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Review

Oligoclonal bands and kappa free light chains: Competing parameters or complementary biomarkers?

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ABSTRACT

Background: The 2024-revised McDonald criteria for multiple sclerosis (MS) proposed to incorporate cerebrospinal fluid (CSF)-specific oligoclonal bands and kappa free light chains (KFLC) as diagnostic biomarkers. While the 2017-revised criteria highlighted CSF-specific oligoclonal bands to indicate intrathecal IgG synthesis, significantly enhancing early MS diagnosis, KFLC have emerged as additional marker. Now, the question rises of whether both biomarkers serve as competing or complementary tools in MS diagnostics.

Methods: In this narrative review, we extensively searched the literature on oligoclonal bands and KFLC determination in CSF and serum across neurological disorders, with a focus on MS, using the PubMed database to demonstrate the complementarity of both biomarkers.

Results: Oligoclonal bands have long been a reliable marker of intrathecal IgG synthesis in MS, valued for their high diagnostic sensitivity, unique patient "fingerprints," clonality differentiation, semi-quantitative analysis, and pre-analytic robustness. However, they present challenges in standardization, labor-intensity, method variability, examiner dependency, and limited data on non-IgG immunoglobulins. Quantitative KFLC measurement provides rapid, examiner-independent, and cost-effective assessment across all immunoglobulin classes but might have lower specificity, lacked consensus on standardized interpretation in recent years, and is not yet supported by comprehensive prospective multinational studies on its prognostic role.

Conclusion: Both oligoclonal bands and KFLC have unique strengths and limitations that complement each other, potentially serving as complementary markers for evaluating intrathecal Ig synthesis in MS diagnosis. Further evidence is needed to establish the value of KFLC in MS diagnosis, thus multicenter prospective studies are being conducted to compare the diagnostic utility of both markers.

1. Introduction

At the recently held ECTRIMS congress (European committee for treatment and research in multiple sclerosis), the 2024 revised McDonald criteria for diagnosing multiple sclerosis (MS) were presented [1]. For CSF, oligoclonal bands and kappa free light chains (KFLC) were proposed as biomarkers to assess for an intrathecal immunoglobulin synthesis representing a chronic inflammatory state [1]. Comparing the 2017 and 2010 revisions of the McDonald criteria, incorporation of CSF-restricted oligoclonal bands as a substitute for the criterion of clinical or radiological dissemination in time led to earlier and more accurate MS diagnoses as well as considerable increase in definite MS diagnoses, particularly in patients with a first clinical demyelinating event, enabling timely initiation of immunotherapies [2–5]. However, there remains a significant lack of comparative studies assessing the roles of oligoclonal bands and KFLC in MS. This gap underscores the need for further research to clarify the relative diagnostic and prognostic value of these biomarkers in MS.

Oligoclonal bands are isoelectrically focused and subsequently stained immunoglobulin G (IgG) antibodies [6]. Detection of CSF-specific oligoclonal bands, i.e., presence of oligoclonal bands in CSF without corresponding bands in serum, currently serves as the gold standard for detecting intrathecal IgG synthesis [6]. Despite their high sensitivity to detect intrathecal IgG synthesis, oligoclonal bands are not free of weaknesses (semi-quantitative method, rater-dependency, varying sensitivity), thus the search for additional biomarkers indicating intrathecal inflammation has continued. Recently, free light chains have emerged as a promising candidate for detecting intrathecal Ig synthesis [7]. Free light chains exist in two isoforms, kappa (mostly monomeric) and lambda (mostly dimeric), and represent surrogate markers for plasma cell activity [7–9]. These free light chains are small molecules, which are produced in excess compared to intact Ig, leading to their presence in blood and CSF until they are excreted via urine resulting in a short half-life time [7–9]. The monomeric kappa isoform demonstrated very high sensitivity in detecting intrathecal Ig synthesis, making it the preferred parameter for analysis [7]. Two automated turbidimetric and nephelometric assays are available for quantifying concentrations of kappa free light chains (KFLC) in paired CSF and serum samples [7]. Several evaluation methods have been proposed to calculate intrathecal synthesis of KFLC [7]. Depending on the evaluation approach and the selected cut-off values, diagnostic sensitivities comparable to those of oligoclonal bands can be achieved [7]. Moreover, various pre-analytical factors - such as blood contamination of CSF, storage duration and conditions, and immunomodulatory acute therapies (e.g., intravenous methylprednisolone, plasmapheresis/immunoadsorption, intravenous immunoglobulins) - have been studied, highlighting the substantial robustness of KFLC [7]. Based on these promising results, testing for intrathecal KFLC synthesis is in the process of being incorporated into clinical practice. However, several questions remain unresolved. One particularly contentious issue is whether testing for intrathecal KFLC synthesis has the potential to replace oligoclonal band testing. The objective of this review is to evaluate the strengths and weaknesses of detecting oligoclonal bands and KFLC in MS and other neuroimmunological diseases, aiming to demonstrate the complementary value of applying both biomarkers.

