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ORIGINAL COMMUNICATION

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Elevated levels of kappa free light chains in CSF support the diagnosis of multiple sclerosis

Abstract *Background* Numerous studies have demonstrated elevated kappa free light chains (KFLCs) in CSF of multiple sclerosis (MS) patients. However, so far only small cohorts have been examined, and generally only through qualitative KFLCs analysis. Using a recently developed free light chain (FLC) immunoassay, it is now possible to quantitatively measure KFLCs by automated nephelometry. Our objective was to determine the extent to which KFLC levels in CSF correlated with the diagnosis of MS and CISSMS (clinically isolated syndrome suggestive of MS) compared to oligoclonal banding (OCB) and the immunoglobulin G (IgG) index. *Methods* CSF and serum samples from 438 unselected patients, including a MS group of 70 patients (41 MS, 29 CISSMS), were analysed using nephelometry and isoelectric focusing. We then retrospectively correlated results with patients' diagnoses. *Results* Of the MS group (n = 70), 67 patients had elevated KFLCs using the KFLC index (≥ 5.9), 64 patients showed OCB and 56 patients presented with an elevated IgG index (≥ 0.6). Sensitivities were 0.96 for the KFLC index, 0.91 for OCB and 0.80 for the IgG index. The specificity of the KFLC index for the MS group (0.86) was lower than that of OCB (0.92) but distinctly higher compared to the IgG index (0.77). *Conclusion* In this study, an elevated KFLC-index represented the most sensitive and specific quantitative diagnostic parameter for MS. As it is measured by automated, routinely available laboratory methods, KFLC quantitation can provide a rapid and reproduceable indication of intrathecal immunological processes supporting current MS diagnostic criteria.

Key words multiple sclerosis · CSF · oligoclonal IgG · kappa free light chain · kappa free light chain index

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The study was performed in accordance with the ethical standards.

Introduction

The diagnosis of MS or a CISSMS is a life-changing event for patients, generally followed by an expensive long-term therapy associated with numerous potential side effects. As several studies describe the benefits of early treatment, all possible effort should be taken to ensure both correct and early diagnosis [10, 15, 17]. To that end, different diagnostic criteria incorporating alterations to MRI and CSF examinations have been published over the years, the most recent and widely accepted being the McDonalds criteria [24] and their revised form [27]. However, recent studies investigating MRI criteria for MS show the limitations of this technique in equivocal MS cases [22, 26]. Therefore, it is imperative that other investigative procedures, such as CSF examination, are established for MS diagnosis.

Isoelectric focusing (IEF) on agarose gel followed by immunoblotting is the gold standard for OCB detection [1]. Recent studies show high diagnostic performance with reported sensitivities of > 95 % [18, 21, 25, 35] (although others report lower sensitivities of around 90 % [4, 9, 29]). Since the interpretation of a single weak band

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can be the difference between a 'positive' or 'negative' result, the evaluation of CSF immunoblots should be restricted to experienced specialists, and additional techniques are needed to assist OCB interpretation. This is particularly true since the diagnostic value of one single band in CSF remains unclear [5]. The McDonalds criteria accord an elevated IgG index the same diagnostic relevance as positive OCB. This has been widely criticised [12, 21] as a number of studies report sensitivities around 75 % or lower for the IgG index in diagnosing MS [1, 20]. Removal of the IgG index from the MS diagnostic algorithm has already been recommended [25].

The kappa free light chain (KFLC) may represent a useful marker for the diagnosis of MS. Plasma cells produce an excess of kappa and lambda light chains during the production of intact immunoglobulins and these are secreted as free light chains (FLCs). Due to the high fractional excretion and catabolism of the kidneys the half-life of FLCs in human serum is only a few hours. In the 1980s several study groups demonstrated KFLC levels in the CSF of MS patients [2, 6, 32, 33] and subsequently KFLC was identified as a potential marker for MS diagnosis [8, 12, 19, 30]. Results were reinforced by a study on OCB negative MS patients who displayed detectable KFLC levels in CSF [13]. In 2001, Bradwell et al. introduced a highly specific immunoassay for nephelometric or turbidimetric FLC quantitation [3]. Using this assay, different study groups have demonstrated a strong correlation of elevated KFLC levels in CSF with positive OCB and the diagnosis of MS in small cohorts [7, 11]. Our purpose was to evaluate the diagnostic performance of quantitative KFLC and LFLC measurement in CSF in a large cohort and to formulate a threshold value for the diagnosis of MS/CISSMS.

