Diagnostic challenges in patients with temporal lobe seizures and features of autoimmune limbic encephalitis

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Abstract

Background and purpose: Consensus criteria for autoimmune limbic encephalitis (ALE) allow for a diagnosis even without neuronal antibodies (Abs), but it remains unclear which clinical features should prompt neuronal Ab screening in temporal lobe epilepsy patients. The aim of the study was to investigate whether patients with temporal lobe seizures associated with additional symptoms or signs of limbic involvement may harbor neuronal Abs, and which clinical features should prompt neuronal Ab screening in these patients.

Methods: We identified 47 patients from a tertiary epilepsy center with mediotemporal lobe seizures and additional features suggestive of limbic involvement, including either memory deficits, psychiatric symptoms, mediotemporal magnetic resonance imaging (MRI) hyperintensities or inflammatory cerebrospinal fluid (CSF). Neuronal Ab testing was carried out at two independent reference laboratories (Bielefeld-Bethel, Germany, and Barcelona, Spain). All brain MRI scans were assessed by two reviewers independently.

Results: Temporal lobe seizures were accompanied by memory deficits in 35/46 (76%), psychiatric symptoms in 27/42 (64%), and both in 19/42 patients (45%). Limbic T2/fluid-attenuated inversion recovery signal hyperintensities were found in 26/46 patients (57%; unilateral: n = 22, bilateral: n = 4). Standard CSF studies were abnormal in 2/37 patients (5%). Neuronal Abs were confirmed in serum and/or CSF in 8/47 patients (17%) and were directed against neuronal cell-surface targets (leucine-rich glioma inactivated protein 1: n = 1, contactin-associated protein-2: n = 1, undetermined target: n = 3) or glutamic acid decarboxylase in its 65-kD isoform (n = 3, all with high titers). Compared to Ab-negative patients, those who harbored neuronal Abs were more likely to have uni- or bilateral mediotemporal MRI changes (8/8, 100% vs. 18/38, 47%; p = 0.01, Fisher’s exact test).

Conclusions: In patients with temporal lobe seizures and additional limbic signs, 17% had neuronal Abs affirming ALE diagnosis. Mediotemporal MRI changes were found in all Ab-positive cases and had a positive likelihood ratio of 2.11 (95% confidence interval 1.51-2.95).

Ismail and Spatola: Equal contribution as first authors.
Wellmer and Schlegel: Equal contribution as senior authors.

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INTRODUCTION

Autoimmune limbic encephalitis (ALE) is an immune-mediated brain inflammation, predominantly involving the gray matter of the medial temporal lobes [1]. A recent consensus paper has suggested that a diagnosis of definite ALE can be made based on the following criteria: (i) subacute onset (<3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system; (ii) bilateral hippocampal T2/fluid-attenuated inversion recovery (FLAIR) abnormalities on brain magnetic resonance imaging (MRI); (iii) at least one of the following: cerebrospinal fluid (CSF) pleocytosis or electroencephalogram (EEG) abnormalities (epileptic or slow-wave activity) involving the temporal lobes; and (iv) reasonable exclusion of alternative causes [1]. Graus et al. [1] did not include antibody status as part of the early diagnostic criteria in view of the fact that antibody (Ab) test results are not available at the time of presentation of patients. Although the Graus criteria for definite ALE have not been validated, they are widely accepted and used in clinical practice.

Although ALE typically presents with these clinical and MRI features, some patients may not develop the full-blown clinical picture, but may instead show isolated memory deficits or seizures, only unilateral involvement of the hippocampus on brain MRI, or symptoms that have developed over a longer period of time (>3 months). In these patients, according to the consensus cited, the diagnosis of ALE needs to be corroborated by detection of Abs targeting the neuronal cell surface (such as leucine-rich glioma inactivated protein 1 [LGI1], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPAR], γ-aminobutyric acid B receptor [GABABR]) or intracellular proteins (such as Hu, Ma2) in the serum or CSF [2–5].