2. Materials and methods

2.1. Search strategy

The data presented and discussed in this review were extracted from a comprehensive investigation of the NIH National Library of Medicine's PubMed.gov database (https://pubmed.ncbi.nlm.nih.gov/). The search terms used were "kappa free light chains AND multiple sclerosis", "oligoclonal bands AND multiple sclerosis", "kappa free light chains AND NMOSD", "kappa free light chains AND MOGAD", and "kappa free light chains AND autoimmune encephalitis". After reviewing over 400 retrieved articles, those with clear descriptions of patient cohorts, detailed explanations of the diagnostic methods used, and direct comparisons of both methods were included in this narrative review. Excluded publications were duplicates, those without specification of laboratory methods and unclear description of included patients.

A summary of key questions in given in Table 1.

3. Results and discussion

3.1. Oligoclonal bands

Oligoclonal bands, accepted as the current gold standard for detecting intrathecal IgG synthesis, were initially introduced in the 2017-revised McDonald criteria and subsequently also proposed as additional diagnostic criterion in the revision of 2024 [1,2]. Various methods are available to determine CSF-specific oligoclonal bands. In line with the recommendations from the 1994 consensus report, modern techniques primarily utilize isoelectric focusing in polyacrylamide gels or agarose to separate IgG in both CSF and serum [6]. This approach

Table 1
Key questions for determination of oligoclonal bands and kappa free light chains (KFLC) in the diagnosis of multiple sclerosis (MS).

Key questions	Ref.
1. **What do oligoclonal bands and KFLC detect?**	6, 10, 64
- Oligoclonal bands detect an intrathecal IgG synthesis, while KFLC reflect intrathecal synthesis of IgG, IgA, and IgM.	
- Oligoclonal bands testing provides (semi-)quantitative results, whereas KFLC testing yields quantitative results	
2. **How are oligoclonal bands and KFLC measured?**	6, 10–13, 17
- Oligoclonal bands are recommended to be detected by isoelectric focusing in polyacrylamide gels or agarose to separate IgG. After separation, patterns are visualized by silver staining, immunofixation, or immunoblotting. Low sample volumes (< 100 μl) are needed.	
- KFLC are automatically detected by nephelometry, turbidimetry, or ELISA. Depending on the assay and system, higher sample volumes are needed (> 100 μl).	
3. **Are there influencing factors on KFLC, and how do they affect KFLC concentrations?**	7, 30, 59-61, 63, 64, 90
- Patient-related factors might lead to lower KFLC indices and intrathecal fractions, such as renal dysfunction, age, and monoclonal gammopathies. The effect of sex is less clear, although higher concentration in females have been suggested.	
- Pre-analytical factors are rather negligible and appear to have no significant impact on KFLC concentrations. This includes a moderate blood contamination of CSF, storage duration up to 14 days by either room temperature or 4 °C, and the use of EDTA or serum tubes.	
- Immune-based therapies have varying effects on KFLC:	
- Decreased serum KFLC concentrations with intravenous methylprednisolone.	
- Reduced intrathecal fractions in MS patients treated with high-efficacy disease-modifying therapies compared to untreated patients.	
- No significant effect on KFLC concentrations observed with plasmapheresis, immunoadsorption, intravenous immunoglobulin (IVIG), or treatments like interferon β-1a, fingolimod, and alemtuzumab.	
4. **What is the role of oligoclonal bands and KFLC in the context of MS?**	1, 2, 7, 22, 23, 96–107
- Oligoclonal bands are a diagnostic criterion in both the 2017 and the proposed 2024 revisions of the McDonald criteria for MS, while KFLC are only considered in the proposed 2024-revised criteria.	
- Oligoclonal bands have a positive predictive value for the conversion of CIS to MS, whereas the prognostic role of KFLC is not yet fully established.	
5. **What are the strengths of oligoclonal band detection compared to KFLC measurement?**	6, 7, 31
- Oligoclonal bands are, depending on the detection method, more sensitive than KFLC in detecting an intrathecal IgG synthesis. They also present a unique pattern for each individual patient (a "fingerprint") and allow for the assessment of Ig clonality (poly-, oligo-, or monoclonal)	
6. **What are the strengths of KFLC measurement compared to oligoclonal band detection?**	7, 48, 49, 64, 69
- KFLC measurement is automated, providing fast, labor- and cost-effective results. It yields quantitative, rater-independent data and can be applied to other body fluids beyond CSF.	
7. **What are the main weaknesses of oligoclonal band and KFLC determination?**	6, 7, 17, 48, 49
- Oligoclonal bands require visual interpretation by specialized personnel, making the results rater-dependent. The determination is time- and cost-intensive, technically demanding, and the sensitivity can vary depending on the detection method.	
- KFLC interpretation lacks a fully standardized method despite existing consensus statements. Additionally, there is a lack of comprehensive prospective multicenter studies to thoroughly assess sensitivity and specificity in the diagnosis of MS.	
8. **Which biomarker should be determined in the diagnostic work-up?**	
- To reflect the complementary value of both biomarkers, university hospitals and tertiary care centers should perform both oligoclonal band detection and KFLC measurement in CSF and serum samples.	
- If the assessment of only one biomarker is available, the following algorithm is recommended:	
A) Oligoclonal bands, the standard for detecting intrathecal IgG synthesis in MS, should be performed in all patients.	
B) If oligoclonal bands are negative or yield borderline results, and there is a suspicion of inflammatory processes in the CNS, further testing with KFLC should be considered.	
C) KFLC may be used as an alternative when oligoclonal band detection is unavailable.	

provides the highest diagnostic sensitivity compared to alternative methods, support media, and separation matrices [6,10,11]. By employing this technique, IgG molecules with varying isoelectric points (approximately 6.5–9.0) can be effectively separated using a pH gradient in conjunction with an electric field [6,10]. After separation, the resulting IgG bands and banding patterns are visualized through techniques such as silver staining, immunofixation, or immunoblotting [12,13].