Methods

Patients

Between 2001 and 2006, CSF and serum samples were collected from 438 consecutive unselected patients who underwent a lumbar puncture. We reviewed the patients' records and established several diagnostic subgroups. The MS group consisted of 70 patients: 41 patients (37 relapsing remitting MS, 4 primary progressive MS) fulfilled the criteria of dissemination in space and time for diagnosis MS according to latest criteria [24, 27]; in none of these cases were the CSF results the decisive diagnostic criterium; 29 patients presented a clinical isolated syndrome with typical MRI alterations, but did not show a dissemination in time, and were classified as CISSMS. The remaining 368 patients presented with various neurological diseases, including other CNS inflammatory diseases. These were all summarized as single subgroups: meningitis/encephalitis (n = 41), Guillain-Barré syndrome (GBS) (n = 15), neuroborreliosis (n = 15) and chronic inflammatory demyelinating polyneuropathy (CIDP) (n = 7).The subgroup meningitis/encephalitis was characterized by typical clinical impression and significantly elevated cell count in CSF. A bacterial pathogen in CSF was detectable in 18 cases (9x streptococccus pneumoniae, 8x neisseria meningitidis, 1x mycobacterium tuberculosis); the isolation of viral antigens was successful in 4 cases (3x herpes simplex virus, 1× enterovirus). A further subgroup presenting no major clinical or paraclinical sign of inflammation was established to define reference ranges of KFLC and LFLC in CSF, and the KFLC index and the LFLC index: 56 patients underwent a lumbar puncture to allow either dementia exploration, exclusion of subarachnoidal bleeding or examination of suspected normal pressure hydrocephalus; 45 of these patients showed no sign of severe inflammation (leukocytes < 10000 cells/µl and CRP < 35 mg/l [threshold value 5 mg/l] in serum; IgG index < 0.6; normal cell count in CSF; albumin ratio < 0.06; body temperature < 37 °C) and were considered a control population for establishment of reference FLC levels in serum and CSF. In 192 patients CSF examination excluded a primary suspected intrathecal infection. Most represented diagnoses were peripheral facial palsy (n = 27), epileptic disorders (n = 33) and hemicrania or tension type headache (n = 31). All together 234 patients were not assigned to a special diagnosis-bound subgroup but were part of the non-MS group (n = 368) including all subgroups beside our MS group.

Sample collection and laboratory analyses

A cubital vein was punctured and 6 ml blood collected into a gel-containing standard tube (Vacuette tube, Greiner Bio-One, Kremsmünster, Austria) for analysis of routine chemistry, immunoglobulins and FLC. Another 4 ml blood was collected into a K_3-EDTA-containing tube (Greiner Bio-One) for a complete blood count. CSF was processed within 2 hours after lumbar puncture or stored at –80 °C until further examination.

Routine chemistry analyses were performed on a Hitachi 917 chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany), serum albumin and immunoglobulin concentrations were quantified using a Cobas Integra 700 (Roche Diagnostics) with reagents supplied by the analyzer's manufacturer. CSF albumin and immunoglobulin concentrations were determined by nephelometry on a Behring ProSpec (Dade-Behring, Marburg, Germany) using reagents supplied by the analyzer's manufacturer. The IgG index was calculated according to the following formula: (CSF IgG/serum IgG)/(CSF albumin/serum albumin). Detection of oligoclonal IgG banding was realized with isoelectric focussing on agarose gel on a Helena SPIFE 2000 automated electrophoresis system (Helena BioSciences Europe, Sunderland, UK) and subsequent immunoblotting using the Helena IgG IEF Kit (Helena BioSciences). In collaboration with other laboratories, our OCB detection unit participates in an external quality control for OCB with round trials twice a year. The complete blood count was performed on a Sysmex XE-2100 hematology analyzer (Sysmex-Toa, Kobe, Japan); CSF cell count was assessed microscopically using a Fuchs-Rosenthal chamber.