In patients with new-onset temporal lobe seizures or epilepsy, the question of ALE is often raised. In these cases, the diagnosis of ALE can be even more challenging given that, in patients with temporal lobe epilepsy, memory deficits and hippocampal changes on MRI may be caused by the seizures themselves. However, diagnosing ALE is important because of the therapeutic and prognostic implications: seizures in the context of ALE often respond better to immunotherapy than to antiepileptic drugs (AEDs), only rarely result in chronic epilepsy [6], and if so, respond less favorably to epilepsy surgery than non-ALE-related temporal lobe epilepsy syndromes [7,8].

To address this common challenge in epilepsy, we aimed to investigate whether patients with temporal lobe seizures associated with additional symptoms (e.g., short-term memory problems) or abnormalities on MRI, or in the CSF suggestive of limbic involvement, may harbor neuronal Abs, and which clinical features should prompt neuronal Ab screening in these patients.

MATERIALS AND METHODS

Patients

We reviewed the medical records of adult (older than 14 years) patients from inpatient and outpatient clinics of the Department of Neurology, University Hospital Knappschaftskrankenhaus Bochum and its tertiary Epilepsy Center "Ruhr-Epileptology", Germany, from January 2011 to December 2015.

Inclusion criteria for this study were prominent seizures of mesiotemporal lobe origin (e.g., epileptic aura with ascending gastric feeling, dysautonomia, ictal or postictal aphasia, automatisms), associated with at least one additional sign or symptom of limbic involvement: memory deficits; psychiatric symptoms; limbic T2/FLAIR abnormalities on brain MRI; or inflammatory CSF changes.

Memory deficits were identified by neuropsychological testing or by patient history. The patients’ cognitive functions were tested in a comprehensive neuropsychological assessment performed by neurologists. This assessment included specific tests for temporal lobe functions, including tests of verbal and visual memory (Verbal Learning and Memory Test), [9] verbal fluency (Regensburg Word Fluency Test), [10] verbal and figural short-term as well as working memory (Diagnosticum für Cerebralschädigung [DCS-R]), [11] visuospatial organization (Rey Complex Figure Test), [12] and attention (alertness tests from the Testbatterie zur Aufmerksamkeitsprüfung [TAP]) [13].

Psychiatric symptoms, including emotional lability and depression, were assessed during patient history-taking by a semi-structured interview. Depression was also assessed using the Beck Depression Inventory (BDI-II) score, and was defined as a BDI-II score ≥9 in combination with clinical judgment.

Limbic T2/FLAIR abnormalities on brain MRI were assessed using the standardized epilepsy protocols proposed by Wellmer et al. [14], which allow the detection of virtually all common epileptogenic lesion entities. MRI was initially evaluated by neuroradiologists with longstanding expertise in the diagnosis of epileptogenic and inflammatory lesions of the central nervous system and was then re-assessed independently by another expert (F.G.W.), who was blinded to the results of the previous radiologists, clinical data and Ab results. For final classification of limbic T2/FLAIR signal abnormalities (bilateral vs. unilateral vs. absent) in cases of disagreement between the two reviewers, consensus was obtained in the presence of a third expert (C.G.B.). Acutely reversible postictal hippocampal changes were considered seizure-related phenomena and were disregarded in this classification.

Inflammatory CSF changes were defined by lymphocytic CSF pleocytosis (>5 cells/µl). CSF cell count was started in each case within 30 min after lumbar puncture to prevent CSF leukocyte-count drop.
After extensive diagnostic work-up, alternative causes of the seizures (e.g., glioma or herpes simplex encephalitis) were excluded. Patients with a full-blown picture according to the diagnostic criteria of definite ALE before obtaining of Ab results were also excluded.

Demographic and clinical information, including age, sex, seizure type and frequency, other neurological symptoms, tumor association, comorbidities, EEG findings, and outcome at last follow-up were also available.