Oligoclonal band patterns are typically categorized into five different standard types [6]. Supplemental Fig. 1 illustrates the five different oligoclonal band patterns, utilizing an in-house method that employs polyacrylamide gels as the separation matrix followed by silver staining. Type 1 shows no oligoclonal bands in either CSF or serum and is typically observed in healthy individuals [6]. Type 2, which shows oligoclonal bands exclusively in the CSF, indicates pure intrathecal production of IgG. In contrast, type 3, characterized by additional identical oligoclonal bands in both serum and CSF, suggests systemic involvement [6]. Type 4, where identical bands are present in both serum and CSF, is predominantly observed in older patients [6]. This pattern is thought to reflect the patient's immunological history, likely due to past infections, with a passive diffusion of systemically produced antibodies [6]. The type 5 pattern indicates the presence of an IgG paraprotein and should prompt further investigation for conditions such as monoclonal gammopathy of unknown significance (MGUS) or myeloma [6]. Generally, oligoclonal bands are assessed based on the presence of intrathecal IgG synthesis (patterns 2 and 3) and are therefore commonly classified as a qualitative method. By identifying at least five different patterns and counting the absolute number of bands, semi-quantitative results can be obtained. A higher number of oligoclonal bands is associated with a more severe disease course in MS patients and a higher risk of conversion to definite MS in patients with clinically isolated syndrome [14,15].

The 2017 McDonald criteria recommend a cut-off of 2 CSF-restricted oligoclonal bands for a pathological test result when using standard assays [2]. Similarly, external proficiency tests for oligoclonal bands in Germany, such as those conducted by INSTAND, require at least 2 CSF-restricted bands for a CSF/serum sample pair to be interpreted as CSF-specific oligoclonal band positive [16]. Polyacrylamide gels with silver staining can resolve more than 50 bands over a distance of approximately 4.5 cm, enabling the discernment of 3–4 bands per millimeter. This capability provides superior sensitivity compared to standard assays. Consequently, in agreement with other experts in isoelectric focusing, weakly positive patterns (2–3 CSF-specific oligoclonal bands detected by silver staining after isoelectric focusing in polyacrylamide gels) are classified as borderline positive (type 2a or type 3a) [6,17,18]. The significance of a single CSF band still remains a manner of

discussion. There is evidence that a single CSF band is associated with diseases characterized by the involvement of intrathecal humoral immune responses and the finding of an intrathecal KFLC synthesis in such patients further supports the recommendation notion that this abnormality should be regularly reported, thus alerting clinicians of possible inflammatory disorders of the CNS [19–21]. However, in clinical daily routine a single band in CSF is often not considered significant and is not reported in most cases [6,17–21].

3.2. Strengths of oligoclonal band determination

The exceptional diagnostic sensitivity of CSF-specific oligoclonal bands in patients with MS, capable of detecting even low levels of intrathecal IgG synthesis, led to their re-implementation into the 2017 and 2024 diagnostic criteria for MS [1,2]. The prevalence of CSF-specific oligoclonal bands in MS patients was reported to be 90–99 %, whereby the range might be explained by the patient collectives included and the detection method employed [7]. Using detection methods such as separation in agarose gels followed by immunoblotting, oligoclonal bands are detected in 90–95 % of MS cases. The use of high-resolution polyacrylamide gels with subsequent silver staining allows for higher resolution of IgG antibodies. This technique facilitates the detection of up to 50 oligoclonal bands in individual samples, resulting in a detection rate of oligoclonal bands in 99 % of all MS patients [7,17]. Moreover, the presence of CSF-specific oligoclonal IgG bands has been identified as a prognostic factor for conversion to definite MS in individuals with a clinically isolated syndrome, demonstrating a remarkably high positive predictive value of 97 % (median time to conversion: 10–11 months; median follow-up time: 47 and 72 months) [3,22,23]. Given that the identification of CSF-specific oligoclonal IgG bands is a characteristic hallmark in MS patients, the absence of oligoclonal bands in individuals presenting with expected clinical features should prompt consideration of alternative differential diagnoses, such as neuromyelitis optica spectrum disorders or MOG-antibody associated encephalomyelitis, and a careful reassessment to avoid potential misdiagnosis of MS [24,25]. In rare cases, oligoclonal bands may be absent at disease onset. In such situations, a follow-up lumbar puncture at a later time (e.g., a year later) may be considered [22,23]. However, there is evidence suggesting the existence of a permanent oligoclonal band-negative MS subtype (1–6 %), and these patients appear to differ immunogenetically from those with oligoclonal bands, particularly in terms of HLA-DRB1 genotypes [26].

Another strength of oligoclonal band determination is its stability against patient-related, treatment-related, and pre-analytical factors that could potentially influence results. Oligoclonal bands have been shown to remain stable even in the presence of moderate blood contamination in CSF as well as in the context of various treatments, such as plasma exchange or immunoadsorption, intravenous immunoglobulins, intravenous methylprednisolone, and various disease-modifying MS therapies [27–30].