Both CSF and serum FLC concentrations were analyzed on a Behring ProSpec using the serum free light chain immunoassay (Freelite™, The Binding Site, Birmingham, UK) according to the manufacturer's instructions. When performing 20 replicate tests on polyclonal sera, the KFLC assay showed an intraassay CV of 7.9 % at 0.7 mg/l and an interassay CV of 8.7 % at 14 mg/l. For the LFLC assay the intraassay CV was 10 % at 0.9 mg/l and the interassay CV was 7 % at 32 mg/l [16]. Results were expressed as serum and CSF FLC concentrations, and as FLC indices determined by the following ratio: (CSF FLC/serum FLC)/(CSF albumin/serum albumin). In cases of FLC values below the detection limit we used the corresponding detection limit (KFLC: 0.06 mg/l and LFLC: 0.08 mg/l) for calculation.

Statistical analysis

Data are presented as medians and ranges. As confirmation that the different variables were normally distributed was not possible, comparisons between groups were assessed using non-parametric methods (the Kruskal–Wallis test and the Mann–Whitney U-test). A two-sided p-value less than 0.05 was considered to indicate statistical

difference. Receiver Operating Characteristics (ROC) curve analysis was used to describe the relative performance (sensitivity and specificity) of the parameters investigated. Statistical calculations were performed with Statistica for Windows 5.1 (Statsoft, Tulsa, OK, USA).

Results

In patients with normal pressure hydrocephalus, undefined dementia or a primary suspected but unconfirmed subarachnoidal bleeding and with no major clinical or paraclinical sign of inflammation (n = 45), we found low levels of both KFLC and LFLC in the CSF. Four samples had KFLC levels below the detection limit of the assay and six samples had LFLC levels below the detection limit of the assay. Serum FLC levels were within the published normal reference ranges [16], resulting in low KFLC and LFLC indices. Median FLC values in CSF in this control subgroup were 0.18 mg/l (0.13–0.22) for KFLC and 0.16 mg/l (0.13–0.2) for LFLC. Median values of 1.35 (0.94–2.21) for the KFLC index and 1.23 (0.91–1.54) for the LFLC index were determined (Table 1).

Highly elevated serum levels of KFLC and/or LFLC were found in two patients suffering from lymphoproliferative diseases (patient 1: serum: KFLC 453 mg/l, LFLC 114 mg/l; CSF: KFLC 2.14 mg/l, LFLC 0.68 mg/l; KFLC index: 0.62; LFLC index: 0.78; patient 2: serum: KFLC 60.9 mg/l, LFLC 31 mg/l; CSF: KFLC 1.53 mg/l, LFLC 1.03 mg/l; KFLC index 2.09, LFLC index 2.77). In sera of several patients with severe systemic inflammation, we detected moderately elevated levels of both KFLC and LFLC. All other patients, including the MS group, exhibited FLC levels in serum within or close to the published normal ranges of healthy donors [16]. Five patients presenting lymphoproliferative diseases affecting the CNS displayed extremely elevated FLC levels in CSF. Other patients with diseases not associated with CNS inflammation showed FLC levels in CSF comparable to those of the control group. Remarkably, a mild deterioration of the blood-CSF barrier (measured by albumin ratio) had no major influence on the FLC values in the CSF (data not shown).

In the CSF of the MS group, we typically found high elevated KFLC levels and moderately elevated LFLC levels. There was no major difference between patients with either definite MS or a CISSMS. Other diseases associated with intrathecal infection (meningitis/encephalitis, neuroborreliosis) and inflammatory diseases with typical CSF alterations (GBS, CIDP) generally showed moderate increases of both KFLC and LFLC levels in CSF (Table 1, Fig. 1).

As expected, most patients in the MS group had qualitatively detectable intrathecal IgG production, with 64/70 patients exhibiting OCB. For the non-MS group (n = 368), 30 patients displayed OCB, including patients with meningitis/encephalitis (n = 4) and neuroborreliosis (n = 7). Overall, OCB detection achieved a sensitivity of 0.91 and a specificity of 0.92 for diagnosing MS/CISSMS in this cohort (Table 2). The most common quantitative assessment of IgG production in CSF is the IgG index. We examined three different thresholds (≥0.6; ≥0.65; ≥0.7) to evaluate optimum diagnostic performance of the IgG index in our cohort. Lowest threshold of ≥0.6 did not exceed a sensitivity of 0.8 combined with a specificity of 0.77 (Table 2, Fig. 2).