Immunological studies

Serum and/or CSF samples were tested at the Bielefeld-Bethel laboratory (Krankenhaus Mara, Epilepsy Center Bethel, Germany) for the presence of Abs against neuronal using indirect immunofluorescence on mouse brain. Samples were also tested by cell-based assays for Abs against several neuronal cell-surface targets (the N-methyl-D-aspartate receptor [NMDAR], glutamic acid decarboxylase in its 65-kD isoform [GAD65], leucine-rich glioma inactivated protein 1 [LGI1], contactin-associated protein-2 [CASPR2], α-amino-3-hydroxy-5-methyl-4-isoxazolepropanic acid receptor [AMPAR], γ-aminobutyric acid B receptor [GABABR] and glycine receptor [GlyR]) using cell-based assays (Euroimmun, Lübeck, Germany), as previously described [15]. Ab titers were determined as the last of serial dilutions of serum and/or CSF that showed visible reactivity. All these samples were also tested for Abs against Hu, Ri, Yo, CV2, Amphiphysin, Ma2, Recoverin, Sox1, Zic4, and DNER (Tr) by immunoblot.

Serum and/or CSF samples were retested for Abs against neuronal cell-surface and intracellular targets in the neuroimmunology laboratory of the Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS; Hospital Clinic, Barcelona, Spain) using immunohistochemistry on rat brain sections, in-house HEK293 (human embryonic kidney) cell-based assays, live neurons, and immunoblot assays, as previously reported [3,4,16].

Antibody results were considered positive in case of positive cell-based assays/immunoblot and a suggestive pattern of reactivity by tissue-based assays (indirect immunohistochemistry/immunofluorescence on rodent brain). The Abs against undetermined target were considered positive in case of positive neuropil patterns by tissue-based assays and live neurons. GAD Abs were only considered relevant if the serum titer was higher than 1:1500 or if they were present in the CSF. Final antibody diagnoses were made by consensus between the two laboratories (in Bielefeld and in Barcelona). In the serum of one patient, Abs against glycine receptor were detected only using a cell-based assay in one laboratory; therefore, this Ab was not considered positive in this study.

Follow-up data

Follow-up information about memory deficits, residual neurological symptoms (including seizure persistence and frequency), current treatment with AEDs and functional status (assessed using the modified Rankin scale [mRS]) was obtained through a structured clinical questionnaire via phone call by F.S.I. to the patient or caregiver, or collected from medical records. Repeated neuropsychological assessment and BDI-II scores were available from patients who were re-evaluated at the epilepsy center. Patients were considered to be seizure-free if they had not experienced any seizure for a period of at least 6 months prior to last follow-up.

Standard protocol approvals, registrations, and patient consents

This study received full approval by the ethical committee of the Ruhr-University Bochum (16–5762-BR). Written informed consent was obtained from all patients or their proxy for the storage and use of serum, CSF, and clinical information, including evaluation of the brain MRI, for research purposes.

Statistical analysis

Comparison between patients with and without neuronal Abs, in terms of demographics, clinical features and paraclinical results, was performed with a two-tailed Fisher’s exact test and Mann–Whitney U-test. p values <0.05 were taken to indicate statistical significance.

RESULTS

We identified 47 patients with seizures of mediotemporal lobe semiology and features of limbic involvement fulfilling the inclusion criteria of the present study. None of the patients fulfilled the diagnostic criteria for definite ALE proposed by Graus et al. [1] before obtaining of Ab results. Figure 1 provides an overview of the diagnostic procedures and their results in this study.

The median (range) age at seizure onset was 44 (14–81) years, four patients were aged 14–18 years, and 30 (64%) were female. None of the 47 patients recalled prodromal symptoms (such as flu-like symptoms or diarrhea) before onset of neurological symptoms. Temporal lobe seizures occurred at a median (range) frequency of 2 (0.02–70) seizures/week. None of the patients had seizures of non-temporal lobe semiology. Seizures were refractory to multiple (≥2) AEDs in 12/36 patients (33%) with available data. Seizures were accompanied by neuropsychiatric symptoms, including memory deficits, emotional lability and depression in 19/42 patients. Symptoms persisted for more than 3 months (median [interquartile range] 24 [6–51] months) in 39/47 patients (83%). In particular, memory complaints were found in 35/46 patients (76%), and were confirmed by neuropsychological testing in all 35. Bilateral temporo-mesial dysfunction (involving both verbal and visuospatial modalities) was detected in 8/35 patients (23%), whereas spatial disorientation was reported in 11/24 patients (46%) with documented data.
symptoms were found in 27/42 patients (64%) and ranged from emotional lability to depression. Emotional lability was reported in 24/40 patients (60%). BDI-II score was assessed in 42 patients; depression based on a BDI-II score ≥9 was found in 18/42 (43%). Tumors were found in 2/47 patients (4%; adenocarcinoma of the lung, n = 1, and prostate carcinoma, n = 1), diagnosed within 5 years preceding or following the onset of neurological symptoms. An association with other autoimmune conditions occurred in 6/47 patients (13%), including diabetes type 1 (n = 3), autoimmune thyreoiditis (n = 2) and systemic lupus erythematosus (n = 1).