A pivotal feature of the oligoclonal band pattern is its uniqueness to each individual patient, making it a characteristic, permanent “fingerprint” [31]. However, changes in this band pattern can occur in patients experiencing altered disease activity while undergoing immunomodulating treatments, especially highly effective immunotherapies [32,33]. In a phase II trial investigating rituximab in patients with RMS, a reduction of B and T cells in CSF and a change in the amount of CSF-specific oligoclonal bands (increase as well as decrease of band numbers) were reported [33]. Similarly, treatment with cladribine in 29 treatment-naive subjects with RMS resulted in the disappearance of oligoclonal bands in 55 % of the patients, compared to baseline testing where 100 % of the patients were positive for oligoclonal bands [34]. In a subset of MS patients treated with natalizumab, disappearance of CSF-specific oligoclonal bands occurred in 16–18 % of cases [35,36]. However, partial loss of bands and loss in intensity of bands have also been observed [35,36]. On the other hand, despite the promising therapeutic results of stem cell depletion in MS, oligoclonal bands persisted in 74 % of patients after 765 days and in 50 % after 1500 days [37]. The analysis of pre- and post-therapy patterns by side-by-side comparison of initial CSF and follow-up CSF samples would be of great interest as potential therapy response marker and could enable the use of oligoclonal bands to detect the influence of the therapy. This requires the simultaneous separation of the stored (deep-frozen) initial CSF with the follow-up sample [35].

Importantly, oligoclonal bands act as a safeguard against false-positive quantitative IgG synthesis, which can occur in specific situations, such as when CSF withdrawal is performed immediately after intravenous infusion of high volumes or 1–2 days after plasmapheresis, or when nephelometric or turbidimetric measurements of IgG result in falsely elevated IgG concentrations. In such cases, the absence of oligoclonal bands can help identify these inaccuracies, ensuring more accurate diagnostic outcomes.

3.3. Weaknesses of oligoclonal band determination

The main limitation of utilizing oligoclonal band determination in the diagnosis of MS arises from the existence of various detection methods with different levels of diagnostic sensitivity [7]. The proportion of MS patients meeting the clinical and radiological criteria for MS according to the 2017 McDonald criteria and identified as positive for oligoclonal bands varied distinctly depending on the detection method, ranging from 85 % to 100 % [7,38,39]. It has been noted that sites employing isoelectric focusing on polyacrylamide gels as opposed to agarose, and using silver staining rather than immunoblotting or immunofixation, tend to achieve higher diagnostic sensitivity [7]. This variation underscores the importance of method selection in the accurate detection of oligoclonal bands and, consequently, in the reliable diagnosis of MS. There is only one study that directly compared different methods for determining oligoclonal bands. In this study, three centers, each employing a distinct method of oligoclonal bands detection, conducted a small survey on the performance of immunoblotting using Helena® agarose gels, immunofixation using Sebia® agarose gels, and polyacrylamide gels (EDC) with silver staining [17]. The results revealed significant differences in the median number of detected oligoclonal bands: 16 for polyacrylamide gels, 7 for Sebia® gels, and 4 for Helena® gels [17]. Of the 23 patients analyzed who were oligoclonal bands positive by the silver staining, 6/23 (26 %) did not display CSF bands and were thus classified as negative using the Sebia® method [17]. By using the Helena® method, 6 out of 19 patients (32 %) did not display CSF bands and were thus classified as negative, but all 19 were positive by employing the silver staining [17]. This study underscored the substantial variability in the sensitivity of different oligoclonal bands determination methods, particularly in samples where accurate detection is most challenging (supplemental Fig. 2).

Beyond the method-dependent differences in sensitivity for separating different IgG clones, the interpretation of the test results during visual inspection can be rater-dependent. Depending on the rater’s experience and diligence, weaker bands may either be counted or overlooked, leading to potential variability in band counting [6,17,18,40]. Such variability can lead to false positive or negative findings in borderline cases. This problem tends to arise more frequently with immunofixed agarose gels, which often show a diffuse background or ambiguous bands, as well as discrepancies between the intensities of bands in serum and CSF [17]. In the case of immunoblots, the process can further complicate the accuracy of assessments; strong bands are enhanced, while faint bands are less efficiently transferred and may diminish in visibility over time [17]. Additionally, the formation of disturbing air bubbles during the preparation and processing of gels cannot be fully avoided, introducing another variable that can affect the clarity and interpretability of the results (which also has to be considered during nephelometric measurement of KFLC). These difficulties in interpretation leading to inter-center variability reinforce the

importance of networks of specialized laboratories that reciprocally interact and participate to external quality control schemes (such as INSTAND), for promoting quality and reliability of the results [16,40]. If the recently developed semi-automated nanoscale capillary electrophoresis methods might provide more robust and objective results, needs to be investigated in multicenter studies [41,42].