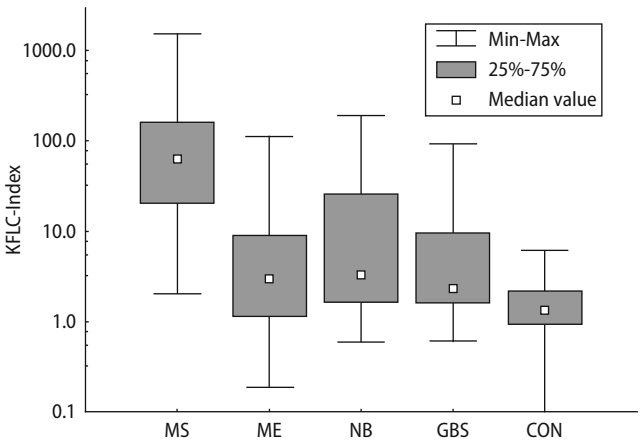

Fig. 1 Median values and ranges of KFLC index in different subgroups; *MS* MS subgroup; *ME* meningitis/encephalitis subgroup; *NB* neuroborreliosis subgroup; *GBS* Guillain-Barré syndrome subgroup; *CON* control subgroup

Table 1 Median values (lower quartile-upper quartile) of FLCs in CSF and FLC indices in different subgroups

	KFLC (mg/l) in CSF	LFLC (mg/l) in CSF	KFLC index	LFLC index
MS group (n = 70)	4.12 (1.4–8.77)	0.67 (0.25–1.54)	65.74 (22.25–159.42)	9.62 (4.27–37.25)
Definite MS (n = 41)	4.62 (1.41–10)	0.72 (0.29–1.46)	78.97 (19.58–189.39)	9.34 (4.49–29.24)
CISSMS (n = 29)	2.95 (1.39–8.65)	0.53 (0.24–1.57)	63.03 (29.91–95.19)	12.24 (3.31–42.3)
Control group (n = 45)	0.18 (0.13–0.22)	0.16 (0.13–0.2)	1.35 (0.94–2.21)	1.23 (0.91–1.54)
Encephalitis/meningitis (n = 41)	0.55 (0.32–1.27)	0.57 (0.27–1.27)	3.01 (1.13–9.03)	2.1 (1.07–5.27)
Guillain-Barré syndrome (n = 15)	0.8 (0.25–1.44)	0.35 (0.27–0.69)	2.33 (1.63–9.39)	1.88 (1.27–3.48)
Neuroborreliosis (n = 15)	0.59 (0.14–5.94)	0.82 (0.14–5.48)	3.3 (1.74–24.65)	2.19 (1.33–30.17)
CIDP (n = 7)	0.34 (0.22–2.03)	0.25 (0.22–0.43)	1.34 (1.1–8.09)	1.44 (1.02–2.03)

Table 2 Occurrence of positive OCB, elevated IgG indices (IgGI) and elevated KFLC indices (KI) and resulting sensitivity, specificity and positive and negative predictive values for the diagnosis MS/CISSMS using different thresholds

	All patients n = 438	MS group n = 70 (definite MS n = 41)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Positive OCB	94	64 (39)	0.91	0.92	0.68	0.98
IgGI ≥ 0.6	141	56 (33)	0.80	0.77	0.4	0.95
IgGI > 0.65	110	46 (27)	0.66	0.83	0.42	0.93
IgGI > 0.7	92	43 (26)	0.61	0.87	0.47	0.92
KI ≥ 5.9	117	67 (40)	0.96	0.86	0.58	0.99
KI > 20	80	54 (30)	0.77	0.93	0.68	0.96
KI > 50	46	42 (25)	0.60	0.99	0.91	0.93
KI > 200	11	11 (9)	0.16	1	1	0.86