All patients had available EEG studies, and 36 of the patients (77%) underwent video-EEG for at least 24 h. Temporal lobe EEG changes presenting as focal slowing were detected in 44/47 patients (94%), accompanied by epileptic activity in the temporal region in 42/47 (89%). None of the patients had extratemporal electrographic abnormalities.

Cerebrospinal fluid analysis was abnormal in only 2/37 (5%) samples, showing pleocytosis and increased IgG index and in one of them additional oligoclonal bands.

Brain MRI was performed in all patients except for one with an implanted cardiac pacemaker. Initial and confirmatory imaging review was consistent with each other in two-thirds of cases. Interrater agreement between the two independent experts was 75% (31/47). The 16 disagreements involved the mere presence or the laterality of limbic changes and were resolved to consensus, together with the third expert. Brain MRI was abnormal in 26/46 patients (57%). T2/FLAIR abnormalities involved the limbic system in all of the 26 patients (unilateral, n = 22 [85%], bilateral, n = 4 [15%]).

Samples from all patients were available for neuronal Ab testing in both laboratories (matched serum and CSF from 33/47 patients [70%], only serum from the remaining 14 patients). Neuronal Abs (median [interquartile range] time from onset to first Ab testing, 30 [6–336] months) were confirmed in 8/47 patients (17%; three in matched serum and CSF, three only in serum and two only in CSF) and were directed against neuronal cell-surface targets (LGI1: n = 1, CASPR2: n = 1, undetermined target n = 3) or GAD65 (n = 3, all with high titers). Detailed Ab results in both antibody laboratories are available in Table S1. The Abs with confirmed antigen gave consistent neuropil patterns on immunohistochemistry in all cases. The Abs against undetermined target showed positive neuropil patterns by immunohistochemistry and live neurons. In one case the immunohistochemistry pattern suggested human natural killer-1 antigen (HNK-1) of unknown significance (confirmed by immunoblot [in serum] and HEK cell-based assay [in serum and CSF]). [17] None of the samples harbored onconeural Abs. The clinical features, EEG, CSF and MRI results, tumor association and outcomes in these eight Ab-positive patients are shown in Table 1. In seven of these patients (n = 1 with CASPR2, n = 3 with GAD65 and n = 3 with Abs to undetermined target), symptoms reached their severity peak over more than 3 months. The remaining patient, who experienced LGI1 encephalitis, developed faciobrachial-cranial dystonic seizures without other neuropsychiatric symptoms.
| Patient, sex, age at onset | Tumor or autoimmunity | Main clinical features | CSF analysis | EEG | Brain MRI | Immunotherapy/Cancer treatment | Outcome (mRS 0–6, seizure freedom) | Antibody |
|--------------------------|-----------------------|------------------------|--------------|-----|-----------|---------------------------------|---------------------------------|----------|
| #1, F, 81 years          | None                  | Temporal lobe seizures (faciobrachial-crural dystonic seizures with recurrent falls) | Normal       | Unilateral temporal epileptiform discharges + slowing | Unilateral mediotemporal hypersignal | Yes | NA | LGI1 (serum 1:2000, CSF 1:4) |
| #2, F, 28 years          | DM type 1             | Temporal lobe seizures, memory deficits (left-sided temporo-mesial dysfunction), mood changes (emotional lability) | NA           | Bilateral temporal epileptiform discharges + slowing | Bilateral mediotemporal hypersignal | Yes | NA | GAD65 (serum 1:64,000, CSF 1:128) |
| #3, M, 41 years          | None                  | Temporal lobe seizures, memory deficits (bilateral temporo-mesial dysfunction) | Normal       | Unilateral temporal slowing | Unilateral mediotemporal hypersignal | No | mRS score 1, no | GAD65 (serum 1:32,000, CSF not tested) |
| #4, M, 44 years          | None                  | Temporal lobe seizures, memory deficits (left-sided temporo-mesial dysfunction) | Normal       | Bilateral temporal epileptiform discharges + slowing | Bilateral mediotemporal hypersignal | No | NA | GAD65 (serum 1:32,000, CSF 1:250) |
| #5, F, 60 years          | None                  | Temporal lobe seizures, memory deficits (right-sided temporo-mesial dysfunction), mood changes (emotional lability, depression) | Normal       | Unilateral temporal epileptiform discharges + slowing | Unilateral mediotemporal hypersignal | Yes | NA | CASPR2 (serum 1:500, CSF negative) |
| #6, M, 55 years          | MGUS                  | Temporal lobe seizures, memory deficits (left-sided temporo-mesial dysfunction) | Normal       | Unilateral temporal epileptiform discharges + slowing | Unilateral mediotemporal hypersignal | No | mRS score 1, no | Neuropil (in serum and CSF, undetermined target; additional HNK-1 IgG Abs in serum and CSF) |
| #7, F, 48 years          | None                  | Temporal lobe seizures, memory deficits (left-sided temporo-mesial dysfunction), spatial disorientation, mood changes (emotional lability, depression) | Normal       | Unilateral temporal slowing | Unilateral mediotemporal hypersignal | No | mRS score 3, no | Neuropil (in serum, CSF not tested, undetermined target) |
| #8, F, 32 years          | DM type 1, Autoimmune thyreoiditis | Temporal lobe seizures, mood changes (emotional lability, depression) | NA           | Unilateral temporal epileptiform discharges + slowing | Unilateral mediotemporal hypersignal | No | NA | Neuropil (in serum, CSF not tested, undetermined target) |

