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Diagnostic value of CSF findings in antibody-associated limbic and anti-NMDAR-encephalitis

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ABSTRACT

Purpose: In people with suspected inflammatory CNS disease, cerebrospinal fluid (CSF) is commonly analyzed. Antibody-associated limbic encephalitis (ab-LE) and anti-NMDAR-encephalitis are recognized as two major syndromes of autoimmune epilepsies. Here, we investigated the diagnostic value of CSF findings in these two entities.

Methods: We reviewed patients from our tertiary epilepsy centre with ab-LE and anti-NMDAR-encephalitis in whom CSF examination including oligoclonal bands (OCB) was performed. Ab-LE patients were subdivided according to antibodies (voltage-gated potassium channels, VGKC; glutamic acid decarboxylase, GAD) or presence of onconeural antibodies/presence of tumour into three groups: VGKC-LE, GAD-LE or paraneoplastic LE (PLE). As controls, patients with CSF investigations in whom autoimmune origin was initially assumed but not confirmed later on were included. In addition, a review of published ab-LE and anti-NMDAR-encephalitis cases with reported CSF data was performed.

Results: 55 ab-LE (23 VGKC-LE, 25 GAD-LE, 7 PLE) and 14 anti-NMDAR-encephalitis patients were identified at our centre. OCB were significantly more frequent in ab-LE and anti-NMDAR-encephalitis than in controls. Literature review identified 150 ab-LE and 95 NMDAR cases. Analysis of pooled data confirmed that presence of OCB was significantly more frequent in ab-LE and anti-NMDAR-encephalitis (especially in people with GAD-LE and anti-NMDAR encephalitis) as compared to controls. Sensitivity and specificity of OCB in the pooled ab-LE and anti-NMDAR-encephalitis patients was 34% and 96%, respectively. In patients with ab-LE and anti-NMDAR-encephalitis, the likelihood of OCB in CSF was 8.5-fold higher as compared to controls. Furthermore, in the pooled ab-LE and anti-NMDAR-encephalitis patients, cell counts in CSF were more frequently elevated (especially in those with anti-NMDAR encephalitis) than in controls, whereas protein content of CSF was not different between the groups.

Conclusion: OCB, and to a lesser extent cell counts in CSF, appear to be helpful additional CSF markers in the diagnostic evaluation of people presenting with a constellation suggestive for GAD-LE, PLE and anti-NMDAR-encephalitis, prompting subsequent analysis of specific antibodies.

1. Introduction

There is increasing evidence that autoimmune-mediated mechanisms lead to epilepsy in a considerable proportion of patients.[1] Antibody-associated limbic encephalitis (ab-LE) and anti-NMDAR-encephalitis are the two major syndromes. Ab-LE is described as paraneoplastic or non-paraneoplastic syndrome. Several non-paraneoplastic subforms associated with serologically characterized auto-antibodies (abs) were identified including those with abs against voltage-gated potassium channels (VGKC) and glutamic acid decarboxylase (GAD).[1] Anti-NMDAR-encephalitis was first described as severe encephalopathic syndrome in young women associated with a higher rate of ovarian teratoma,[2] but it also occurs in children, men and in people without teratomas.[3]

In general, these autoimmune-mediated epilepsies are rare and multifaceted, and unfamiliar initial symptoms may hamper the correct diagnosis at an early stage.[4] In other neurological conditions, analysis of cerebrospinal fluid (CSF) is widely used in routine neurological diagnostics to reveal constellations suggestive for ongoing acute or chronic CNS inflammation. Especially the selective presence of unmatched oligoclonal bands (OCB) in CSF but not in serum is considered as a strong, although unspecific marker of chronic CNS inflammation.[5] Here, we asked whether OCB and other CSF features are associated with ab-LE and anti-NMDAR-encephalitis. To this end, we investigated all ab-LE and anti-NMDAR-encephalitis patients at our centre and performed a thorough review of published cases in literature with regard to CSF findings.

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2. Methods

2.1. Patient selection

All patients from our tertiary epilepsy centre in Bonn with diagnosis of ab-LE and anti-NMDAR-encephalitis and complete CSF investigations (see below) were retrospectively included. In all these patients, we have routinely performed 3 Tesla brain MRI, routine EEG for 20 min or 24 h video-EEG telemetry using scalp electrodes (10–20 system), neuropsychological testing, determination of known abs in serum and CSF (also in order to exclude encephalitis due to infectious agents).

