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Research article

Serum and cerebrospinal kappa free light chains in psychiatric syndromes with neuronal and paraneoplastic autoantibodies

Luise M. Groeger [a,1], Kristina auf dem Brinke [b,1], Amina Simou [b], Daniel Luedecke [c], Hannah B. Maier [d], Alexandra Neyazi [e], Jürgen Gallinat [c], Stefan Bleich [d], Thomas Skripuletz [f], Franz F. Konen [f], Jens Wiltfang [a,g], Berend Malchow [a], Dirk Fitzner [b,1], Niels Hansen [a,1,*], CAP (Cerebrospinal Fluid Analysis in Psychiatry) consortium, FoNetPsy (Deutsches Forschungsnetz für Seelische Gesundheit e.V.)

[a] Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Germany
[b] Department of Neurology, University Medical Center Göttingen, Germany
[c] Department of Psychiatry and Psychotherapy, University Hospital Hamburg Eppendorf, Germany
[d] Department of Psychiatry, Hannover Medical School, Social Psychiatry and Psychotherapy, Germany
[e] Department of Psychiatry and Psychotherapy, University of Magdeburg, Germany
[f] Department of Neurology, Hannover Medical School, Germany
[g] German Center for Neurodegenerative Diseases, Göttingen, Germany

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ABSTRACT

Background: Kappa free light chains (KFLC) are a surrogate parameter for intrathecal immunoglobulin G (IgG), immunoglobulin M (IgM) and immunoglobulin A (IgA) synthesis confirming neuroinflammation in the central nervous system (CNS). It is unclear whether KFLC can differentiate primary psychiatric disorders from neural autoantibody-associated psychiatric syndromes.

Methods: We enrolled 76 patients with psychiatric diagnoses ICD-10 (International Classification of Diseases, 10th revision) (F00–09, F10–19, F20–29, F30–39, F40–49) and cerebrospinal fluid (CSF) as well as blood samples from our biobank. Commercial assays were used to determine neural autoantibodies. KFLC in serum and CSF samples were assessed by nephelometry (Siemens Atellica NEPH 630 analyzer). We calculated the relative intrathecal fraction (IF) of KFLC and the KFLC index using KFLC quotient and albumin quotient. Criteria for autoimmune encephalitis and autoimmune-mediated psychiatric syndromes were evaluated in patients to determine an autoimmune basis for the psychiatric symptoms.

Results: Neither the number of patients with elevated KFLC, a KFLC index nor the KFLC IF percentage served as an instrument for differentiating between autoantibody-positive (n = 18) and autoantibody-negative (n = 58) psychiatric patients. Patients with elevated KFLC levels in CSF had a higher proportion of lymphocytes than patients with non-elevated KFLC as a non-significant trend. We observed a non-significant trend towards higher CSF/serum IgM, but no trend for CSF/serum IgA or CSF/serum IgG ratio in patients with elevated KFLC levels than in those with non-elevated KFLC. No probable autoantibody-positive or seronegative autoimmune encephalitis was detected in patients. However, we observed an autoantibody-associated psychiatric syndrome in 6 out of 10 patients with elevated KFLC-IF, and the detection of elevated KFLC improved the diagnosis of probable autoimmune disease in 4 out of 10 patients (40 %).

Conclusions: Elevated KFLC levels may indicate psychiatric patients presenting any intrathecal immunoglobulin synthesis and thus help to evaluate an autoimmune basis in psychiatric syndromes. Furthermore, it should be added as a novel criterion for intrathecal immunoglobulin synthesis in autoimmune-related psychiatric syndromes. Further large-scale research is needed to elucidate the role of KFLC in autoimmune-mediated psychiatric disorders and to verify the observed trends in CSF parameters in patients with elevated KFLC.

* Correspondence to: Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Von-Siebold-Str. 5, Göttingen 37075, Germany.
E-mail address: niels.hansen@med.uni-goettingen.de (N. Hansen).
[1] indicate equally contributing authors.

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1. Introduction

Kappa free light chains (KFLC) are an alternative surrogate parameter for any intrathecal immunoglobulin synthesis [1–4]. However, they indicate both immunoglobulin G (IgG) and immunoglobulin A (IgA) as well as immunoglobulin M (IgM) synthesis unlike oligoclonal bands, which reveal a purely intrathecal synthesis of IgG in the CNS [5]. KFLC are being increasingly considered as a complementary parameter to identify patients with an intrathecal synthesis of IgG and neuroinflammation within the central nervous system (CNS) [5]. They are also being investigated in research into the diagnosis of autoimmune encephalitis to detect inflammation more sensitively. A recently collected cohort of patients with autoimmune encephalitis yielded evidence that the KFLC index's specificity resembles that of oligoclonal bands in defining an inflammatory etiology, but also that it is more sensitive in identifying an inflammatory intrathecal process [6]. A meta-analysis of 32 studies also showed that KFLC possess similar sensitivity and specificity in revealing intrathecal IgG synthesis as oligoclonal bands do [7]. Furthermore, some authors recommend that KFLC, as a measure of intrathecal inflammation, should be combined with an assessment of oligoclonal bands to determine the overall humoral intrathecal immune response [8]. However, the value of KFLC in identifying an inflammatory process as the cause of autoantibody-associated psychiatric syndromes is unclear. This study will evaluate whether KFLCs facilitate the classification of mild CNS inflammation in autoimmune psychiatric syndromes and also in ambiguous or borderline autoimmune psychiatric syndromes (classification criteria: [9]) potentially associated with autoantibodies and that do not meet the classic criteria for autoimmune encephalitis according to Graus [10].The aim of this study is therefore to determine whether KFLC are suitable for better distinguishing primary psychiatric disorders from those with associated autoantibodies as a more specific characterization of the intrathecal humoral immune response in psychiatric patients without confirmed autoimmune encephalitis.

2. Methods

2.1. Cohort recruitment and composition

We enrolled 76 psychiatric patients from the biomaterial bank in the University Medical Center Göttingen's Department of Psychiatry and Psychotherapy in this retrospective study to analyze their serum and cerebrospinal fluid (CSF) samples for KFLC. KFLC were assessed in these patients to better evaluate the significance of the associated autoantibodies and find evidence of intrathecal synthesis of immunoglobulins as a further item relevant for evaluation of autoimmunity in psychiatric syndromes. Criteria for autoimmune-based psychiatric syndromes [9] were recently published, which enable us to postulate an immune-mediated genesis of psychiatric syndromes but which can also classify mild inflammation in psychiatric syndromes according to the hypothesis of mild inflammation in mental disorders [11,12] somewhat more sensitively and subtly, as they are less strict than the Graus criteria [10]. This could also include cases not meeting the classic criteria for autoimmune encephalitis, but where there are additional indications of smoldering inflammation in the brains of these patients. The study patients had diagnoses from the diagnostic groups according to ICD-10 (International Classification of Diseases, 10th revision) (F00-F09: Organic, including symptomatic, mental disorders, F10-F19: Mental and behavioral disorders due to psychoactive substance use, F20-F29: Schizophrenia, schizotypical and delusional disorders, F30–39: Mood disorders and F40–49: Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders). This study was approved by the ethics committee of the University Medical Center in Göttingen (AZ9/2/2016, AZ 1/6/2020, AZ 16/2/2021Ü), registered in DRKS (German Register of Clinical Studies) (DRKS00032459, DRKS00024041) and was in accordance with the current Declaration of Helsinki. Our inclusion criterion was the availability of biomaterial in the Department of Psychiatry and Psychotherapy's biomaterial bank and/or the availability of sample material belonging to the CAP (Cerebrospinal fluid analysis in Psychiatry) consortium stored within that same biomaterial bank. A further inclusion criterion was the presence of a psychiatric diagnosis requiring the collection of CSF and blood for differential diagnosis. The recruited patients with an F00-F49 diagnosis underwent a lumbar puncture for differential diagnosis of an organic mental disorder. Study subjects could only be enrolled if they or their legally authorized representative agreed to the collection of biomaterial as a donation, and to its storage and subsequent analyses, and was able to make such a statement of intent. The background and objectives of the biobank and/or CAP Register study were explained beforehand. A standard exclusion criterion for inclusion in the biobank is the inability to provide consent. In detail, the participants were informed in detail and given an information leaflet prior to submitting their biomaterial, which took place as part of routine clinical diagnostics. In addition, each participant in the study signed a declaration of consent for the donation and storage of their biomaterial, usage of clinical data and for additional research with the biomaterial and corresponding clinical data.