Another challenge with oligoclonal band determination is its limited scope when it comes to other body fluids and different immunoglobulin classes. Oligoclonal bands represent isoelectrically focused and subsequently stained IgG antibodies. Some authors have highlighted the determination of oligoclonal IgA and IgM bands [43–45]. However, these classes have a higher molecular weight (IgA as a dimer, IgM as a pentamer), which prevents their migration even in agarose gels. This necessitates manipulations, such as size reduction by breaking disulfide bonds, to allow for proper migration and analysis [43–45]. While not commonly used in routine clinical practice, oligoclonal IgM bands have been proposed as potential diagnostic and prognostic parameter [44,45]. They have been linked to accelerated conversion to clinically definite MS, more aggressive disease courses with more frequent relapses, and early increases in lesion burden and brain atrophy [44,45]. A few authors have attempted oligoclonal band determination in lacrimal fluid instead of CSF [46,47]. However, oligoclonal band detection in tears is no alternative because of a much lower prevalence of oligoclonal bands as compared to CSF, a high proportion of samples with insufficient material, and uncertainties about the origin of tear IgG [46,47].

An argument against the routine use of oligoclonal band determination in diagnostic procedures is the associated cost and the time required to obtain results. This process requires experienced personnel for determination, detection, and interpretation of results, making it a time-consuming task [7,48,49]. However, compared to the cost of treatment or non-treatment, such considerations deemed negligible.

3.4. Kappa free light chains

Similar to IgG, free light chains are produced by plasma cells and serve as surrogate markers for humoral inflammatory processes [7–9]. Free light chains are produced in excess compared to intact Ig, and as a result, they are released into both the peripheral blood and CSF, where they are termed “free” as opposed to integrated in the Ig molecule [7–9]. Due to the irreversible inactivation of one of the two light chain-encoding genes during B cell maturation, light chains exist in two forms: kappa (primarily monomeric) and lambda (primarily dimeric). These light chains are excreted by the kidneys, resulting in a short in vivo half-life of 2–6 h, in contrast to the half-life of IgG, which lasts several days [7–9]. KFLC has shown greater potential than LFLC in diagnosing neuroinflammatory conditions in several studies and is therefore the primary focus of this article. Although KFLC concentrations are simpler to assess and interpret compared to oligoclonal bands, the interpretation of results, particularly when values are borderline, should always be conducted in conjunction with other CSF data and performed by experts who possess specialized knowledge in CSF diagnostics.

3.5. Strengths of kappa free light chain measurement

KFLC measurement offers a quantitative assessment approach, with the immediate availability of results as greatest advantage (KFLC within minutes; oligoclonal bands within hours to days) [7]. Currently, KFLC concentrations are measured fully automated using nephelometry and turbidimetry, making their interpretation independent of the examiner [7]. In addition, commercially available ELISA assays may also be employed for measurement of KFLC [50]. The automated measurement process for KFLC contributes to a more cost-effective diagnostic approach compared to oligoclonal band determination [7,48,49].

Although oligoclonal bands and KFLC measurement differ in their approach, they have shown comparable diagnostic sensitivity in MS patients, dependent on how KFLC results are interpreted [7,51]. In MS patients diagnosed according to the 2017 McDonald criteria, KFLC results showed similar findings, across the utilization of different interpretation methods for KFLC (Reiber’s diagram, Presslauers function, KFLC indices between 2.9 and 9.4), various assay types (nephelometry, turbidimetry), and MS patients from different nations [7,52–55]. An intrathecal synthesis could be detected in 72 %–100 % of patients by KFLC determination and 85 %–100 % by oligoclonal bands detection [7,56,57]. Applying KFLC indices between 0.92 and 20, a diagnostic sensitivity and specificity of 87 % could be achieved [7,49,58]. In contrast, interpretation of KFLC concentrations in Reiber’s diagram using the hyperbolic function as reference lead to a diagnostic sensitivity of 97 % and specificity of 75 % in MS patients [7].

Another strength of KFLC determination is its robustness against various patient-related, treatment-related, and pre-analytical influencing factors. Second-line acute immunomodulatory treatments like intravenous immunoglobulins, plasmapheresis, or immunoadsorption, storage conditions (up to 14 days at 4 °C or room temperature; EDTA or serum tubes), moderately effective MS DMTs, and even blood contamination of CSF (up to 20,000 erythrocytes/μl) have not shown significant impacts on KFLC concentrations [7,30,59–64].

Comparative assessments of turbidimetric, nephelometric assays, and ELISA-based methods have shown a good overall correlation in KFLC concentrations [7,65,66]. Moreover, Natali et al. reported substantial concordance in pathological KFLC results, indicating minimal discordance when testing is conducted across different laboratories and using varying platforms/assays [67]. Dekeyser et al. reported similar results but proposed the employment of method-dependent cut-off values of the KFLC index for Binding Site and Siemens assays respectively [68]. The few influencing factors that have to be considered include elevated serum KFLC concentrations due to impaired renal function or monoclonal gammopathies, intravenous methylprednisolone therapy, highly effective disease-modifying therapies (DMTs) for MS, and a progressive MS disease course [27,30,59–64]. While the influence of sex and age on KFLC concentrations remains controversial, it is likely related to changes in renal function associated with these factors [7,60].

Additionally, the assessment of KFLC concentrations can be easily extended to other body fluids beyond CSF and serum, including lacrimal fluid, urine, and saliva [7,69]. However, studies investing KFLC in other body fluids partly reported conflicting results in terms of diagnostic utility or changes of concentrations under treatment [7].