Ab-LE and anti-NMDAR-encephalitis was defined by new-onset epilepsy (seizure onset not longer than 5 years prior to first assessment at our centre independently of seizure frequency and whether seizures were the sole or predominant clinical symptom) and the presence of abs in serum or CSF. According to additional clinical symptoms and specific antibodies, the following two syndromes were distinguished:

1. *Ab-LE*: Patients with "limbic" signs and symptoms (≥1 of the following: seizures of temporal lobe semiology, disturbance of episodic memory, affective disturbances), brain MRI revealing mesiotemporal encephalitis (T2/FLAIR hyperintensity without atrophy) and presence of specific abs and/or identification of a tumour.[1,6] In all patients serum was tested for presence of the following abs: VGKC, GAD, onconeural abs, N-methyl-D-aspartate-receptor (NMDAR).
2. *Anti-NMDA-encephalitis*: Patients were assessed according to described clinical features and identification of NMDAR-abs.[2]

As controls, we included all patients who have undergone CSF investigations for initial suspicion of autoimmune origin which has not been confirmed later on. The diagnosis of non-autoimmune epilepsy was based on the absence of known abs, absence of typical MRI findings (e.g. initial swelling of mesiotemporal structures and subsequent remission or development of atrophy) and the presence of other plausible aetiology for epilepsy.

2.2. Review of the literature

We performed a systematic review of the literature using the following search terms: limbic encephalitis, limbic encephalitis VGKC, limbic encephalitis GAD, anti-NMDAR-encephalitis. Limits were defined as: published in the last 10 years, only items with link to full text, humans, type of article (Clinical Trial, Randomized Controlled Trial, Case reports, Classical article, Journal Article), subsets MEDLINE, language English. All previous publications from our institution in Bonn were excluded to avoid data interferences. Only publications with data of CSF with OCB determination and clearly assigned to individual patients were included in further analysis.

2.3. Comparison of patient cohorts

First, CSF data of the ab-LE and anti-NMDAR-encephalitis patients of our centre were compared to our control group (see Section 2.6). Second, we have pooled all CSF data (including our own patients and the published cases) and compared these pooled data to our local controls. Individual CSF data were not reported in all of the published patients. In those cases missing data were excluded from analysis.

2.4. CSF analysis

All data were obtained in clinical routine diagnostics. Complete CSF analysis included cell count, protein content, and evaluation of blood-CSF-barrier function, intrathecal IgG synthesis by Reiber-scheme and by OCB. White cell counts >5/μl without erythrocytosis and CSF protein >500 mg/l were defined as abnormally elevated. As internationally accepted parameter for blood-CSF function age-dependent albumin-CSF/serum-quotient Q_{Alb} was used.[5] Intrathecal IgG synthesis as an indicator for humoral immune response was assessed quantitatively by IgG-CSF/serum-quotient Q_{IgG} (values >0.7 indicating for intrathecal synthesis)[5] and qualitatively by OCB in isoelectric focusing (IEF) according to international consensus.[7] Unmatched OCBs in CSF and not in serum were considered as markers for autochthone intrathecal IgG production. If available, repeated CSF investigations in patients were considered in the same manner.

2.5. Ab determination

Ab testing was performed as follows: Serum VGKC-abs were assessed by radioimmunoprecipitation assay (RIA; normal values <100 pmol/l, AV, Weatherall Institute, Oxford, UK and EUROIMMUN laboratory, Luebeck, Germany).[8] Identification of GAD-abs in serum was performed by RIA using ^{125}I-GAD (normal values ≤1 U/ml, AV)[6] or by indirect immunofluorescence (IFT, nomal values <1:10, EUROIMMUN). "Well characterized" onconeural abs were also tested by a commercially available routine test using an immune-dot-blot for Hu, Ma, amphiphysin, CV2/CRMP5 abs (Ravo Diagnostika, Freiburg, Germany). NMDAR-abs were tested by specific immunofluorescence test (IFT, AV and EUROIMMUN).[9]

Table 1
CSF features of ab-LE and anti-NMDAR-encephalitis in the Bonn patients.