2.2. Clinical data assessments

Electroencephalographs (EEGs) were also taken in patients via the 10/20 EEG system (Natus EEG system, Planegg, Germany) focusing on these parameters: any specific EEG patterns such as frontal irregular delta activity or temporal irregular delta activity showing localized slowing or epilepsy-typical potentials. Magnetic resonance imaging (MRI) data (1.5 Tesla) was done in the Department of Neuroradiology, University Medical Center Göttingen or other neuroradiologic care centers in Göttingen. The MRI patterns investigated were generalized atrophy, focal atrophy, hippocampal atrophy, vascular lesions or dilated CSF spaces. In addition, T2 sequences of the brain and temporal lobes were derived from magnetic resonance images and visually analyzed in 17 patients in whom we had detected antibodies. In addition to those clinical parameters, we also collected information such as any current or past tumors and recent immunosuppressant therapy. Our patients also underwent neurological examination to identify any mydriasis, cranial nerve palsy, paralysis of the eye muscles, hypomimia, facial hypesthesia, pyramidal tract signs, paralysis of the upper or lower extremities, hyper- or hyporeflexia, rigor, spasticity, tremor, movement disorder, paresthesia of the upper or lower extremities, postural instability or gait disturbance. In addition, we investigated "red flags" [8,9] such as aphasia, mutisms, dysathria, faciobrachial dystonic seizures, autonomic dysfunction, seizures, central hypoventilation, focal neurological deficits, decreased level of consciousness, hyponatremia, infectious prodrom, movement disorder, new onset of headache, adverse response to antipsychotics or antidepressants or other psychopharmacologic drugs, paresthesia, optic hallucinations, other autoimmune disorder, presence of a current or recent tumor, presence of a malignant neuroleptic syndrome, or severe cognitive dysfunction. We also considered "yellow flags" [8,9] such as confusion, dynamic course, early treatment resistance, fluctuating psychopathology and psychomotor symptoms. We assessed certain items from the AMDP (Association for Methodology and Documentation in Psychiatry system) [13] to identify psychopathological behavior, ie, psychomotor symptoms, orientation disorders, concentration disorders, short- and long-term memory, formal thought disorders, suspiciousness, phobia, obsession, compulsions, delusions, visual hallucinations, auditory hallucinations, bodily hallucinations, gustatory or olfactory hallucinations, ego disturbances, affective disorders, listlessness, circadian disorders, social detachment, aggressiveness and suicidality, self-harm, lack of feeling ill and lack of insight into illness.

2.3. Cerebrospinal fluid analysis

CSF is processed immediately after collection as in vitro cytolysis occurs rapidly. Upon receipt, biomaterial samples were handled within a time frame of 1–2 h to guarantee accurate cell counting. The CSF probes were centrifuged to disconnect the cells from the CSF. The neuronal destruction markers such as p-tau181 and t-tau as well as the Reiber scheme were specified on the same day. All serum samples were stored and sent as aliquots with 500 µl serum to the Clinical Immunological Laboratory for the detection of autoantibodies. In addition, CSF aliquots (300 µl) were transferred to the Clinical Immunological Laboratory. The CSF parameters we examined were the cell count, proportion of erythrocytes, lymphocytes and monocytes. In addition, albumin, the total protein, IgA, IgM, IgG, CSF/serum IgG, IgA and IgM ratio as well as CSF serum albumin ratio were determined. Intrathecal IgG synthesis and blood brain barrier dysfunction were calculated. In addition, dementia-specific biomarkers such as phosphorylated tau protein 181 (p-tau181), amyloid-β42 (Aβ42), amyloid-β 40 (Aβ40) and the amyloid-β42 / amyloid-β40 (Aβ42/Aβ40 ratio) and total tau protein (t-tau) were determined in the CSF. The CSF was analyzed in the Laboratory for Neurochemistry in the Department of Neurology at the University Medical Center Göttingen. Markers of amyloid-β pathology such as Aβ42, Aβ40, amyloid-β dependent tau pathology such as p-tau181 and neurodegeneration such as t-tau were also determined in this laboratory.

2.4. Neural autoantibodies

We also examined neuronal and paraneoplastic autoantibodies in the serum and CSF of all patients. The autoantibodies we examined with an immunoblot were anti-glutamic acid decarboxylase 65 (GAD65), -Zic4, -Titin, -TR/Delta/Notch-like Epidermal Growth Factor-Released (TR/DNER), -Recoverin, -SRY-Box Transcription Factor 1 (SOX1), -Ma1, -Ma2, -Amphiphysin, -cronveinten 2/ collapsing response mediator protein (CV2/CRMP5) antibodies. In addition, a recombinant cell indirect immunofluorescence test was used for autoantibody testing against Rho GTPase Activating Protein 26 (ARHGAP26), myelin, immunoglobulin-like cell adhesion molecule 5 (IgLON5), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1/2 (AMPAR1/2), N-Methyl-D-Aspartate receptor (NMDAR), Leucin rich glioma inactivated protein 1 (LGI1), gamma-Aminobutyric acid receptor B1/ 2 (GABAB1/2), Dipeptidyl-peptidase-like protein-6 (DPPX), Flotilin 1/2, potassium voltage-gated channel subfamily A member 2 (KCNA2) and Contactin-associated protein-like 2 (CASPR2).

2.5. Nephelometric measurement of kappa free light chains

The concentrations of KFLC in plasma and cerebrospinal fluid samples were determined by nephelometry on the Siemens Atellica NEPH 630 analyzer (Device ID: 111 493). This method quantifies KFLC based on the light scattering of antigen-antibody complexes. Measurements were taken according to the manufacturer's instructions using Siemens Atellica-specific reagents and calibration protocols. Plasma and CSF sample results were expressed in milligrams per liter (mg/L). Quality control was checked applying internal standards and external reference materials, with coefficient of variation (CV) values consistently within the acceptable range defined by the manufacturer.

2.6. Calculating free kappa light chain parameters

The KFLC quotient (Q_{KFLC}) was calculated as follows:

Q_{KFLC} = CSF KFLC / Serum KFLC.

The KFLC index was specified by relying on the albumin quotient (Qalb):

KFLC index = (CSF KFLC/serum KFLC)/(CSF albumin/serum albumin).

As a surrogate marker of intrathecal IgG synthesis, the percentage of the intrathecal fraction of KFLC (KFLC IF) is particularly important. The amount of intrathecally synthesized KFLCs was calculated as described by Reiber et al. [14] and Süße et al. [15]. To determine the hyperbolic reference interval, we applied the formula proposed by Reiber et al. [14], which is valid within the range of Q_{Alb} at $Q_{KFLC} = 0.5 = 500 \times 10^{-3}$. To compute the hyperbolic reference interval:

Q_{KFLC} (Q_{lim}) = $3.27 \times [(QAlb^2 + 33)]^{0.5} - 8.2 \times 10^{-3}$ (for QAlb < 155×10^{-3})

Q_{KFLC} (Q_{mean}) = $1.95 \times [(QAlb^2 + 16)]^{0.5} - 4.85 \times 10^{-3}$ (for QAlb < 256×10^{-3})

Q_{KFLC} (Q_{low}) = $0.78 \times [(QAlb^2 + 16)]^{0.5} - 2 \times 10^{-3}$ (for QAlb < 643×10^{-3}).

The intrathecal synthesis of KFLC was quantified by the relative intrathecal fraction, which was calculated as follows:

KFLC IF = (KFLC loc / KFLC CSF) × 100 or

alternatively, KFLC IF = (1 - Q_{lim} /Q_{KFLC}) × 100%.

For statistical analyses, the absolute concentration of intrathecally synthesized KFLC (KFLC loc) was determined according to this equation in relation to Q_{mean}. We defined an increased KFLC based on an IF > 10 %. We relied on the KFLC IF as a parameter to measure whether KFLC were elevated, and not the KFLC index. The KFLC index is indeed a validated measurement parameter, and several studies have proven it as a highly reliable parameter; its simple cut-off value serves to assess the intrathecal immune response in multiple sclerosis [5]. In addition, the KFLC index also incorporates the albumin quotient as a surrogate marker of blood-brain barrier function and thus its functionality. Nevertheless, the KFLC index as a parameter with a linear cut-off value does not account for the Reiber scheme's hyperbolic function. Thus, the non-linear diffusion of blood-dependent proteins of different sizes across an intact blood brain barrier cannot be considered. By using the KFLC IF, the blood brain barriers physiological functions are therefore considered. Assessing KFLC with the KFLC IF is superior to assessment with the KFLC index, as a recently published study of patients with multiple sclerosis demonstrated [15]. This explains why we chose KFLC IF as the decisive parameter to assess the increase in KFLC in this study.