Lastly, KFLC is a bystander product of the synthesis of all Ig classes, meaning that intrathecally synthesized KFLC potentially reflects not only IgG but also IgA and IgM synthesis [7,64]. Consequently, the assessment of KFLC provides a more comprehensive view of the extent of the humoral immune response in patients with MS. This makes KFLC assessment applicable not only to neurological disorders characterized by predominant intrathecal IgG synthesis, such as MS, but also to a broader range of central nervous system diseases that involve intrathecal immunoglobulin synthesis [7,70,71]. Nevertheless, this general reflection of an Ig synthesis of all classes might also be regarded as a weakness of KFLC, since the source of the KFLC synthesis (IgG, IgA, IgM) cannot be differentiated. A notable prevalence of pathological KFLC and especially LFLC results has been documented in patients with infectious CNS diseases, particularly in cases of neuroborreliosis [72,73]. However, literature on KFLC in infectious CNS but also other neuroinflammatory diseases such as NMOSD, MOGAD and autoimmune mediated encephalitis is still scarce. In terms of NMOSD and MOGAD, the few publications with relatively low numbers of included patients (NMOSD $n = 28$, MOGAD $n = 40$) reported similar rates of intrathecal KFLC synthesis and CSF-specific oligoclonal bands, which were significantly lower than in MS patients [74–78]. Intrathecal KFLC synthesis was detected in up to 56 % of NMOSD patients, compared to oligoclonal bands, which were found in 33 % of NMOSD patients [74,75]. Concerning autoimmune mediated encephalitis, there is currently only one

published work, which reported a similar diagnostic sensitivity of intrathecal KFLC synthesis and oligoclonal bands in patients with evidence pathognomonic antibodies (NMDA $n = 6$, LGI 1 n = 4, CASPR2, IgLON5, GAD65, GABA(a), DPPX, PNMA2, Anti-Yo, AGNA, VGCC each $n = 1$) [79]. Moreover, KFLC determination holds potential for application in patients with neurological involvement in rheumatological disorders, such as Neuro-Sjögren, which needs further investigation [69].

3.6. Weaknesses of kappa free light chain measurement

In recent years, the primary limitation of KFLC measurement has been the lack of consensus on standardized interpretation methods [7]. Since the initial assessments of KFLC concentrations in neurological conditions, various interpretation methods, each with different decision limits, have been proposed. These interpretation methods include absolute CSF KFLC concentrations, with cut-offs ranging from 0.103 mg/L to 7 mg/L; CSF/serum KFLC quotients, with cut-offs ranging from 4.9 to 30; the KFLC index, which is derived from the KFLC quotient divided by the albumin quotient, with thresholds ranging from 0.92 to 20; as well as linear and non-linear functions involving the CSF/serum albumin quotient (Q-Albumin) [7,50,51]. In the past few years the KFLC index was preferably employed due to the simple cut-off calculation, high reliability, and consideration of Q-Albumin as a surrogate parameter for blood-CSF barrier function [7,80,81]. Although a consensus statement recommended the usage of a KFLC index of 6.1, which was proposed for inclusion into the 2024 revision of the McDonald criteria, many other cut-off values for the KFLC index were still proposed and published with the most commonly assessed KFLC indices ranging around 6 [1,7,82–85]. However, linear cutoff values, like the KFLC index, do not account for the physiological non-linear diffusion of blood-derived proteins of varying sizes across an intact blood–CSF barrier. As a result, there has been an emergence of interpretation methods for KFLC concentrations that are more in line with physiological principles. Various authors have proposed utilizing Q-Albumin-dependent, predominantly non-linear functions to define a threshold that corresponds to the principles of diffusion [86–88].

In the first comparative studies, a range of commonly employed interpretation methods (including Reiber's KFLC diagram, Presslauer's non-linear function, Senel's linear function, and the linear KFLC index of 5.9) underwent evaluation within a real-world patient cohort comprising individuals with MS and clinically isolated syndrome [86–89]. The findings of the study indicated that Reiber's diagram is most accurate due to its superior diagnostic sensitivity and physiological alignment [89]. Furthermore, Reiber's diagrams have been widely accepted for detecting intrathecal IgA, IgG, and IgM for years. Accordingly, it could be expanded to include a fourth diagram for KFLC. Despite the acceptance for determining intrathecal IgG, IgA, and IgM synthesis, and the numerous recent studies confirming the appropriateness of Reiber's diagram for KFLC in MS patients, it has not yet been acknowledged as a standardized interpretation method for KFLC [20,30,57,59,74]. In addition, interpreting KFLC concentrations, high serum values, e.g. in patients with age-related renal dysfunction and monoclonal gammopathies should be considered since diagnostic sensitivity of quotient diagrams such as Reiber's diagram and indices is decreased [60,90]. Especially in the rare events of monoclonal gammopathies, the additional information of the monoclonality of IgG provided by oligoclonal band patterns cannot be assessed by KFLC determination [90].

An additional weakness of utilizing KFLC measurement for MS diagnosis is the lack of prospective multicenter studies [7]. To date, only a limited number of multicenter studies have been conducted [91–95]. These studies focused solely on assessing KFLC indices for diagnosing MS in patients with both MS and clinically isolated syndrome [91–95]. To establish a widely accepted interpretation method for KFLC concentrations, it will be necessary to conduct prospective, multicenter studies that also include the evaluation of Reiber's KFLC diagram not only evaluating MS patients but also patients suffering from other neurological disorders.