Bonn patients	Elevated cell counts (>5/μl)	Elevated protein content (>500 mg/l)	Blood-CSF-disturbance	Intrathecal IgG synthesis (Q_{IgG})	Intrathecal IgG synthesis (OCB)
All (*N* = 69)	11	16	19	2	25
Ab-LE all (*N* = 55)	9	11	14	2	18
VGKC-LE (*N* = 23)	3	6	8	1	0
GAD-LE (*N* = 25)	3	2	4	1	14
PLE (*N* = 7)	3	3	2	0	4
NMDAR (*N* = 14)	2	5	5	0	7
Non-autoimmune controls (*N* = 28)	1	8	9	0	1
p-Values (all vs. controls)	0.17[a]	0.61[a]	0.81[a]	1[a]	**<0.001**[a]
p-Values (ab-LE vs. controls)	0.15[a]	0.42[a]	0.61[a]	0.55[a]	**0.002**[a]
p-Values (NMDAR vs. controls)	0.25[a]	0.73[a]	1[a]	1[a]	**<0.001**[a]

Ab-LE: antibody associated limbic encephalitis; VGKC: antibodies to VGKC; GAD: antibodies to GAD; PLE: paraneoplastic LE; NMDAR: anti-NMDAR-encephalitis; Q_{IgG}: IgG-CSF/serum-quotient according to Reiber[5]; OCB: unmatched oligoclonal bands in CSF, not in serum.
[a] Fisher exact test, significances after Holm–Bonferroni corrections are highlighted in bold.

Table 2
Clinical characteristics of patients with ab-LE and anti-NMDAR-encephalitis in Bonn.

Bonn patients	Gender	Median age at onset in years (range)	Median disease duration in months (range)
All (N = 69)	41 ♀	38 (8–73)	10 (0–252)
Ab-LE all (N = 55)	28 ♀	43 (8–73)	10 (0.3–252)
VGKC-LE (N = 23)	7 ♀	57 (20–73)	7 (0.3–23)
GAD-LE (N = 25)	16 ♀	25 (8–65)	40 (1–252)
PLE (N = 7)	5 ♀	47 (14–60)	34 (0.4–71)
Anti-NMDAR-Enzephalitis (N = 14)	13 ♀	25 (17–58)	16 (0–168)
Non-autoimmune controls (N = 28)	16 ♀	41 (16–73)	13 (0.6–116)

For abbreviations see legend in Table 1.

2.6. Statistics

For nominal data, Fisher's exact test was used. Due to multiple comparisons, p-values were adjusted according to the Holm–Bonferroni stepwise correction procedure, p-value <0.05 were considered significant. Sensitivity and specificity were calculated according to gold-standard test. For assessing the value of performed diagnostic tests, the likelihood ratio was calculated with values >1 indicating positive association with disease.

3. Results

3.1. Patient characteristics

A total of 69 patients with ab-LE and anti-NMDAR-encephalitis were identified in Bonn: 55 ab-LE and 14 anti-NMDAR encephalitis patients. Ab-LE patients were subclassified according to ab identification (VGKC-LE, GAD-LE) or onconeuronal abs and detected tumour (paraneoplastic LE, PLE; two patients had onconeuronal ab without detected tumour), for distribution and clinical patient details, see Tables 1 and 2. Twenty-eight control patients were included. They were finally diagnosed as having psychogenic non-epileptic seizures (N = 7), syncope (N = 5), structural epilepsies of other origin than auto-immune mediated mechanisms (N = 6: 2 tumour, 1 infarction, 1 severe head trauma, 2 dysplasia), psychiatric disorders (N = 5: 2 depression, 1 anxiety, 1 psychosis, 1 obsessive–compulsive disorder), dementia (N = 3) or with other conditions (N = 2: 1 transitory ischaemic attacks, 1 normal pressure hydrocephalus) or no identified disease (N = 1). The patient positive for OCB was a 68-year-old woman with a new-onset structural epilepsy due to infarction.

3.2. Review of the literature

Four hundred and fifty-seven articles matched searching criteria, 58 studies matched inclusion criteria: 36 dealt with ab-LE (VGKC: 12; GAD: 8: onconeural: 13; various: 3) and 22 focused on anti-NMDAR-encephalitis. In a total of 245 reported ab-LE and anti-NMDAR-encephalitis patients, CSF data were individually assigned as follows: 150 ab-LE patients (86 VGKC, 24 GAD, 33 PLE, 7 with combination of abs) and 95 NMDAR patients. Details and references of literature are given in Supplementary Table 1.