2.7. Statistics

To calculate and graphically illustrate KFLC values, we used a freely available software tool found at www.albaum.it. SPSS and Sigma Stat (version 11) were used for statistical analysis. CSF data such as cell count, proteins and neuronal cell destruction markers were analyzed between the groups with elevated KFLC versus non-elevated KFLC data using Mann Whitney U tests. Although these were exploratory analyses, we analyzed several parameters - and thus a Bonferroni correction. The frequencies of clinical data such as psychopathology items, "red flags", "yellow flags", EEG findings, MRI results, frequency of blood-brain barrier disorder, presence of autoantibodies and neurological deficits were compared in the patients with elevated KFLC versus those with non-elevated KFLC using Fisher's exact tests. In addition, KFLC parameters were analyzed with age as a variable with Spearman Rho correlations. The significance level was set at $p < 0.05$.

3. Results

3.1. Clinical characterization of groups

18 patients had autoantibodies in serum and/or CSF, while 58 had no autoantibodies in serum or CSF. In serum we detected autoantibodies against Amphiphysin (n = 1), Titin (n = 3), KCNA2 (n = 1), Recoverin

(n = 1), Flotillin 1/2 (n = 2), ARHGAP26 (n = 1), Zic4 (n = 1), IgLON5 (n = 1), GABAB1/2 (n = 1), GAD65 (n = 3) and Myelin (n = 1) within the antibody-positive group of patients. CSF autoantibodies against Titin (n = 3), Zic4 (n = 1), GAD65 (n = 1) were also detected in the antibody-positive group. Our antibody-positive group included 7/18 (39 %) patients fulfilling the criteria for possible autoimmune encephalitis due to Graus criteria [10]. We observed no bilateral or unilateral T2 temporal lobe hyperintensities in 17 antibody-positive patients. One antibody-positive patient underwent no MRI, instead cranial computer tomography, meaning temporal hyperintensities could not be assessed. T2 MRI sequences were analyzed in n = 57 antibody-negative and n = 17 antibody-positive patients. 43 of 76 patients (56.7 %) had an F00-F09 diagnosis, 6 of 76 (7.9 %) had F10-F19 diagnoses, 12 of 76 (15.7 %) had F20-F29 diagnoses, 29 of 76 (38.2 %) had F30-F39 diagnoses and finally 8 of 76 (10.5 %) had F40–49 diagnoses. Table 1 shows the autoantibody-positive and -negative groups' diagnosis groups in detail. Eighteen patients presented more than one primary diagnosis. The patient groups did not differ in terms of gender (antibody-positive: 8/18 women and for antibody-negative: 35/58 women) ($p = 0.23$), while age was significantly higher in the autoantibody-positive group (69.8 ± 15.2 years) than in the autoantibody-negative group (57.7 ± 19.9 years) ($p < 0.05$). If age is examined as a variable correlating with the KFLC parameter, note that an older age correlated with an increase in KFLC in both serum and the CSF and as a quotient (Spearman correlation age with KFLC CSF: r = 0. 48, $p < 0.001$; age with KFLC serum: r = 0.42, $p < 0.001$ as well as KFLC CSF quotient: r = 0.35, $p < 0.005$; n = 76). However, both the IF% of the KFLC CSF (r = -0.02, $p = 0.89$) and the KFLC index (r = 0.08, $p = 0.51$) are independent of age, and those parameters do not correlate with age.

3.2. Free kappa light chains in psychiatric patients

KFLC in the CSF of autoantibody-positive patients did not differ significantly from those without autoantibodies (Table 2). Furthermore, we also detected no relevant difference in KFLC in serum or in the Q_{KFLC} in autoantibody-positive versus autoantibody-negative patients (Table 2). Other KFLC parameters such as the KFLC IF mean, Q_{mean} and Q_{lim} did not differ either between autoantibody-positive and autoantibody-negative groups (Table 2). The KFLC IF percentage tended to be higher, but not significantly so, with high variability in autoantibody-positive (9.62 ± 20.02) compared to negative patients (3.94 ± 14.77; $p = 0.33$, Table 2). In contrast, the KFLC index was very similar in both groups and did not differ significantly.

3.3. Cerebrospinal fluid in psychiatric patients with elevated free kappa light chains

The CSF showed a trend towards a higher percentage of lymphocytes in the group of psychiatric patients with elevated KFLC (85 %, CI 25 %-75 %, 83.2–87 %, n = 8) compared to those without (78 %, CI 25–75 %, 70.8–86 %) ($p < 0.05$, but not a significant trend after Bonferroni correction, Table 3). It is also impressive to note the trend that the CSF serum IgM ratio is higher in patients with increased KFLC (0.89 %, CI 25–75 %, 0.35–1 %, n = 7) than in those without elevated KFLC (0.31 %, CI 25–75 %, 0.22–0.55 %, n = 44) ($p < 0.05$, but not a significant trend after Bonferroni correction, Table 3). However, there were no significant group differences in terms of lactate, cell count, neuronal damage markers and percentage of erythrocytes, percentage of monocytes, total protein content, albumin content, IgG, IgA, IgM content, CSF/serum IgG, IgA or IgM ratio, antibody specific indices for measles, rubella, VZV, HSV, EBV and CMV (Table 3). Markers of amyloid pathology showed as a trend that amyloid-β1–40 was higher in patients with elevated KFLC (Aβ1–40 12,279 pg/mL, CI 25–75 %, 10,904–15,267 pg/mL) than in those without increased KFLC (10,319 pg/mL, CI 25–75 %, 8151–13,291 pg/mL) ($p < 0.05$, but not a significant trend after Bonferroni correction) (Table 3). The other neuronal damage markers such as p-tau181, t-tau protein and the amyloid β markers such as Aβ1–42 or the ratio Aβ1–42/1–40 were also not different between elevated and non-elevated KFLC groups (Table 3).

Table 1
Psychiatric main diagnoses of patients with and without neural autoantibodies.

ICD-10 diagnosis	Abs+ (n = 18)	Abs- (n = 58)
F00-F09: Organic, including symptomatic, mental disorders	14/18 (77.7 %)	29/58 (50.0 %)
F10-F19: Mental and behavioral disorders due to psychoactive substance use	1/18 (5.5 %)	5/58 (8.6 %)
F20-F29: Schizophrenia, schizotypical and delusional disorders	0/18 (0.0 %)	12/58 (20.7 %)
F30-F39: Mood disorders	4/18 (22.2 %)	25/58 (43.1 %)
F40-F49: Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	1/18 (5.5 %)	7/58 (13.8 %)

Abbreviations: Abs- = autoantibody-negative patients, Abs+ = autoantibody-positive patients, ICD-10 = International Classification of Diseases, 10th revision, n = number.

Table 2
Kappa free light chains in psychiatric patients with versus without neural autoantibodies.

Parameter	No presence of autoantibodies	Presence of autoantibodies	P-value
Q_{Alb}	6.33 ± 0.33	5.73 ± 2.10	0.33
KFLC CSF mg/L	0.23 ± 0.32	0.28 ± 0.28	0.59
KFLC serum mg/L	16.59 ± 7.14	15.66 ± 7.36	0.65
Q_{KFLC}	15.53 ± 27.71	16.78 ± 13.65	0.80
KFLC IF mean	8.52 ± 19.90	18.76 ± 27.57	0.17
Q_{mean}	12.12 ± 3.69	11.23 ± 2.97	0.31
Q_{lim}	20.27 ± 6.19	18.75 ± 4.99	0.31
KFLC IF %	3.94 ± 14.77	9.62 ± 20.02	0.33
KFLC index	3.25 ± 9.59	3.32 ± 3.41	0.11

Abbreviations: KFLC CSF = Kappa free light chains cerebrospinal fluid, KFLC IF % = kappa free light chains intrathecal fraction percentage, KFLC IF mean = mean of kappa free light chains intrathecal fraction, Q_{Alb} = quotient albumin, Q_{KFLC} = quotient of kappa free light chains, Q_{lim} = quotient limen, Q_{mean} = quotient mean.

3.4. Characterization of psychiatric patients with elevated free kappa light chains

No differences emerged between patients with elevated KFLC compared to those psychiatric patients without elevated KFLC in their psychopathology, neurological deficits, "red flags", "yellow flags", MRI and EEG abnormalities, tumor presence, usage of immunotherapy and blood brain barrier disturbances (Table 4). We found increased KFLC in both autoantibody-positive and autoantibody-negative psychiatric patients (Fig. 1, Table 5). In addition, we distinguished between psychiatric patients with and without evidence of intrathecal synthesis of specific antiviral autoantibodies who presented increased KFLC (Fig. 2, Table 5). Since we found that KFLC do not differentiate between neural autoantibody-positive or antiviral-specific autoantibody-positive from -negative patients, assessing them does not help answer this question. According to the criteria for autoimmune-related psychiatric syndromes [9] we detected a probable autoimmune-related psychiatric syndrome in 6 of 10 patients (60 %) with an elevated intrathecal KFLC fraction, while no autoimmune-related psychiatric syndrome was detected in 4 of 10 (40 %). The detection of KFLC improved diagnosis of an autoimmune basis in 4 out of 10 patients (40 %) (Table 5). In the other 6 out of 10 (60 %), KFLC did not add value to their autoimmune psychiatric syndrome diagnosis. KFLC are therefore useful in confirming an

Table 3
Cerebrospinal fluid investigations in psychiatric patients with and without elevated kappa free light chains.

