects true intrathecal κFLC synthesis, the key pathologic process in MS.

The formula used to calculate the κFLC index is as follows (all units measured in mg/dL):

$$\text{κFLC index} = \frac{(\text{CSF κFLC})}{(\text{serum κFLC})} \div \frac{(\text{CSF albumin})}{(\text{serum albumin})}$$

or equivalently:

$$\text{κFLC index} = \frac{(\text{CSF κFLC/serum κFLC})}{(\text{CSF albumin/serum albumin})}$$

- CSF κFLC is measured using nephelometry or turbidimetry.
- Serum κFLC is measured using the same assay method.
- CSF albumin/serum albumin forms the QAlb.
- The κFLC index is unitless because all measurement units cancel out.

The 2024 McDonald criteria recommends a κFLC index cutoff value of 6.1 to denote a positive result.

CSF κFLC Index Evidence

During the 2000s and early 2010s, multiple studies demonstrated that the CSF κFLC index, which normalizes CSF values to serum and CSF albumin to account for BBB permeability, produced diagnostic performance comparable with CSF OCBs in MS cohorts.[5] Comparative and meta-analytic data indicate that the κFLC index achieves higher area under the receiver operating characteristic curve and better reflects true intrathecal production, especially when the blood–CSF barrier is disturbed. Most comparative data favor the κFLC index over raw CSF κFLC concentration for diagnostic accuracy in MS.[17-19] Recent expert consensus therefore recommends the κFLC index as the preferred readout, with isolated CSF κFLC measurement serving as a pragmatic, method-independent screening tool. The CSF κFLC index is the metric recommended by the 2024 McDonald criteria for the diagnosis of MS.[5]

In a multicenter study involving 174 participants with primary progressive MS (PPMS), Hegen and colleagues[20] found that the κFLC index demonstrated a diagnostic sensitivity of 93%, comparable to the 88% sensitivity of OCBs in this population. Although interpretation of OCBs is rater-dependent and the study focused specifically on individuals with PPMS, these findings provide evidence that the κFLC index can serve as a reliable alternative to OCB testing in diagnosing PPMS using a cutoff of 6.1.

Conclusion

The κFLC index is recognized as a quantifiable, automated, potentially more standardized biomarker than OCBs. Its growing adoption reflects an effort to combine diagnostic accuracy with pragmatic laboratory implementation, especially in settings seeking objective and scalable testing.

The 2024 revision of the McDonald criteria formally incorporates the κFLC index as an acceptable measure of positive CSF, based on evidence that κFLC measurement offers diagnostic performance comparable to OCB measurement with improved standardization. The IACCTMS affirms that the κFLC index is an appropriate paraclinical test for MS diagnosis and can be regarded as interchangeable with CSF-unique OCBs. However, the κFLC index should always be interpreted in the context of clinical and MRI findings. Barriers such as the need for widespread training in κFLC index testing and potential resistance to changing established diagnostic protocols may limit the adoption of this biomarker in some clinical settings. ■

1. Tobin WO. Early diagnosis and treatment are associated with improved outcomes in patients with multiple sclerosis. Neurology. 2021;97(17):799–800. doi:10.1212/WNL.0000000000012738
2. Schumacher GA, Beebe G, Kibler RF, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis. Ann N Y Acad Sci. 1965;122:552–568. doi:10.1111/j.1749-6632.1965.tb20235.x
3. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol. 2001;50(1):121–127. doi:10.1002/ana.1032. doi:10.1002/ana.1032
4. Thompson AJ, Banwell BL, Barkhof F, et al; International Panel on Diagnosis of Multiple Sclerosis. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–173. doi:10.1016/S1474-4422(17)30470-2
5. Montalban X, Lebrun-Frénay C, Oh J, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria [erratum 2025;24(11):e13]. Lancet Neurol. 2025;24(10):850–865. doi:10.1016/S1474-4422(25)00270-4
6. Marcus JF, Waubant E. Updates on clinically isolated syndrome and diagnostic criteria for multiple sclerosis. Curr Neurol Neurosci Rep. 2013;13(12):408. doi:10.1007/s11910-013-0408-x
7. Dobson R, Ramagopalan S, Davis A, Giovannoni G. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. J Neurol Neurosurg Psychiatry. 2013;84(8):909–914. doi:10.1136/jnnp-2012-304695
8. Higgins V, Chen Y, Freedman MS, et al. A review of laboratory practices for CSF oligoclonal banding and associated tests. Crit Rev Clin Lab Sci. 2025;62(5):363–385. doi:10.1080/10408363.2025.2490166
9. Kaloff CR, Haas IG, Boyd J, et al. Coordination of immunoglobulin chain folding and chain assembly is essential for the formation of functional IgG. Immunity. 1995;2(6):589–599. doi:10.1016/1074-7613(95)90007-1
10. Laskov R, Scharff MD. Synthesis, assembly, and secretion of myeloma proteins. J Exp Med. 1970;131(3):515–534. doi:10.1084/jem.131.3.515
11. Presslauer S, Milosavljevic D, Huebl W, et al. Kappa free light chains: diagnostic and prognostic relevance in MS and CIS. PLoS One. 2014;9(2):e89945. doi:10.1371/journal.pone.0089945
12. Dispenzieri A, Katzmann JA, Kyle RA, et al. Immunoglobulin free light chain assay and polyclonal free light chains. Clin Chem Lab Med. 2016;54(6):907–919. doi:10.1515/cclm-2015-0862
13. Tumani H, Teunissen C, Süssmuth SD, et al. Clinical relevance of CSF protein analysis. Clin Chem Lab Med. 2014;52(5):631–646.
14. Akçay F, Keleş MS, Kiziltunç A. Evaluation of serum IgG, IgA, IgM and C3 values by nephelometric methods. Erciyes Med J. 1998;20(4):260–265.
15. Presslauer S, Milosavljevic D, Huebl W, et al. Validation of kappa free light chains as a diagnostic biomarker in multiple sclerosis and clinically isolated syndrome: a longitudinal study. Mult Scler. 2016;22(14):1789–1797. doi:10.1177/1352458515594044
16. Saadeh RS, Bryant SC, McKeon A, et al. CSF kappa free light chains: cutoff validation for diagnosing multiple sclerosis. Mayo Clin Proc. 2022;97(4):738–751. doi:10.1016/j.mayocp.2021.09.014
17. Hegen H, Freedman MS, Sellebjerg F, et al. The kappa free light chain index in multiple sclerosis: International recommendations from an expert panel. Mult Scler. 2023;29(7):881–895. doi:10.1177/13524585231159107
18. Ferraro D, Franciotta D, Bedin R, et al. Kappa free light chains index in the differential diagnosis of multiple sclerosis and CNS inflammatory diseases. Sci Rep. 2020;10(1):20329. doi:10.1038/s41598-020-77240-5
19. Hegen H, Arrambide G, Gnanapavan S, et al. Cerebrospinal fluid kappa free light chains for the diagnosis of multiple sclerosis: a consensus statement. Mult Scler. 2023;29(3):279–294. doi:10.1177/13524585221134217
20. Hegen H, Berek K, Cavalla P, et al. Diagnostic value of kappa free light chain index in patients with primary progressive multiple sclerosis: a multicentre study. Front Immunol. 2023;14:1327947.

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