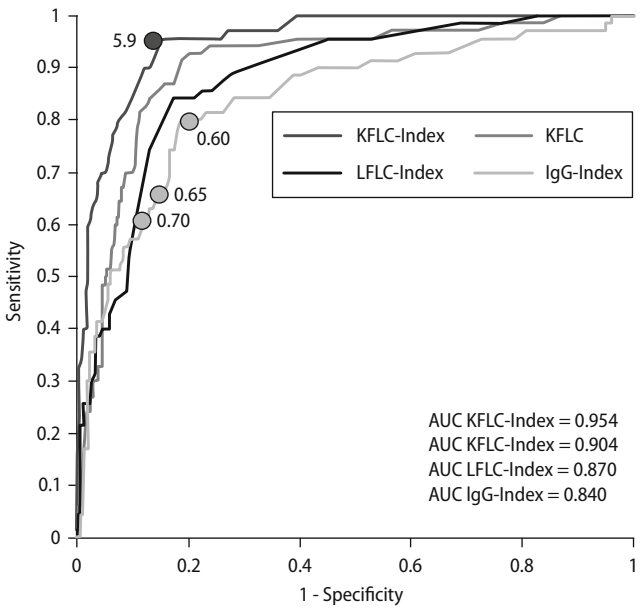

Fig. 2 Performance of KFLC index, KFLC, LFLC index and IgG index in MS/CISSMS diagnostics demonstrated as ROC curves and AUC values

We calculated KFLC and LFLC indices and compared these with results of common tests for intrathecal inflammation and with the original diagnoses. There was moderate correlation between LFLC-indices and OCB and the IgG index in our MS group. However, elevated KFLC indices correlated strongly with the diagnoses of definite MS or CISSMS. The best performing threshold value for MS diagnosis was a KFLC index ≥ 5.9 (Table 2, Fig. 2). This threshold value represents the lowest KFLC index of a MS patient with detectable intrathecal inflammation identified by positive OCB in our cohort. Within the MS group, KFLC indices ranged from 2.03–1514 (median 65.74). Only three patients (one definite MS, two CISSMS) exhibited a KFLC index < 5.9, combined with negative OCB and a normal IgG index (< 0.6). Three other patients from the MS group (one definite MS, two CISSMS) also had no OCB, but did present elevated KFLC indices (6.84; 9.29; 20.39). Using this threshold value (KFLC index ≥ 5.9) we observed a sensitivity of 0.96 and a specificity of 0.86 for diagnosing MS/CISSMS in our cohort (Table 2).

The KFLC index in our MS group was significantly higher than in all other subgroups investigated ($p < 0.001$). Furthermore the subgroups meningitis/encephalitis ($p = 0.003$), neuroborreliosis ($p = 0.001$) and GBS ($p = 0.009$) presented statistical significant higher KFLC index values compared to the control group, in contrast to the CIDP group ($p = 0.315$).

Positive OCB correlated strongly with KFLC index values ≥ 5.9. Out of 94 patients with detectable OCB, 84 presented with elevated KFLC indices. Eight patients who presented positive OCB but had KFLC index values below 5.9 had no clinical signs of intrathecal inflammation, one patient was suffering from meningitis and one patient from suspected myelitis. There was poor correlation between elevated IgG index and elevated KFLC index.

Furthermore we found no correlation between MS type (relapsing remitting MS, primary progressive MS), Expanded Disability Status Scale (EDSS) score at time of lumbar puncture, disease duration, or number or localization of MRI abnormalities and the value of KFLC or KFLC index in our cohort (data not shown).

Discussion

It has been known for decades that KFLC levels are elevated in the CSF of MS patients. Development of a sensitive immunoassay for serum or CSF FLC quantitation has allowed incorporation of FLC analysis into routine laboratory diagnostic algorithms. In this study we report FLC measurement as a reliable method for detection of intrathecal inflammation with high correlation between elevated KFLC-indices (≥ 5.9) and the diagnosis MS/CISSMS. Our results strongly suggest that the KFLC index should be determined together with OCB as part of the routine MS diagnostic algorithm. Additional LFLC

index determination can support the exclusion of alternative diagnoses.