	Elevated KFLC				Non elevated KFLC				
Parameter	**Median**	**CI 25 %**	**CI 75 %**	**N**	**Median**	**CI 25 %**	**CI 75 %**	**N**	**p-value**
Lactat mmol/L	1.6	13.8	1725	10	1.5	1.3	1.7	65	0.55
Cell count/µL	0,5	0	1.5	10	0	0	1	66	0.63
Lymphocytes %	85	83.3	87	8	78	70.8	86	58	0.043
Monocytes %	14	12	15.8	8	19	10.5	24.3	58	0.16
Neutrophile granulocytes %	1	1	1	3	2	4	8	35	0.01
Total protein mg/L	328	254	551	10	341	296	447	66	0.91
Albumin mg/L	216	144	359	10	249	192	325	66	0.47
IgG mg/L	26	16.9	39.8	10	25.3	20.2	33.8	66	0.95
IgA mg/L	4	1.9	7.2	10	3.1	1.8	4.3	66	0.23
IgM mg/L	0.7	0.3	1.2	7	0.3	0.3	0.5	44	0.07
Ratio CSF/Serum albumin	5.1	3.4	8.4	10	5.8	4.7	7.9	66	0.39
Ratio CSF/Serum IgG	2.7	1.8	4.3	10	2.8	2.7	3.4	66	0.99
Ratio CSF/Serum IgA	1.8	0.8	2.6	10	1.4	0.9	1.9	66	0.46
Ratio CSF/Serum IgM	0.9	0.4	1	7	0.3	0.2	0.6	44	0.04
Measles ASI	0.8	0.7	0.8	7	0.9	0.8	1	45	0.06
Rubella ASI	0.9	0.9	1	6	0.9	0.8	1	50	0.46
VZV ASI	0.9	0.8	1.9	6	0.9	0.8	1	46	0.90
HSV ASI	1	0.9	1.9	8	1	0.9	1	42	0.19
EBV ASI	0.8	0.8	0.8	1	0.8	0.7	0.8	12	1,00
CMV ASI	0.8	0.8	0.8	1	0.8	0.8	0.8	13	1,00
Total Tau protein pg/mL (<450 pg/mL)	321	279	418.5	9	214	139	419	59	0.08
P-tau181 pg/mL (<61 pg/mL)	65	42	88	9	48	33	76	60	0.25
Aβ1–42 pg/mL(>450 pg/mL)	1329	767	1761	9	1017	651	1309	57	0.07
Aβ1–40 pg/mL	12279	10904	15267	9	10319	8151	13291	59	0.05
Ratio Aβ1–42/1–40 × 10 (>0.5)	1.1	0.7	1.4	9	1	0.7	1.2	57	0.61

Abbreviations: Aβ1–40 = amyloid- β1–40, Aβ1–42 = amyloid-β1–42, ASI = anti-viral specific antibody index, CI = confidence interval, CMV = Cytomegaly virus, HSV = Herpes simplex virus, VZV = Varizella zoster virus, EBV = Ebstein Barr virus, IgG = Immunoglobulin G, IgA = Immunoglobulin A, IgM = Immunoglobulin M, KFLC = Kappa free light chains, P-tau181 = phosphorylated tau protein 181. The reference range is indicated within the brackets.

autoimmune basis for symptoms, but only in a minority of psychiatric patients. When we applied the Graus criteria for autoimmune encephalitis [10] to our patient cohort, none of them met the criteria for probable autoantibody-negative or antibody-positive autoimmune encephalitis.

4. Discussion

The main finding of our investigation is that in general, KFLC might be helpful on individual patients in whom neural autoantibodies have been identified to implement therapeutic strategies. This can be particularly relevant when it is not possible to diagnose probable autoimmune encephalitis with or without autoantibodies, but certain indications such as the presence of autoantibodies suggest an inflammatory subtype of the mental disorder or mental syndrome. Thus, in 40 % of patients with elevated KFLC in our study, having investigated KFLC helped us to diagnose an autoimmune-related psychiatric syndrome and thereby facilitate immunotherapeutic approaches. But we cannot assume that KFLC can differentiate between patients with and those without neural autoantibodies. KFLC should thus serve as a complementary tool in patients with neural autoantibodies, but they do not help us in pre-screening for the presence of neural autoantibodies. Note also that the clinical phenotype did not differ between patients with elevated KFLC. No relevant memory-associated differences appeared between groups. In other words, our findings failed to confirm study results indicating that patients with impaired verbal memory had increased KFLC [16].

4.1. Expanding upon the criteria for autoimmune pathophysiology in psychiatric syndromes

KFLC can play a relevant role in cases of a recent subacute onset of psychiatric symptoms, as KFLC reflect more than oligoclonal bands within the CSF - namely intrathecal IgA, IgM and IgG synthesis, whereas oligoclonal bands represent pure intrathecal IgG synthesis [5]. Early autoantibody production in the CNS is therefore probably enabled by the KFLC, and it is particularly helpful for the early diagnosis of psychiatric syndromes with a possible organic genesis to determine these, especially if none of the usual autoantibodies have been detected. The KFLC could therefore also be incorporated within criteria for autoimmune psychosis or an autoimmune psychiatric syndrome to supplement the diagnostic options for autoimmune pathophysiology. This is particularly the case in patients suffering suspected seronegative autoimmune psychosis.

4.2. Potential lymphocyte dominated inflammation and high kappa light chains

Although we identified no obviously elevated KFLC in our psychiatric patients with neural autoantibodies, the findings listed below should be investigated in more detail in future research. Firstly, patients with elevated KFLC seem to present more lymphocytes as a non-significant trend overall than those without elevated KFLC. However, this is only a trend that should be further investigated in a study with a larger cohort with autoimmune based psychiatric syndromes. However, note that as the total cell count was not increased in these patients, correlating the cell count with the KFLC IF is not meaningful. It is therefore possible that lymphocyte-dominated inflammation coexists with the intrathecal immune response and increased KFLC. Flow cytometry would therefore be important in future studies in patients with elevated KFLC to see whether this is reflected in subsets of lymphocytes such as CD8 + or CD4 + cells and whether these are elevated as well. Several studies have reported increased T- and B-lymphocytes in antibody-mediated encephalitis [17–21], so the finding may be consistent with that. Elevated lymphocyte populations are detected in conjunction with autoimmune processes and suggest an autoimmune response in the CNS. The trend in data on lymphocyte-dominated inflammation in the CNS is consistent with an autoimmune pathophysiology involving the production of autoantibodies.

Table 4
Diagnostic and clinical parameter in psychiatric patients with and without elevated kappa free light chains.