Abbreviations: Abs, antibodies; CASPR2, contactin-associated protein 2; CSF, cerebrospinal fluid; DM, diabetes mellitus; EEG, electroencephalogram; HNK-1, human natural killer-1 antigen; GAD65, glutamic acid decarboxylase 65; IgG, immunoglobulin G; LGI1, leucine-rich glioma-inactivated protein 1; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NA, not available.
Involvement of the leg associated with recurrent falls as in our case is rare and atypical compared to the cases with faciobrachial dystonic seizures, so the diagnosis could not be detected for weeks in another hospital. After obtaining of the Ab results, the patient with LGI1 Abs fulfilled the diagnostic criteria for definite ALE according to Graus et al. [1]. The other Ab-positive patients with limbic involvement presented with a chronic course of disease, therefore, they did not meet the formal criterion with a subacute onset.

Overall, the eight patients harboring neuronal Abs were more likely to show mediotemporal lobe changes on MRI than those without Abs (8/8, 100% vs. 18/38, 47%, respectively; p = 0.01, Fisher’s exact test), but did not otherwise differ in terms of demographic features, seizure types, refractoriness to AEDs or outcome (data not shown). Accordingly, mediotemporal MRI changes had a positive likelihood ratio of 2.11 (95% confidence interval [CI] 1.51–2.95).

Information on treatment was available from 46 patients. Sixteen of these (35%) received immunotherapy, three of whom later turned out to be Ab-positive. Immunotherapy included intravenous methylprednisolone in all. Another patient received additional second-line therapy with cyclosporine and azathioprine. Of the two patients with tumor, the one with lung cancer received specific oncological treatment, and the other one with prostate carcinoma received only tumor growth surveillance. In five out of eight Ab-positive patients immunotherapy was not administered because there was no realistic chance to influence the further disease course through immunotherapy since most patients presented late in their course and showed stable findings at that time.