Lastly, the prognostic role of KFLC concentrations and their association with other parameters for disease activity is not entirely clear. There is a lack of consistency in the reports regarding the correlation between KFLC concentrations and MRI-based indicators of CNS inflammation [7,96,105]. Certain studies indicated significant correlations between increased CSF KFLC concentrations and factors such as brain atrophy, brain lesion patterns, or T2-lesion volume [7,98,100,101,105]. However, other studies have not found substantial associations between KFLC levels and brain damage as identified by MRI, including the localization and extent of MRI abnormalities [7]. Similarly, several studies have shown a significant correlation between elevated CSF KFLC concentrations and early disability, cognitive impairment, rapid disability progression, or an accelerated transition from clinically isolated syndrome to a confirmed MS diagnosis [7,98,100–107]. In contrast to these findings, other studies have not found such relationships [7,97,99].

The range of results reported could be due to the diversity of the studies themselves. These studies employed differing diagnostic criteria for MS (diagnostic criteria of 2005, 2010, 2017), various interpretation methods, and analyzed different parameters such as CSF KFLC concentration and KFLC index [7]. Moreover, the predominant approach of a retrospective analysis introduces the potential for selection bias when enrolling patients. In addition, the inclusion of MS patients with different disease duration and disease-related disabilities, the limited number of investigated patients, and the short follow-up time might be other factors leading to the reported heterogeneous results.

In summary, the lack of consensus on KFLC interpretation methods in recent years, along with differing study approaches, has led to variable findings in its diagnostic and prognostic roles in MS. A significant challenge lies in the fact that the presently favored KFLC index method, although simple, does not fully reflect the physiological circumstances of CSF flow and diffusion. The ideal interpretation method for assessing intrathecal synthesis is represented by the Reiber's diagram, which has gained significant acceptance for determining intrathecal IgG, IgA, and IgM synthesis. However, the Reiber's diagram is not yet universally employed. Prospective multicenter studies are required to validate these approaches, and there remains uncertainty about the prognostic significance of KFLC.

3.7. Diagnostic specificity of oligoclonal bands and kappa free light chains

The use of oligoclonal bands as a biomarker for MS is often criticized due to their perceived lack of specificity. KFLC are no exception in this context and are expected to be even less specific than oligoclonal bands, as they include free light chains from other immunoglobulin classes, such as IgA and IgM, in addition to IgG [8,9]. However, the specificity of CSF-restricted oligoclonal bands as well as KFLC largely depends on the reference populations used. In one meta-analysis, a weighted average sensitivity of 88 % (52 %–100 %) and specificity of 89 % (69 %–100 %) intrathecal KFLC synthesis to identify patients with CIS and MS was reported [108]. Another meta-analysis demonstrated that CSF-specific oligoclonal bands have a specificity of 94 % for diagnosing MS compared to normal controls. However, this specificity drops to 61 % when other inflammatory and infectious diseases are considered [109]. It is widely recognized that humoral immune responses occur across a broad spectrum of infectious or inflammatory CNS disorders and certain autoimmune conditions, yet these are unlikely to be falsely diagnosed as MS [25,110]. Surprisingly, 5–10 % of symptomatic controls (without underlying neurological diseases) and patients with non-inflammatory neurological diseases exhibit oligoclonal bands [111]. Notably, in these cases, detection of oligoclonal bands with silver staining after isoelectric focusing revealed weakly positive patterns, with about 50 % displaying only 2–3 bands (classified as types 2a and 3a) [111]. In

apparently healthy controls only 3/82 (3.7 %) exhibited weakly positive oligoclonal band patterns with 4, 3, or 2 CSF-specific bands respectively [111]. This observation is in line with the separate designation of oligoclonal band patterns with only 2–3 bands as borderline positive (type 2a or 3a) [6,17,18]. The presence of clinically irrelevant oligoclonal bands may reflect a long-lasting sero-scar from former event, e.g. after subclinical (viral) CNS infections [111].

3.8. Evidence of oligoclonal bands and kappa free light chains in the diagnosis of MS

Oligoclonal bands are considered the gold standard for detection of an intrathecal IgG synthesis because 1) the method of determination is already established since the 1970ies, 2) oligoclonal bands are well-investigated in different patient collectives and conditions and 3) a consensus for the interpretation is existing already since the 1990ies [6]. Therefore, oligoclonal bands are not only considered in national guidelines but also international recommendations and diagnostic criteria for MS [1,2].

In contrast, few multicenter studies investigated KFLC to date and the recently revised McDonald criteria were the first guideline to consider both biomarkers, KFLC and oligoclonal bands, for inclusion [1,91–95]. However, a broader consensus on the interpretation of KFLC concentrations has yet to be established. Although there are mono- and bicentric studies emphasizing the superiority of Reiber's diagram in detecting intrathecal KFLC synthesis over other interpretation methods, firm evidence in form of large multicenter studies are missing.