Parameter	Elevated KFLC		Non-elevated Elevated KFLC		p-value
	% of total N	N	% of total N	N	
Presence autoantibodies serum	40	10	21	66	0.24
Presence autoantibodies CSF	0	10	6	66	1.00
Blood brain barrier disturbance	10	10	23	66	0.69
TIRDA	17	6	46	11	0.33
FIRDA	17	6	46	11	0.33
Delta Brush	0	6	18	11	0.52
Temporal focal slowing	17	6	9	11	1.00
Generalized atrophy	60	10	49	63	0.74
Focal atrophy	40	10	40	63	1.00
Hippocampal atrophy	10	10	3	63	0.36
Vascular lesions	70	10	13	63	0.18
Extented cerebrospinal fluid rooms	50	10	37	63	0.49
Tumor	0	10	2	63	1.00
Treatment with immunosuppressive drugs	10	10	3	65	0.35
Cerebral nerve palsy	0	9	8	62	1.00
Oculomotor paresis	11	9	2	62	0.24
Hypomimia	13	8	2	63	0.21
Paresis upper extremities	0	9	2	62	1.00
Hyporeflexia	11	9	18	62	1.00
Rigor	0	9	7	62	1.00
Tremor	11	9	11	62	1.00
Paresthesia or hypo- or hyperesthesia upper extremtities	11	9	3	62	0.34
Postural instability	0	9	7	62	1.00
Paresthesia or hypo- or hyperesthesia lower extremtities	11	9	8	61	0.58
Gait disturbance	22	9	16	62	0.64
Aphasia, mutism or dysarthria	11	9	2	63	0.24
Autonomic disturbance	0	9	3	63	1.00
Epileptic seizures	0	9	2	63	1.00
Hyponatreamia	0	9	2	63	1.00
Infectious prodrome with fever	0	9	2	63	1.00
Movement disorder	0	9	5	63	1.00
New onset severe headache or clinically significant change in headache pattern	0	9	3	63	1.00
Adverse response to antipsychiotics or antidepressants or other psychopharmacological drugs	44	9	25	63	0.25
Optic hallucinations	11	9	3	63	0.33
Other autoimmune disorders	0	9	5	63	1.00
Presence of a tumor, or history of a recent tumor	10	10	6	63	0.53
Severe cognitive dysfunction	40	10	42	64	1.00
Confusion	20	10	3	65	0.08
Dynamic course	20	10	29	65	0.72
Early resistance to therapy	10	10	2	65	0.25
Fluctuating psychopathology	40	10	25	65	0.44
Psychomotor symptoms	30	10	26	65	1.00
Orientation disturbance	10	10	27	66	0.44
Disturbed apperception	30	10	21	66	0.68
Disturbed concentration	60	10	76	66	0,44
Disturbed short-term memory	70	10	71	66	1
Disturbed long-term memory	70	10	67	66	1
Formal thought disorder	50	10	64	64	0.49
Suspicousness	30	10	20	64	0.44
Phobia	0	10	6	64	1
Obsessions	0	10	9	64	0.59
Obsessive-impulsions	0	10	2	64	1
Compulsions	0	9	8	65	1
Delusions	20	10	11	64	0.60
Acustic hallucinations	40	10	14	64	0.07
Bodily hallucinations	0	9	2	65	1
Olfactory or gustatory hallucinations	11	9	0	65	0.12
Ego-Disturbances	0	10	17	64	0.34
Affective disorder	80	10	0.8	64	1.00
Lack of drive	80	10	67	64	0.72
Circardian Disturbances	0	9	2	65	1.00
Social detachment	56	9	48	65	0.73
Aggressiveness	20	10	5	64	0.13
Suicidality	50	10	22	64	0.11
Self-harm	0	10	3	64	1.00
Lack of feeling ill	0	10	2	64	1.00
Lack of insight into illness	10	10	3	64	0.36

Abbreviations: % of total N = percentage of total number, CSF = cerebrospinal fluid, FIRDA = frontal irregular delta activity,
KFLC = kappa free light chains, TIRDA = temporal irregular delta activity.

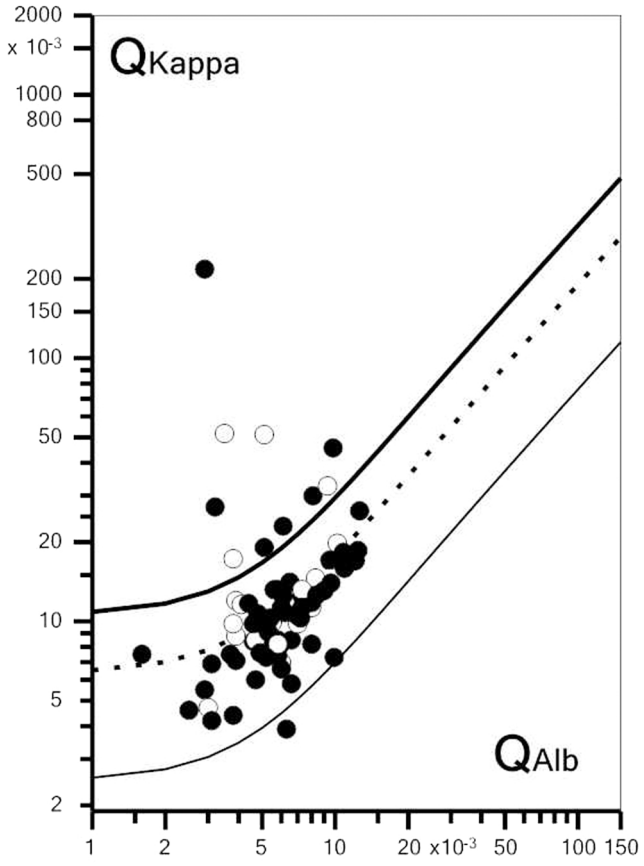

Fig. 1. Kappa free light chains in all autoantibody-positive and -negative patients. Quotient-diagrams also called Reiber diagrams in double logarithmic exhibition of Q_{KFLC} (Q_{Kappa}), i.e. KFLC CSF/serum ratio, opposed to Q_{Alb}, i.e. Albumin CSF/serum ratio. The area above Q_{lim} means an intrathecal KFLC synthesis, Q_{lim} is represented by the thick upper line and the Q_{mean} is demonstrated by the dotted middle line whereas the Q_{low} is indicated by the thin lower line. A black dot indicates an autoantibody-negative and a white dot an autoantibody-positive patient. Abbreviations: KFLC CSF = Kappa free light chains cerebrospinal fluid, Q_{Alb} = quotient of albumin, Q_{KFLC} (Q_{Kappa}) = quotient of kappa free light chains, Q_{lim} = quotient limen, Q_{low} = quotient low, Q_{mean} = quotient mean.

4.3. Amyloid beta and kappa free light chains

Another exciting finding is that the Aβ40 is over-expressed as a non-significant trend in patients with elevated KFLC compared to patients without elevated KFLC. We recommend that this trend should also be

Table 5
Psychiatric patient cohort with elevated kappa free light chains intrathecal fraction.

Parameter	1	2	3	4	5	6	7	8	9	10
Gender	Male	Female	Female	Female	Male	Female	Male	Male	Female	Male
Age years	75	65	85	78	61	28	54	55	67	50
Diagnosis ICD−10	F01.3	F03	F00.2	F33.2	F33.3	F25.1	F33.2	F00.0	F33.1	F20.0
Comorbidity ICD−10	C61, I10.0, E78	F33.2, G43	E05, D51	F06.7, F10.1	I10.0	-	F41.2,	E29, E79.0, E55.0	M79.70, G40.0, G25.81, C43.6	-
Abs blood	+	+	+	+	-	-	-	-	-	-
Abs CSF	-	-	-	-	-	-	-	-	-	-
Type abs blood	Titin	Flotilin 1/ 2	GABAB1/2 R	REC	-	-	-	-	-	-
Type abs CSF	-	-	-	-	-	-	-	-	-	-
CSF lactate mmol/l	1.6	1.4	1.8	1.5	1.6	1.2	1.5	1.9	1.7	1.3
CSF cells per µl	0	1	0	1	0	0	3	0	1	10
CSF lymphocytes %	na	87	83	83	87	97	85	na	84	85
CSF monocytes %	na	13	16	17	12	3	15	na	15	12
CSF total protein mg/L	585	336	281	237	539	224	418	641	319	259
CSF albumin mg/L	354	216	147	135	373	117	256	452	216	182
CSF IgG mg/L	78.8	30.5	17.7	14.3	32.4	14	34.5	55.5	20.9	21.5
CSF IgA mg/L	12.1	4.3	1.4	2	4,2	1.3	3.8	5.5	3	20.4
CSF IgM mg/L	3.4	0.3	< 0.15	< 0.18	0.59	< 0.15	0.7	0.9	0.3	1.2
CSF/serum albumin	9.3	5.1	3.8	3.5	8.1	6.6	6.1	9.8	5.1	2.9
CSF/serum IgG	4.2	2.6	1.7	1.8	4.7	2.7	3.2	5.6	2.8	2.1
CSF/serum IgA	2.3	2.2	0.6	0.8	2.2	1.2	1.4	3.3	1.4	11.3
CSF/serum IgM	1.0	0.3	< 0.2	< 0.3	1.0	< 0.7	3.5	0.0	0.4	2.8
OCB	-	-	-	-	-	-	-	-	-	-
BBD	-	-	-	-	-	-	-	+	-	-
CSF Measles ASI	na	0.7	na	0.7	na	1	0.8	0–8	0.8	0.6
CSF Rubella ASI	na	0.9	na	na	na	0.8	1	0.9	1	0.7
CSF VZV ASI	na	0.8	0.9	0.7	1	0.6	0.9	0.4	-	-
CSF HSV ASI	na	2.6	1	1.9	1	0.9	0.9	0.9	0.9	-
CSF EBV ASI	na	na	na	na	na	na	na	na	na	0.8
CSF CMV ASI	na	na	na	na	na	na	na	na	na	0.8
CSF T-tau pg/mL (<450 pg/mL)	512	307	421	282	276	433	416	386	155	321
CSF p-tau181 pg/mL (<61 pg/mL)	89	65	86	54	45	76	70	91	38	40
CSF Aβ1–42 pg/mL (>450 pg/mL)	2367	788	645	746	1329	646	1883	1302	1581	1639
CSFAβ1–40 pg/mL	15860	10319	12279	11200	10607	7769	12214	15146	13292	15388
CSF Ratio Aβ1–42/ 1–40 × 10 (>0.5)	1.5	0.8	0.5	0.7	1.3	0.8	15.	0.9	1.2	1.1
MRI general atrophy	+	+	+	+	+	-	+	-	-	-
MRI focal atrophy	-	-	-	-	-	+	+	+	+	-
MRI hippocampal atrophy	-	-	-	-	-	-	+	-	-	-
MRI vascular lesions	+	+	+	+	+	-	+	-	+	-
MRI extended cerebrospinal fluid roooms	-	-	-	+	+	+	+	-	+	-
Tumor presence/ history	+	-	-	-	-	-	-	-	-	-
Immunotherapy	-	+	-	-	-	-	-	-	-	-
Type of immunotherapy	-	High dosage steroids	-	-	-	-	-	-	-	-