Outcome information with regard to seizures was available in 38 patients (80%). The median (interquartile range) time from disease onset to follow-up interview was 60 (48–84) months. Seizure freedom was achieved in 13/38 patients (34%), all on AEDs; the remaining 25 patients experienced a median (range) frequency of 0.1 seizures/week (0–2). Neuropsychiatric outcome, including neuropsychological assessment and BDI-II at follow-up, was available for 23 patients (49%). At last follow-up, memory deficits persisted in 14/23 patients (61%) and significantly improved or resolved in nine (39%). Depression improved or resolved in 12/23 patients (52%). The median (range) mRS score (scale 0–6) at follow-up was 2 (0–5) compared to 1.5 (0–3) at maximum disease severity. In Ab-negative patients (n = 39), a definite ALE diagnosis could not be finally made and no alternative diagnoses were reached. The origin of temporal lobe seizures remained unclear in these cases.

DISCUSSION

In the present study population with mediotemporal lobe seizures and other features of limbic involvement, but not typical according to Graus et al. [1] diagnostic criteria for definite ALE, neuronal Abs were found in 17% of the patients. GAD65 Abs, similar to CASPR2 Abs and Abs against undetermined target, were detected in our patients with long-lasting symptoms (>3 months). This confirms that several Abs can be produced for long periods independent of the time of symptom onset [19–22]. In previous studies with GAD65 Abs, the chronic disease course with long-standing therapy-resistant temporal lobe epilepsy was described [19,20]. Also 42% of the study population with LGI1-encephalitis reached the full-blown clinical picture >3 months [21]. In another study, the median time from onset to maximum disease severity in patients with LGI1 Abs was 22 weeks [22]. Thus, ALE can have a more chronic disease onset/course and Abs can be detected for a long time in these patients, contributing to the definite diagnosis. The frequency of neuronal cell-surface Ab detection in patients with full-blown ALE varied in previous studies between 45% and 82% [19,23,24], and nonneuronal Abs were detected in 60% [25]. In further studies focusing on epilepsy, the presence of neuronal Abs was reported in 3%–20.5% of patients, [26–30] varying in the majority of studies between 3% and 5% [28–30] and in two studies higher Ab presence was reported in 11% and 20.5% of patients [26,27]. This difference in Ab prevalence between studies is attributable to differences in study design and study population (patient series from an epilepsy center or patient series with the selection criteria of a full-blown ALE) as well as methods and scope of Ab testing. The low prevalence of Abs in an unselected group of epilepsy patients reinforces the validity of the limbic encephalitis criteria as, in patients with definite diagnosis of ALE, the frequency of neuronal Abs is much higher. In this regard, our study population differs from the populations of full-blown ALE with higher frequency of detected Abs [19,23–25]. If we further exclude patients with unknown Abs, the frequency is 10.6% compared to the 3%–5% that is reported in most epilepsy series (range 3–20.5%) [26–30]. These data suggest that the studied series is heterogeneous and the MRI features should guide the evaluation for neuronal Abs. However, Abs of unknown significance are relevant to the final diagnosis because they showed characteristic positive neuropil patterns on immunohistochemistry and live neurons, supporting the autoimmune origin of the disease. Studies demonstrated that patients with limbic encephalitis associated with Abs against intracellular targets, GAD65 or LGI1 have a higher risk of developing epilepsy [19,31,32]. Geis et al. [32] suggested distinguishing between seizures in the context of antibody-mediated encephalitis, which are frequent in the acute phase, but can in most cases resolve after re- mission of neuroinflammation, and persistent seizures in the context of a chronic epileptic syndrome who might have, or not, an inflammatory origin. Most patients with chronic epilepsy with a suspected autoimmune component have GAD65 Abs and a smaller number LGI1 or other neuronal Abs [27,29,30,32–34]. Similarly, the antibody repertoire in this series confirms what is found in series with isolated or predominant epilepsy where GAD65 Abs are the most prevalent. On the other hand, the study does not confirm previous publications suggesting that GlyR Abs are also prevalent in these patients [26,35].