Within the non-MS group (n = 368) we found 50 samples with elevated KFLC indices (≥ 5.9) resulting in a lower specificity for MS diagnosis compared to OCB. However, in our study most other diseases associated with a KFLC index rise are not likely to mimic the clinical symptoms of MS and often present with a parallel rise of the LFLC index. Beside MS/CISSMS, cases of meningitis/encephalitis (n = 18) were the most common diagnoses associated with KFLC indices ≥ 5.9 in our cohort (Fig. 1). Consideration of clinical indications together with other CSF analyses (including elevated LFLC and LFLC index) are likely to prevent misdiagnosis of MS in these patients. While increased KFLCs are suggestive of MS diagnosis, alternative diagnoses should be considered if these are associated with concurrent significant elevation of LFLC levels. A similar conclusion can be made with regard to other inflammatory diseases frequently associated with KFLC indices ≥ 5.9 such as neuroborreliosis, GBS and CIDP. Moreover, FLC analysis is quantitative, and measurement of the absolute FLC levels provides additional information. If the threshold of the KFLC index was adjusted to > 20, as proposed for MS diagnosis by Desplat-Jego et al. [7], specificity would rise to 0.93 but only 54/70 patients in the MS group would have exhibited pathological values (sensitivity of 0.77) in our cohort. Very high values of KFLC > 200 were only detectable in the MS group (n = 11). These findings demonstrate that very high values for the KFLC index correlate strongly with MS diagnosis. However, reliable identification of nearly all MS cases in our cohort was achieved using a threshold of 5.9, a level associated with an increased sensitivity of 0.96. In the absence of long-term studies, the interpretation of low, moderate or high elevation of FLC indices with respect to MS diagnosis is for individual clinicians to decide.

When alternatively selecting the highest KFLC index value of the control group (KFLC index of 6.18) as threshold value as proposed by Fragnart et al. [8], we achieve similar results: sensitivity of 0.94 and specificity of 0.88 for MS/CISSMS diagnostics.

Most patients in our cohort only underwent a single lumbar puncture. Therefore we do not have data on any fluctuation of CSF FLC levels over time, or on whether high KFLC indices predict future OCB. One patient with PPMS showed a stable KFLC index when puncture was repeated after 5 years (284.02 at time 0, 308.96 at 5 years). In suspected MS patients with ambiguous CSF results (e.g., no OCB but elevated KFLC index), it may well be useful to repeat CSF examination after a certain period of time.

Signs of intrathecal inflammation in the form of an elevated IgG index are a rare finding in GBS patients and detectable OCBs are untypical for this disease [23]. In our cohort out of 15 GBS – patients, two presented with OCB (performed twice), three had an elevated IgG index (≥ 0.6) and in seven patients we detected an elevated KFLC index. Studies on larger cohorts will be needed for a clear statement whether FLC quantitation is of clinical interest in these patients.

There was no CSF of a non-neurological control group available. However, our control group shows similar KFLC levels as presented by Fischer et al. [11] with values around the detection limit. A mild deterioration of the blood-brain barrier in 18 out of our 45 control patients (albumin ratio: 0.006 < n < 0.06) had no visible influence on the FLC values in CSF. It is unlikely that CSF of healthy volunteers contains higher amounts of FLCs and lower levels would not be reliably measurable with our detection method. The assays we use were established for FLC detection in serum and urine and little is known about their performance in FLC quantification in CSF especially for low FLC concentrations. Nevertheless we obtained reproducible results for FLC measurement in CSF and the relevant values of our MS group were distinctly above the quoted detection limits.

Beside HIV infection [14], MS/CISSMS is the only inflammatory disease reported to cause predominant elevation of one of the two FLCs in a body fluid. The reason for this phenomenon is still unknown. FLCs may have immunological functions [34] and the consequences of prolonged elevation of KFLC in CSF remain to be determined. Such investigations could deliver valuable information concerning the disease course of MS.

We had no patients with a HIV infection participating in our study, which could modify the specificity of the KFLC index.

We did not find a correlation between KFLC index values and the EDSS score at time of lumbar puncture in our cohort (data not shown), but we do not have long-term data. However, high KFLC levels in CSF were generally associated with positive OCB. MS patients with no OCB, who generally present a lower EDSS score displayed only moderately elevated KFLC indices (range 2.03–20.39, mean 7.25). It has been reported previously that patients with no or low humoral CSF abnormalities tend to have a benign MS characterized by a mild disease course [31, 36]. It is to be expected that low KFLC levels may be associated with less aggressive disease progression in MS, as a recent study showed [28]. The extent to which these results might influence future therapeutic strategies is not yet clear and should be subject of further studies.