(*continued on next page*)

Table 5 (*continued*)

Parameter	1	2	3	4	5	6	7	8	9	10
Gender	Male	Female	Female	Female	Male	Female	Male	Male	Female	Male
Neurological deficits	Oculomotor paresis, hypomimia, tremor, severe cognitive dysfunction, confusion	Severe cognitive dysfunction, aphasia, mutism or dysathria	Gait disturbance	Hyporeflexia, paresthesia extremitites, sensory gait disturbance	-	-	-	Severe cognitive dysfunction	-	Confusion
Psychopathological features	Fluctuating psychopathology, orientation disturbances, memory disturbance, optic hallucinations, distrust	Memory disturbances, mood disturbed, loss of drive, aggressiveness, social detachment	Fluctuating psychopathology, disturbed apperception, memory and concentration, acoustic hallucinations, loss of drive, affective disturbances, suicidality	Concentration and memory disturbances, Rumination, affective disturbances, loss of drive, suicidality	Psychomotor slowing, concentration and memory disturbances, rumination, distrust, delusions, acoustic hallucinations affective disturbances, loss of drive, social detachment, suicidality	Psychomotor slowing, fluctuating psychopathology, apperception disturbances, ruminations, distrust, delusions, acoustic hallucinations, affective disturbances, loss of drive, social detachment, suicidality, aggressive behavior	Psychomotor slowing, concentration and memory disturbances, retarded thinking, affective disturbances, loss of drive, social detachment, suicidality	Apperception, concentration and memory disturbances, circumstantial thinking, lack of insight into illness	Fluctuating psychopathology, concentration and memory disturbances, loss of drive, social detachment	Optic hallucination, acoustic hallucinations, affective disturbances, loss of drive
CSF KFLC mg/L	1.2	0.6	0.4	0.7	0.3	0.3	0.5	0.5	0.4	2.4
Serum KFLC mg/L	37.6	11.3	21.6	12.9	9.0	10.5	23.0	11.4	20.7	11.2
Quotient KFLC	32.7	51.2	17.3	51.7	30.0	27.2	23.0	45.6	19.1	217.8
KFLC IF mean	49.6	80.2	50.4	84.0	51.5	70.6	49.9	62.1	46.9	96.4
Q_{mean}	16.5	10.1	8.6	8.3	14.5	7.9	11.5	17.3	10.1	7.7
Q_{lim}	27.5	16.9	14.3	13.8	24.3	13.3	19.2	29.0	16.9	12.8
KFLC IF%	15.8	66.9	17.2	73.3	19.1	51.0	16.5	36.5	11.4	94.1
KFLC Index	3.6	10.1	4.6	14.8	19.1	8.5	3.8	4.7	3.7	75.1
MMSE	21	26	15	29	22	na	29	na	27	na
GDS	2	7	na	4	-	na	na	na	na	na
Criteria autoimmune based psychiatric syndromes with KFLC	Probable autoimmune based psychiatric syndrome	Probable autoimmune based psychiatric syndrome	Probable autoimmune based psychiatric syndrome	No autoimmune based psychiatric syndrome	Probable autoimmune based psychiatric syndrome	No autoimmune based psychiatric syndrome	No autoimmune based psychiatric syndrome	Probable autoimmune based psychiatric syndrome	No autoimmune based psychiatric syndrome	Probable autoimmune based psychiatric syndrome
Criteria autoimmune based psychiatric syndromes without KFLC	Possible autoimmune based psychiatric syndrome	Possible autoimmune based psychiatric syndrome	Possible autoimmune based psychiatric syndrome	No autoimmune based psychiatric syndrome	Possible autoimmune based psychiatric syndrome	No autoimmune based psychiatric syndrome	No autoimmune based psychiatric syndrome	Probable autoimmune based psychiatric syndrome	No autoimmune based psychiatric syndrome	Probable autoimmune based psychiatric syndrome
Facilitation of diagnosis via KFLC	+	+	+	-	+	-	-	-	-	-

Abbreviations: Abs = neural autoantibodies, ASI = anti-viral specific antibody index, Aβ1–40 = amyloid- β1–40, Aβ1–40 = amyloid- β1–40, Aβ1–42 = amyloid-β1–42, Aβ1–42 = amyloid-β1–42, BBD = blood brain barrier disturbance, CMV = Cytomegaly virus, CSF = cerebrospinal fluid analysis, EBV = Ebstein Barr virus, GABA1/2 R = Gamma aminobutyric acid 1/ 2 receptor, GDS = Geriatric Depression Scale, HSV = Herpes simplex virus, ICD-10 = International Classification of Diseases, 10th revision, IgA = Immunoglobulin A, IgG = Immunoglobulin G, IgM = Immunoglobulin M, KFLC = Kappa free light chains, KFLC CSF = Kappa free light chains cerebrospinal fluid, KFLC IF % = kappa free light chains intrathecal fraction percentage, KFLC IF mean = kappa free light chains intrathecal fraction mean, MMSE = Mini Mental Status examination, OCB = oligoclonal bands, P-tau181 = phosphorylated tau protein 181, Q_{Alb} = quotient albumin, Q_{KFLC} = quotient kappa free light chains, Q_{limen} = quotient limen, Q_{mean} = quotient mean, VZV = Varizella zoster virus.

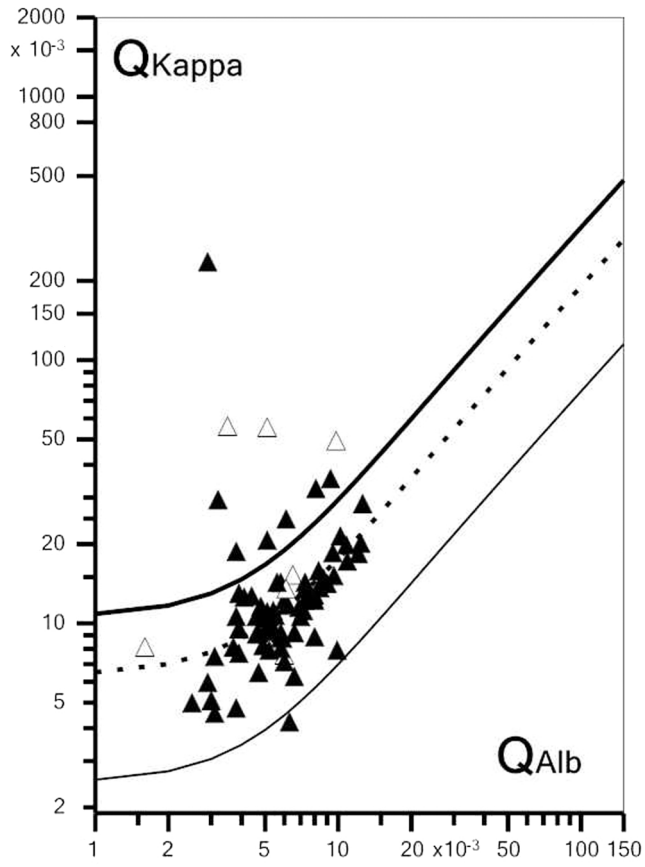

Fig. 2. Kappa free light chains in patients with elevated anti-viral specific antibody index. Quotient-diagrams also called Reiber diagrams, in double logarithmic exhibition of Q_{KFLC} (Q_{Kappa}), i.e. KFLC CSF/serum ratio, set against Q_{Alb}, i.e. Albumin CSF/serum ratio. The area above Q_{lim} refers to intrathecal KFLC synthesis, Q_{lim} is represented by the thick upper line and the Q_{mean} is demonstrated by the dotted middle line, whereas the Q_{low} is indicated by the thin lower line. A black triangle indicates a patient with anti-viral specific antibody index negativity and a white triangle a patient with anti-viral specific antibody index positivity. Abbreviations: KFLC CSF = Kappa free light chains cerebrospinal fluid, Q_{Alb} = quotient of albumin, Q_{KFLC} (Q_{Kappa}) = quotient of kappa free light chains, Q_{lim} = quotient limen, Q_{low} = quotient low, Q_{mean} = quotient mean.

investigated in a large-scale cohort of autoimmune based psychiatric syndromes. This may be attributable to the fact that polyclonal immunoglobulin light chains are also found in amyloid deposits, as a study of dialysis-related amyloidosis demonstrated [22]. It is therefore conceivable that in patients presenting increased KFLC, part of their increased KFLC result from amyloid degradation via the natural clearance of amyloid from the brain, which would thus modify the inflammatory immune response and its natural clearance function. Thus, it is possible that the trend of an increased amyloid beta 40 may be the result of the increased clearance of amyloid-β 40 with an overall higher clearance turnover due to inflammation. However, this is hypothetical and should be confirmed in experiments.