3.3. CSF findings

3.3.1. Bonn patients

CSF findings are highlighted in Table 1. Only intrathecal IgG synthesis ascertained by OCB was different between the patient groups: it was more frequent in ab-LE and anti-NMDAR-encephalitis patients than in controls ($p < 0.001$) even when comparing separately anti-NMDAR-encephalitis ($p < 0.001$) and LE ($p = 0.002$). Notably, consideration of ab-LE-subforms revealed that presence of OCB in VGKC-LE was not different to controls, whereas OCB was significantly associated with GAD-LE and PLE (VGKC vs. controls $p = 1$; GAD $p < 0.001$; PLE $p = 0.003$). Sensitivity for OCB amounted only to 36% in the Bonn patients with ab-LE and anti-NMDAR-encephalitis (ab-LE: 33%; NMDAR: 50%), whereas specificity amounted to 96%. The likelihood for OCB in people with ab-LE and anti-NMDAR-encephalitis was 9-fold higher as compared to controls (likelihood ratio; ab-LE: 8.25, NMDAR: 12.5).

Serial CSF investigations were performed in 29 (42%) ab-LE and anti-NMDAR-encephalitis patients (19 ab-LE, 10 NMDAR) over a median period of 15 months (range 1–84), but not in the control group. OCB were positive in 13 of these patients (43%). Interestingly, in those patients in whom OCB was not detected in the first CSF examination, OCB was not revealed in the further course (see Supplementary Table 2).

3.3.2. Pooled data of published cases and patients from Bonn

In published ab-LE and anti-NMDAR-encephalitis patients (N = 245), elevated cell counts were reported in 112/235 (48%) patients and elevated protein counts in 73/229 (32%) patients. OCB were reported in CSF of 82/199 (41%) ab-LE and anti-NMDAR-encephalitis patients: in 35/136 (26%) published ab-LE patients (8/77 VGKC, 13/23 GAD, 14/29 PLE) and in 47/63 (75%) published NMDAR patients.

Table 3
CSF features of ab-LE and anti-NMDAR-encephalitis in the pooled Bonn and published patients.

Pooled data	Elevated cell counts (>5/μl)	Elevated protein content (>500 mg/l)	Intrathecal IgG synthesis (OCB)
All (N = 314)	123/304	89/298	107/268
Ab-LE all (N = 205)	44/197	59/197	53/191
VGKC-LE (N = 109)	23/106	37/106	8/100
GAD-LE (N = 49)	3/48	5/48	27/48
PLE (N = 40)	18/36	15/36	18/36
Others (N = 7)	0/7	2/7	0/7
Anti-NMDAR-Enzephalitis (N = 109)	79/107	30/101	54/77
Non-autoimmune Bonn controls (N = 28)	1/28	8/28	1/28
p-Values (all vs. controls)	<**0.0001**	1	<**0.0001**
p-Values (ab-LE vs. controls)	0.02	1	0.004
p-Values (NMDAR vs. controls)	<**0.0001**	1	<**0.0001**

For abbreviations see legend in Table 1.

Our CSF findings were pooled with those of previously published cases and compared to our controls (Table 3). Again, presence of OCB was more frequently detected in ab-LE and anti-NMDAR-encephalitis ($p < 0.001$), and more specifically in the subgroup of anti-NMDAR-encephalitis ($p < 0.001$) as compared to controls. Furthermore, cell counts were elevated more frequently in ab-LE and anti-NMDAR-encephalitis patients ($p < 0.001$) than in controls, especially in patients with anti-NMDAR-encephalitis ($p < 0.001$) but not in patients with ab-LE when compared separately.

Values of sensitivity, specificity and likelihood ratios for OCB and for elevated cell counts in CSF are given for the pooled Bonn/published ab-LE and anti-NMDAR-encephalitis patients in Tables 4A and 4B.

4. Discussion

We have found that (i) OCB are more frequently observed in people with ab-LE and anti-NMDAR-encephalitis, particularly in people with GAD-LE and anti-NMDAR encephalitis, and that (ii) abnormally elevated cell counts are associated with anti-NMDAR encephalitis. Thus, CSF findings may be a useful marker in the diagnostic evaluation of people in whom autoimmune-mediated epilepsy is suspected, prompting further examinations including detailed search for antibodies typically associated with subforms of autoimmune-mediated epilepsies.