Disclosure

The authors report no conflicts of interest.

References

1. Andersson M, Alvarez-Cermeño J, Bernardi G, Cogato I, Fredman P, Frederiksen J, Fredrikson S, Gallo P, Grimaldi LM, Grønning M, et al. (1994) Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. J Neurol Neurosurg Psychiatry 57: 897–902
2. Bracco F, Gallo P, Menna R, Battistin L, Tavolato B (1987) Free light chains in the CSF in multiple sclerosis. J Neurol 234:303–307
3. Bradwell AR, Carr-Smith HD, Mead GP, Tang LX, Showell PJ, Drayson MT, Drew R (2001) Highly sensitive, automated immunoassay for immunoglobulin free light chains in serum and urine. Clin Chem 47:673–680
4. Caudie C, Birouk AM, Bancel J, Claudy D, Gignoux L, Vukusic S, Confavreux C (2005) Cytoimmunological profile of cerebrospinal fluid in diagnosis of multiple sclerosis. Pathol Biol 53:68–74
5. Davies G, Keir G, Thompson EJ, Giovannoni G (2003) The clinical significance of an intrathecal monoclonal immunoglobulin band: a follow-up study. Neurology 60:1163–1166
6. DeCarli C, Menegus MA, Rudick RA (1987) Free light chains in multiple sclerosis and infections of the CNS. Neurology 37:1334–1338
7. Desplat-Jego S, Feuillet L, Pelletier J, Bernard D, Cherif AA, Boucraut J (2005) Quantification of immunoglobulin free light chains in cerebrospinal fluid by nephelometry. J Clin Immunol 25:338–345
8. Fagnart OC, Sindic CJ, Laterre C (1988) Free kappa and lambda light chain levels in the cerebrospinal fluid of patients with multiple sclerosis and other neurological diseases. J Neuroimmunol 19:119–32
9. Falip M, Tintore M, Jardi R, Duran I, Link H, Montalban X (2001) Clinical usefulness of oligoclonal bands. Rev Neurol 32:1120–1124
10. Filippi M, Rovaris M, Inglese M, Barkhof F, De Stefano N, Smith S, Comi G (2004) Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet 364: 1489–1496
11. Fischer C, Ameth B, Koehler J, Lotz J, Lackner KJ (2004) Kappa free light chains in cerebrospinal fluid as markers of intrathecal immunoglobulin synthesis. Clin Chem 50:1809–1813
12. Freedman MS, Thompson EJ, Deisenhammer F, Giovannoni G, Grimsley G, Keir G, Ohman S, Racke MK, Sharief M, Sindic CJ, Sellebjerg F, Tourtellotte WW (2005) Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. Arch Neurol 62: 865–870
13. Goffette S, Schluep M, Henry H, Duprez T, Sindic CJ (2004) Detection of oligoclonal free kappa chains in the absence of oligoclonal IgG in the CSF of patients with suspected multiple sclerosis. J Neurol Neurosurg Psychiatry 75:308–310
14. Grimaldi LM, Castagna A, Maimone D, Martino GV, Dolci A, Pristera R, Lazzarin A, Roos RP (1991) Kappa light chain predominance in serum and cerebrospinal fluid from human immunodeficiency virus type 1 (HIV-1)-infected patients. J Neuroimmunol 32:259–268
15. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW (2000) Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 343:898–904
16. Katzmann JA, Clark RJ, Abraham RS, Bryant S, Lymp JF, Bradwell AR, Kyle RA (2002) Serum reference intervals and diagnostic ranges for free kappa and free lambda immunoglobulin light chains: relative sensitivity for detection of monoclonal light chains. Clin Chem 48:1437–1444
17. Kinkel RP, Kollman C, O'Conner P, Murray TJ, Simon J, Arnold D, Bakshi R, Weinstock-Gutman B, Brod S, Cooper J, Duquette P, Eggenberger E, Felton W, Fox R, Freedman M, Galetta S, Goodman A, Guarnaccia J, Hashimoto S, Horowitz S, Javerbaum J, Kasper L, Kaufman M, Kerson L, Mass M, Rammohan K, Reiss M, Rolak L, Rose J, Scott T, Selhorst J, Shin R, Smith C, Stuart W, Thurston S, Wall M, CHAMPIONS Study Group (2006) IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology 66: 678–684
18. Kostulas VK, Link H, Lefvert AK (1987) Oligoclonal IgG bands in cerebrospinal fluid. Principles for demonstration and interpretation based on findings in 1114 neurological patients. Arch Neurol 44:1041–1044
19. Krakauer M, Schaldemose Nielsen H, Jensen J, Sellebjerg F (1998) Intrathecal synthesis of free immunoglobulin light chains in multiple sclerosis. Acta Neurol Scand 98:161–165
20. Lefvert AK, Link H (1985) IgG production within the central nervous system: a critical review of proposed formulae. Ann Neurol 17:13–20
21. Link H, Huang YM (2006) Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness. J Neuroimmunol 180:17–28
22. Masjuan J, Alvarez-Cermeño JC, García-Barragán N, Díaz-Sánchez M, Espiño M, Sádaba MC, González-Porqué P, Martínez San Millán J, Villar LM (2006) Clinically isolated syndromes: a new oligoclonal band test accurately predicts conversion to MS. Neurology 66:576–578
23. Mata S, Galli E, Amantini A, Pinto F, Sorbi S, Lolli F (2006) Anti-ganglioside antibodies and elevated CSF IgG levels in Guillain-Barré syndrome. Eur J Neurol 13:153–160
24. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 50: 121–127
25. McLean BN, Luxton RW, Thompson EJ (1990) A study of immunoglobulin G in the cerebrospinal fluid of 1007 patients with suspected neurological disease using isoelectric focusing and the Log IgG-Index. A comparison and diagnostic applications. Brain 113: 1269–1289
26. Nielsen JM, Korteweg T, Barkhof F, Uitdehaag BM, Polman CH (2005) Overdiagnosis of multiple sclerosis and magnetic resonance imaging criteria. Ann Neurol 58:781–783
27. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 58:840–846
28. Rinker JR 2nd, Trinkaus K, Cross AH (2006) Elevated CSF free kappa light chains correlate with disability prognosis in multiple sclerosis. Neurology 67:1288–1290