4.4. Limitations

Note that the limitation of KFLC as a surrogate marker for intrathecal IgG synthesis is the lack of consistent interpretation methods [23]. Nevertheless, applying Reiber's diagram together with relying on the hyperbolic function as a reference lead to 97 % diagnostic sensitivity (with moderate sensitivity of 75 % in multiple sclerosis patients) [24]. At the same time, we are aware that the heterogeneity of our cohort is an important limitation and means that we cannot come to any strong conclusions about specific psychiatric diagnoses. The age dependence of KFLC found in our cohort is not confirmed in the literature [24], suggesting different cohorts. In addition, the age dependence of autoantibodies is already reported in the literature [25], which could be due to the age restriction of our cohort from an older age, so that young people with autoantibodies are not part of the cohort. Another limitation is that the cell count was mostly low and therefore the percentage evaluation of the cell counts with division into cell subpopulations could be less reliable. Note that our cohort did not reveal the autoantibodies typically associated with psychiatric symptoms in an autoimmune encephalitis context, ie, anti-NMDAR [26], anti-CASPR2 [27] or anti-LGI1 [28]. This factor should therefore be investigated in another study. The pathogenic relevance of the autoantibodies we detected lacking the evidence of probable autoimmune encephalitis is unclear. KFLC were therefore added as an additional indirect criterion to assess intrathecal immunoglobulin synthesis and thus provide further supporting evidence for an immune-mediated genesis. However, we point out that this criterion is not one of the current criteria for autoimmune-related psychiatric syndromes [9]. However, KFLC may represent indirectly a criterion of intrathecal immunoglobulin synthesis, that should be added to criteria for autoimmune based psychiatric syndromes. In addition, our results should be interpreted with caution regarding the detectable autoantibody spectrum, as our cohort was representative of neither the general population nor a primarily psychiatric collective, but rather a selected cohort of psychiatric patients who underwent organic evaluation.

4.5. Conclusions

In any inflammatory intrathecal process [6], this tool is complementary to oligoclonal bands in diagnostics if an autoimmune origin is suspected in psychiatric syndromes, or if no autoantibodies are present and an inflammatory cause is suspected. Furthermore, KFLC can be important if the production of neural autoantibodies is too early and intrathecal immunoglobulin synthesis in the form of oligoclonal bands is not yet detectable. In addition, this may be the case if autoantibodies against previously unrecognized antigens are present, thus rendering KFLC a supporting feature for the assumption of autoimmunity. KFLC are not a tool that differentiates autoantibody-positive from autoantibody-negative patients, but they might be helpful in differential diagnostics for clarifying whether psychiatric symptoms share an organic basis (autoimmune based psychiatric syndromes). Large scale studies are needed to identify whether the KFLC index is relevant for further differential diagnostic assessment in certain autoantibody diseases, as already shown in a study on myelin oligodendrocyte glycoprotein antibody disease [29]. It could therefore be important in the future to determine the extent to which KFLC or the KFLC indices are increased in autoantibody-associated neuropsychiatric diseases, as there are already indications that KFLC can distinguish multiple sclerosis from other inflammatory diseases of the CNS [30]. In multiple sclerosis, KFLC are already an essential component of differential diagnosis in answering the question of intrathecal immunoglobulin synthesis [31], while this has not yet been applied in autoimmune based psychiatric syndromes. The use of an algorithm that determines the intrathecal fraction of the KFLC could be complementary to detection of oligoclonal bands [32]. This means that despite the probably low differential diagnostic value in a heterogeneous cohort of antibody-positive versus antibody-negative patients, identifying KFLC will prove essential in the assessment of early intrathecal immune response. Nevertheless, this study does not indicate the usefulness of KFLC, but no obvious need for the implementation of KFLC in the guidelines for autoantibody-associated psychiatric disorders and further large-scale studies are needed to better answer this question.

Author contributions

LMG, KAB, DF and NH wrote the article. All other authors revised the

article for important intellectual content.

CRediT authorship contribution statement

Berend Malchow: Writing – review & editing. **Luise M. Groeger:** Writing – original draft, Methodology, Investigation, Data curation. **Jens Wiltfang:** Writing – review & editing. **Niels Hansen:** Writing – original draft, Supervision, Project administration, Conceptualization. **Amina Simou:** Methodology, Investigation. **Dirk Fitzner:** Writing – original draft, Methodology, Investigation. **Auf dem Brinke Kristina:** Writing – original draft, Methodology, Investigation. **Stefan Bleich:** Writing – review & editing. **Jürgen Gallinat:** Writing – review & editing. **Franz F. Konen:** Writing – review & editing. **Thomas Skripuletz:** Writing – review & editing. **Daniel Luedecke:** Writing – review & editing. **Alexandra Neyazi:** Writing – review & editing. **Hannah B. Maier:** Writing – review & editing.

Declaration of Competing Interest

The authors declare no competing interests.

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Data Availability

Data will be made available on request.

References

[1] R. Candeloro, M. Galloppa, L. Lombardo, M. Laudisi, S. Ghisellini, G. Negri, et al., Kappa free light chains in multiple sclerosis as a marker of intrathecal humoral response: a Sex-Disaggregated study (https//doi:), Diagn. (Basel) 14 (2024) 2798, https://doi.org/10.3390/diagnostics14242798.

[2] J. Ferriz, C. Guallart, P. Timoneda, M. Fandos, J. Lopez-Arqueros, A. Sierra-Rivera, et al., Diagnostic approach for multiple sclerosis: optimizing algorithms for intrathecal synthesis of immunoglobulins, lmae101, Lab Med. (2024), https://doi.org/10.1093/labmed/lmae101.

[3] G. De Napoli, M. Gastaldi, P. Natali, R. Bedin, A.M. Simone, M. Santangelo, et al., Kappa index in the diagnostic work-up of autoimmune encephalitis, 123146, J. Neurol. Sci. 463 (2024) 15, https://doi.org/10.1016/j.jns.2024.123146.

[4] M. Morello, S. Mastrogiovanni, F. Falcione, V. Rossi, S. Bernardini, S. Casciani, et al., Laboratory diagnosis of intrathecal synthesis of immunoglobulins: a review about the contribution of OCBs and K-index, J. Mol. Sci. 25 (2024) 5170, https://doi.org/10.3390/ijms25105170.

[5] F.F. Konen, U. Wurster, P. Schwenkenbecher, A. Gerritzen, C.C. Groß, P. Eichhorn, et al., German society for cerebrospinal fluid diagnostics and clinical neurochemistry (DGLN e.V.). oligoclonal bands and kappa free light chains: competing parameters or complementary biomarkers? Autoimmun. Rev. 24 (2025) 103765 https://doi.org/10.1016/j.autrev.2025.103765.

[6] D. Bertram, T. Tsaktanis, A. Berthele, T. Korn, The role of intrathecal free light chains kappa for the detection of autoimmune encephalitis in subacute onset neuropsychiatric syndromes, Sci. Rep. 13 (2023) 17224, https://doi.org/10.1038/s41598-023-44427-6.

[7] H. Hegen, J. Walde, K. Berek, G. Arrambide, S. Gnanapavan, B. Kaplan, et al., Cerebrospinal fluid kappa free light chains for the diagnosis of multiple sclerosis: a systematic review and meta-analysis, Mult. Scler. 29 (2023) 169–181, https://doi.org/10.1177/13524585221134213.

[8] J. Herken, H. Prüss, Red flags: clinical signs for identifying autoimmune encephalitis in psychiatric patients, Front. Psychiatry 8 (2017) 25, https://doi.org/10.3389/fpsyt.2017.00025.