Due to the retrospective design, however, our study has several limitations. First, our clinic is a tertiary reference centre for people with *chronic* epilepsy, and our data is thus biased by the presence of recurrent seizures. People with autoimmune-mediated processes without seizures or people with seizures due to viral or bacterial encephalitis were not considered. Second, because of diagnostic uncertainties and lacking diagnostic "gold-standard", people in whom autoimmune-mediated epilepsy was suspected, but in whom known abs (see methods) were not detected, were excluded from the study. Third, we have selectively included patients in whom CSF and OCB investigations have been performed based on clinical judgement. Therefore, our study is biased for patients with CSF samples and initial assumption of CNS inflammation. For clinical purpose, it would be of outstanding interest to know the predictive positive and negative values of CSF findings for ab-LE and anti-NMDAR-encephalitis. This is, however, not possible, as we cannot reliably estimate the prevalence of ab-LE and anti-NMDAR-encephalitis.

Despite these limitations, our study provides extensive data (including literature review) on the usefulness of CSF findings in a clinically well characterized population including a variety of autoimmune-mediated epilepsy syndromes. We have found that OCB are more frequently observed in people with ab-LE and anti-NMDAR-encephalitis with a likelihood of 8.5-fold higher as compared to controls, suggesting that especially OCB are a useful supportive marker in the diagnostic evaluation of autoimmune-mediated epilepsies. Importantly, when OCB are negative at first CSF examination, the probability of OCB detection in the further course in serial lumbar punctures is low. Whereas specificity is relatively high, sensitivity for OCB in ab-LE and anti-NMDAR-encephalitis was low. Based on these results, negative OCB do of course not exclude autoimmune aetiology such as ab-LE and anti-NMDAR-encephalitis and further investigations such as ab testing and tumour search are required. In this context, it is important to note that we have not included people with suspected limbic encephalitis without detection of known abs in this study, as an international consensus on the "gold-standard" of diagnostic work-up has not been reached yet. Thus, there might also be patients with autoimmune-mediated epilepsies without detected abs, but abnormal CSF findings.

Whereas pathological CSF findings were described frequently in "classic" paraneoplastic LE,[10] knowledge about their occurrence in the recently identified non-paraneoplastic ab-positive subforms is scarce. In people with VGKC-LE only slight increases of protein levels and cell counts in CSF were reported[11] whereas OCB were found in 60% of patients with anti-NMDAR-encephalitis.[3] In line with these reports, none of our patients and only 11% of the published VKGC-LE cases had OCB.

The presence of OCB as a measure of intrathecal ab synthesis in anti-NMDAR encephalitis and GAD-LE suggests that these entities may depend on a primary pathological process within the brain or, alternatively, that they develop after migration of ab-producing cells into the CNS.[1] In contrast, the absence of OCB (and abs within the CSF, as shown by others[1,11]) in people with VGKC-LE is in favour of a primary peripheral synthesis outside of the central nervous system and subsequent diffusion across the blood-CSF barrier where the abs secondarily lead to neuronal hyperexcitability and maybe inflammation.[1,12] This is, however, pure speculation and further neuropathological examinations of brain tissue in affected patients as well as experimental laboratory investigations are required to address these questions.

Table 4A
Sensitivity, specificity and likelihood ratio of OCB for the pooled data (our centre and published patients).

Pooled data OCB	Sensitivity %	Specificity %	Likelihood ratio
All vs. controls	34	96	8.5
Ab-LE vs. controls	28	96	7
VGKC	7	96	1.75
GAD	59	96	14.75
PLE	50	96	12.5
NMDAR vs. controls	67	96	16.75

For abbreviations see legend in Table 1.

Table 4B
Sensitivity, specificity and likelihood ratio of elevated cell counts in CSF for the pooled data (our centre and published patients).

Pooled data Elevated cell counts	Sensitivity %	Specificity %	Likelihood ratio
All vs. controls	40	96	10
Ab-LE vs. controls	22	96	5.5
VGKC	22	96	5.5
GAD	6	96	1.5
PLE	50	96	12.5
NMDAR vs. controls	74	96	18.5

For abbreviations see legend in Table 1.

5. Conclusion

Our data suggest that CSF investigations with determination of OCB are a supportive marker if autoimmune-mediated epilepsies such as GAD-LE, PLE and anti-NMDAR-encephalitis are suspected, whereas it failed to provide significance in VGKC-LE. Ab testings and tumour search should be undertaken to specify the underlying syndrome.

Contributions

Study was designed by MPM and RS. MPM collected the data. Statistical analysis was performed by MPM and RS. MPM, CEE and RS have written the draft and all authors have contributed substantially to the final version.

Disclosure

MPM received payments for congress participation, travel expenses, lecture and manuscript preparation from EISAI and

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2012.12.013.

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