In this context, different studies proposed two-step approaches involving both oligoclonal bands and KFLC to assess for an intrathecal immunoglobulin synthesis aiming to increase diagnostic specificity and reduce costs of laboratory analyses [112–114]. Given that CSF analysis is considered a relatively invasive procedure from the patient's perspective and is usually only performed once in the diagnostic work-up of MS, it can be argued that the maximum amount of information should be extracted from the obtained CSF sample. In the context of MS and its disease course, the cost of a one-time CSF analysis, including the assessment of an additional biomarker, appears negligible when compared to the expenses associated with annual MRI scans and ongoing treatment. To reflect the complementary diagnostic value of oligoclonal bands and KFLC testing in MS, the detection of both biomarkers, as outlined below, is recommended.

4. Conclusion

The determination of oligoclonal bands and KFLC may serve as complementary approaches to evaluate intrathecal Ig synthesis in individuals with MS. Both methods, oligoclonal bands and KFLC, come with their own methodological strengths and limitations that balance each other. Thus, both biomarkers should be considered "allies" rather than "rivals" suggesting the combined use of both for MS diagnosis (Fig. 1).

Presently, the German Society for Cerebrospinal Fluid Diagnostics and Clinical Neurochemistry (DGLN e.V.) suggests using the following algorithm for oligoclonal bands and KFLC in the diagnosis of MS until evidence for the respective interpretation method is provided through multicenter studies.

University hospitals and tertiary care centers should perform both the assessment of CSF-specific oligoclonal bands and the measurement of KFLC concentrations in CSF and serum samples. This should be done in analogy to the currently established methods for assessing intrathecal Ig synthesis, which include both quantitative approaches (IgG index, Reiber diagrams) and a qualitative approach (CSF-specific oligoclonal bands).

In case that either assessment of CSF-specific oligoclonal bands or KFLC concentration is not available, the following algorithm is recommended:

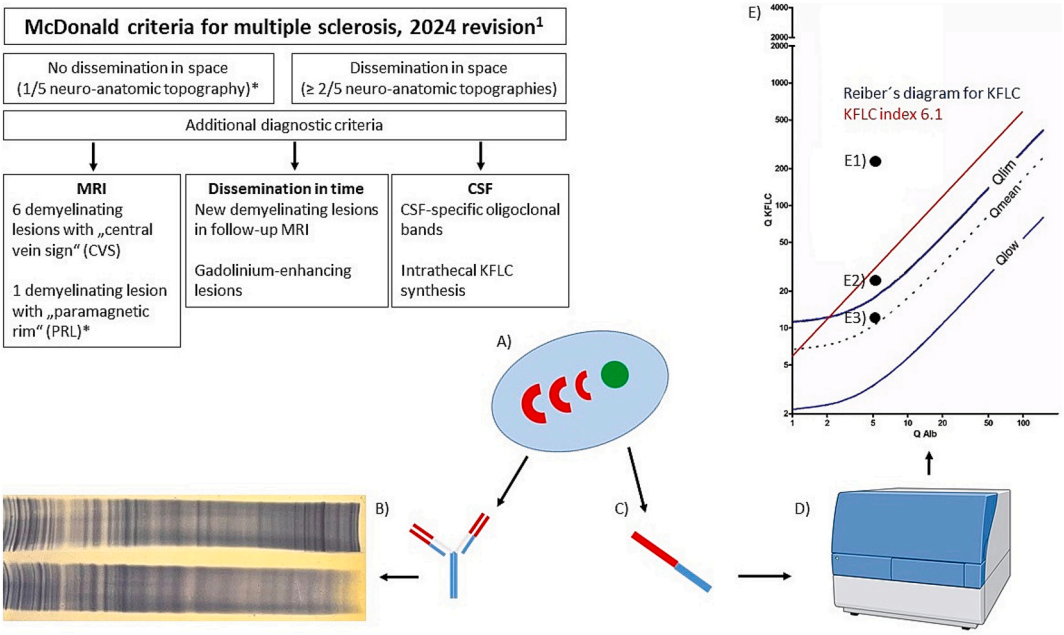

Fig. 1. Diagnostic significance of oligoclonal bands according to the proposed 2024 revision of the McDonald criteria.
The latest revision proposal of the 2024 McDonald criteria, presented at the ECTRIMS Congress, allows for diagnosing multiple sclerosis (MS) when the criteria for dissemination in space are fulfilled.[1] Evidence of intrathecal immunoglobulin (Ig) G synthesis by detection of oligoclonal bands or measurement of kappa free light chains (KFLC) serves as additional criterion to diagnose MS. Plasma cells (A) not only intrathecally synthesize intact IgG, which can be detected by oligoclonal bands (B), but also free light chains (FLC) of different isotypes (monomer = kappa (KFLC, C), dimer = lambda (LFLC), which might be used as surrogate for an intrathecal Ig synthesis. After automated measurement (D), quotient diagrams (e.g. Reiber diagrams) or the KFLC index are employed for interpretation (E). In Reiber's diagram, KFLC are either intrathecally synthesized (above "Qlim", E1 and E2) or diffused from the peripheral blood (between "Qlim" and "Qlow", E3). Some patients reveal intrathecal synthesis of KFLC according to Reiberdiagrams but not to the linear KFLC index (E2).

A) Oligoclonal bands, the standard for detecting intrathecal IgG synthesis in MS, should be performed in all patients.

B) If oligoclonal bands are negative or yield borderline results, and there is a suspicion of inflammatory processes in the CNS, further testing with KFLC should be considered.

C) KFLC may be used as an alternative when oligoclonal band detection is unavailable.

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