Mediotemporal lobe MRI changes are a frequent finding of patients with autoimmune encephalitis. In the present study, all patients with ALE and confirmed neuronal Abs had limbic abnormalities on their brain MRI. In previous studies, increased MRI signal intensity on T2-weighted FLAIR sequences of the medial temporal lobes...
were reported in 80% of patients with ALE mediated by neuronal cell-surface Abs [25,36] and in 60% of patients with ALE associated with onconeuronal Abs. These abnormalities are more frequently bilateral when the cause of adult-onset temporal lobe epilepsy is limbic encephalitis (60%) than when it is related to other causes (22%) [37]. In another study, MRI changes related to limbic encephalitis were demonstrated significantly more frequently in Ab-positive epilepsy patients as compared to Ab-negative and are a component of the antibody prevalence in epilepsy (APE) score [27]. In addition to the APE score, among patients who received immunotherapy, a Response to Immunotherapy in Epilepsy (RITE) score was proposed [38]. According to the diagnostic criteria proposed by Graus et al. [1], definite ALE can be diagnosed if bilateral brain abnormalities on T2-weighted FLAIR MRI are present, highly restricted to the medial temporal lobes, because several nonimmune disorders such as seizures, herpes simplex virus encephalitis, or gliomas can produce similar unilateral MRI abnormalities. On the other hand, patients with definite limbic encephalitis (according to Ab findings) may have unilateral temporomesial MRI alterations, and in some studies they represent the majority of the study population [19,22]. Remarkably, the two independent raters in this analysis, while highly experienced in interpretation of MRI changes in epileptic disorders, initially disagreed on the presence and laterality of MRI changes in a third of cases. Further studies focusing on interrater reliability regarding the MRI changes in ALE patients are needed.

Only 5% of our patients had abnormal CSF, probably due to the late timepoint with regard to the symptoms onset of patients in our study, that is, not comprising the acute inflammatory phase of possible ALE. Previous studies focusing on classic ALE demonstrated a high rate of lymphocytic pleocytosis in CSF analysis in 60%–80% of patients and intrathecal IgG synthesis or oligoclonal bands in approximately 50% of cases with ALE associated with onconeuronal or neuronal cell-surface Abs, except for patients with LG1 antibodies presenting with a lower frequency of CSF pleocytosis (41%) and, rarely, intrathecal IgG synthesis [1,25,39–41].

In summary, neuronal Abs were found in 17% of our patients with mediotemporal lobe seizures and other features of limbic involvement. Mediotemporal MRI changes were found in all Ab-positive cases and had a positive likelihood ratio of 2.11 (95% CI 1.51–2.95). The predominant neuronal Abs were high-titer GAD65, LG1 and CASPR2. Our results suggest that in epilepsy populations with suspected ALE and mediotemporal MRI changes, it is worthwhile to check for neuronal Abs, even if the disease course is chronic.

CONFLICT OF INTERESTS
F.S. Ismail, M. Spatola, F.G. Woermann, S. Popkirov, J. Jungillegens, J. Wellmer, U. Schlegel state that they have no conflict of interest. C.G. Bien obtained honoraria for speaking engagements from UCB (Monheim, Germany) and Desitin (Hamburg, Germany). He receives research support from Deutsche Forschungsgemeinschaft (Bonn, Germany) and Gerd-Altenhof-Stiftung (Deutsches Stiftungs-Zentrum, Essen, Germany).

AUTHOR CONTRIBUTIONS
Fatme Seval Ismail: Conceptualization (equal); Data curation (lead); Formal analysis (equal); Methodology (equal); Project administration (lead); Writing – original draft (equal). Marianna Spatola: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Writing-original draft (equal). Friedrich G. Woermann: Investigation (equal); Writing – review and editing (equal). Stoyan Popkirov: Writing – review and editing (equal). Johannes Jungillegens: Methodology (supporting); Writing – review and editing (equal). Christian G Bien: Investigation (equal); Writing – review and editing (equal). Jörg Wellmer: Conceptualization (equal); Formal analysis (equal); Methodology (equal); Writing – original draft (supporting). Uwe Schlegel: Conceptualization (equal); Formal analysis (equal); Methodology (equal); Supervision (lead); Writing – original draft (equal).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request from any qualified investigator, maintaining anonymization of the patients.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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