29. Rudick RA, Cookfair DL, Simonian NA, Ransohoff RM, Richert JR, Jacobs LD, Herndon RM, Salazar AM, Fischer JS, Granger CV, Goodkin DE, Simon JH, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Munchsauer FE, O'Reilly K, Priore RL, Whitham RH, et al. (1999) Cerebrospinal fluid abnormalities in a phase III trial of Avonex (IFNbeta-1a) for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. J Neuroimmunol 93: 8–14
30. Rudick RA, French CA, Breton D, Williams GW (1989) Relative diagnostic value of cerebrospinal fluid kappa chains in MS: comparison with other immunoglobulin tests. Neurology 39: 964–968
31. Rudick RA, Medendorp SV, Namey M, Boyle S, Fischer J (1995) Multiple sclerosis progression in a natural history study: predictive value of cerebrospinal fluid free kappa light chains. Mult Scler 1:150–155
32. Rudick RA, Pallant A, Bidlack JM, Herndon RM (1986) Free kappa light chains in multiple sclerosis spinal fluid. Ann Neurol 20:63–69
33. Rudick RA, Peter DR, Bidlack JM, Knutson DW (1985) Multiple sclerosis: free light chains in cerebrospinal fluid. Neurology 35:1443–1449
34. Van der Heijden M, Kraneveld A, Redegeld F (2006) Free immunoglobulin light chains as target in the treatment of chronic inflammatory diseases. Eur J Pharmacol 533:319–326
35. Villar LM, Masjuan J, Sádaba MC, González-Porqué P, Plaza J, Bootello A, Alvarez-Cermeño JC (2005) Early differential diagnosis of multiple sclerosis using a new oligoclonal band test. Arch Neurol 62:574–577
36. Zeman AZ, Kidd D, McLean BN, Kelly MA, Francis DA, Miller DH, Kendall BE, Rudge P, Thompson EJ, McDonald WI (1996) A study of oligoclonal band negative multiple sclerosis. J Neurol Neurosurg Psychiatry 60:27–30