[9] N. Hansen, M. Lipp, J. Vogelgsang, R. Vukovich, T. Zindler, D. Luedecke, et al., CAP (Cerebrospinal Fluid Analysis in Psychiatry) consortium. Autoantibody-associated psychiatric symptoms and syndromes in adults: a narrative review and proposed diagnostic approach, Brain Behav. Immun. Health 9 (2020) 100154, https://doi.org/10.1016/j.bbih.2020.100154.

[10] F. Graus, M.J. Titulaer, R. Balu, S. Benseler, C.G. Bien, T. Cellucci, I. Cortese, R. C. Dale, J.M. Gelfand, M. Geschwind, C.A. Glaser, J. Honnorat, R. Höftberger, T. Iizuka, S.R. Irani, E. Lancaster, F. Leypoldt, H. Prüss, A. Rae-Grant, M. Reindl, M. R. Rosenfeld, K. Rostásy, A. Saiz, A. Venkatesan, A. Vincent, K.P. Wandinger, P. Waters, J.Lancet Neurol Dalmau, A clinical approach to diagnosis of autoimmune encephalitis, 15(4):391-404, Lancet Neurol. 2016 (15) (2016 Apr) 391–404.

[11] K. Bechter, Encephalitis, mild encephalitis, neuroprogression, or Encephalopathy-Not merely a question of terminology, Front. Psychiatry 9 (2019) 782, https://doi.org/10.3389/fpsyt.2018.00782.

[12] K. Bechter, The challenge of assessing mild neuroinflammation in severe mental disorders, Front Psychiatry 11 (2020) 773, https://doi.org/10.3389/fpsyt.2020.00773.

[13] Broome, I., Bottlender, R., Rösler, M., Stieglitz, R.D. (Editors). The AMDP system. Manual for assessment and documentation of psychopathology in psychiatry. 9th edition, Hogrefe Verlag. Göttingen, 2017. ISBN 978-0-88937-542-0.

[14] H. Reiber, D. Zeman, P. Kušnierová, E. Mundwiler, L. Bernasconi, Diagnostic relevance of free light chains in cerebrospinal fluid - the hyperbolic reference range for reliable data interpretation in quotient diagrams, Clin. Chim. Acta 497 (2019) 153–162, https://doi.org/10.1016/j.cca.2019.07.027.

[15] M. Süße, H. Reiber, M. Grothe, A. Petersmann, M. Nauck, A. Dressel, Free light chain kappa and the polyspecific immune response in MS and CIS - application of the hyperbolic reference range for most reliable data interpretation, J. Neuroimmunol. 346 (2020) 577287, https://doi.org/10.1016/j.jneuroim.2020.577287.

[16] E. Virgilio, V. Ciampana, C. Puricelli, P. Naldi, A. Bianchi, U. Dianzani, et al., Biomarkers of intrathecal synthesis May be associated with cognitive impairment at MS diagnosis, Int. J. Mol. Sci. 26 (2025) 826, https://doi.org/10.3390/ijms26020826.

[17] N. Hansen, K. Schwing, D. Önder, G. Widman, P. Leelaarporn, I. Prusseit, R. Surges, N. Melzer, C. Gross, A.J. Becker, J.A. Witt, C.E. Elger, C. Helmstaedter, Low CSF CD4/CD8+ T-cell proportions are associated with blood-CSF barrier dysfunction in limbic encephalitis, Epilepsy Behav. 102 (2020) 106682, https://doi.org/10.1016/j.yebeh.2019.106682.

[18] N. Hansen, G. Widman, D. Önder, K. Schwing, P. Leelaarporn, I. Prusseit, R. von Wrede, R. Surges, A.J. Becker, J.A. Witt, C.E. Elger, C. Helmstaedter, Increased T- and B-cells associated with the phenotype of autoimmune limbic encephalitis with mainly memory dysfunction, J. Transl. Autoimmun. 5 (2022) 100167, https://doi.org/10.1016/j.jtauto.2022.100167.

[19] A. Dik, G. Widman, A. Schulte-Mecklenbeck, J.A. Witt, J. Pitsch, K.S. Golombeck, et al., Impact of t cells on neurodegeneration in anti-GAD65 limbic encephalitis, Ann. Clin. Transl. Neurol. 8 (12) (2021) 2289–2301, https://doi.org/10.1002/acn3.51486.

[20] C. Helmstaedter, N. Hansen, P. Leelaarporn, K. Schwing, D. Oender, G. Widman, et al., Specific B- and T-cell populations are associated with cognition in patients with epilepsy and antibody positive and negative suspected limbic encephalitis (https//), J. Neurol. 268 (2021) 455–466, https://doi.org/10.1007/s00415-020-10158-1.

[21] J. Chen, M. Qin, X. Xiang, X. Guo, L. Nie, L. Mao, Lymphocytes in autoimmune encephalitis: pathogenesis and therapeutic target, Neurobiol. Dis. 200 (2024) 106632, https://doi.org/10.1016/j.nbd.2024.106632.

[22] D. Brancaccio, G.M. Ghiggeri, P. Braidotti, A. Garberi, M. Gallieni, V. Bellotti, et al., Deposition of kappa and lambda light chains in amyloid filaments of dialysis-related amyloidosis, 70, J. Am. Soc. Nephrol. 6 (1995) 1262, https://doi.org/10.1681/ASN.V641262.

[23] F.F. Konen, P. Schwenkenbecher, K.F. Jendretzky, S. Gingele, K.W. Sühs, H. Tumani, et al., The increasing role of kappa free light chains in the diagnosis of multiple sclerosis, Cells 10 (2021) 3056.

[24] R. Moulias, J. Proust, A. Wang, F. Congy, M.R. Marescot, A. Deville Chabrolle, A. Paris Hamelin, B. Lesourd, Age-related increase in autoantibodies, -9, Lancet 1 (1984) 1128, https://doi.org/10.1016/s0140-6736(84)92547-9.

[25] N. Rollborn, K. Kultima, A. Larsson, Reference intervals for plasma free kappa and lambda chains and Kappa/Lambda ratio using PENIA, Clin. Lab 69 (2023) 37560857, https://doi.org/10.7754/Clin.Lab.2023.230109.PMID.

[26] N. Hansen, V. Buschatzky, A.K. Bastin, K. Rentzsch, B. Teegen, D. Luedecke, T. Skripuletz, H.B. Maier, S. Bleich, J. Gallinat, H. Esselmann, I.R. Dunay, I. Zerr, D. Fitzner, J. Wilftang, A. Neyazi, B.H. Schott, B. Malchow, CAP (Cerebrospinal Fluid Analysis in Psychiatry) consortium, Neural autoantibodies in psychiatric disorders are associated with antibodies against viral pathogens: a retrospective study of 619 patients, J. Neural Transm. (Vienna) 132 (7) (2025) 1063–1074.

[27] Y. Yi, Y. Zhao, H. Zhou, J. Wang, Identifying anti-LGI-1 encephalitis in psychotic disorders: a clinically focused review, Gen. Hosp. Psychiatry 94 (2025) 74–83.

[28] Y. Jia, M. Li, S. Hu, H. Leng, X. Yang, Q. Xue, M. Zhang, H. Wang, Z. Huang, H. Wang, J. Ye, A. Liu, Y. Wang, Psychiatric features in NMDAR and LGI1 antibody-associated autoimmune encephalitis, Eur. Arch. Psychiatry Clin. Neurosci. 274 (5) (2024) 1051–1061.

[29] R. Deschamps, N. Shor, C. Papeix, M. Boudot de la Motte, C. Bensa, R. Marignier, et al., Relevance of kappa free light chains index in patients with aquaporin-4 or myelin-oligodendrocyte-glycoprotein antibodies, Eur. J. Neurol. 30 (2023) 2865–2869, https//doi.org/10.1111/ene.15897.

[30] L. Michetti, F. Maffina, R. Ravasio, V. Barcella, M. Radaelli, L. Chiudinelli, et al., Free light chains as a reliable biomarker of intrathecal synthesis in the diagnosis of CNS inflammatory diseases, J. Neuroimmunol. 379 (2023) 578091, https://doi.org/10.1016/j.jneuroim.2023.578091.

[31] H. Hegen, G. Arrambide, S. Gnanapavan, B. Kaplan, M. Khalil, R. Saadeh, et al., Cerebrospinal fluid kappa free light chains for the diagnosis of multiple sclerosis: a consensus statement (https//), Mult. Scler. 29 (2023) 182–195, https://doi.org/10.1177/13524585221134217.

[32] M.J. Hannich, M.R. Abdullah, K. Budde, A. Petersmann, M. Nauck, A. Dressel, et al., A new laboratory workflow integrating the free light chains kappa quotient into routine CSF analysis, Biomolecules 12 (2022) 1690, https://doi.org/10.3390/biom12111690.