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ORIGINAL COMMUNICATION

Admission diagnoses of patients later diagnosed with autoimmune encephalitis

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Abstract

Background Since the detection of autoantibodies against neuronal surface antigens, autoimmune encephalitis (AE) has been more frequently diagnosed, especially in patients with symptoms typical of limbic encephalitis, such as seizures, short-term memory deficits, or psychosis. However, the clinical spectrum of AE may be much wider, making correct clinical diagnosis difficult.

Methods We retrospectively analysed symptoms and admission diagnoses at first clinical presentation in 50 AE patients. We included patients with a clinical diagnosis of AE for whom a FDG-PET imaging was available. Final diagnoses were re-evaluated by a blinded investigator according to the most recent consensus suggestions published in 2016 for AE diagnostic criteria. We additionally describe two patients with Morvan syndrome who showed CASPR2 antibodies.

Results In 40 patients (80.0%), the clinical presentation at first admission was typical for AE. Ten patients (20.0%) initially suffered from atypical symptoms; among these patients, isolated headache and cerebellar dysfunction were most frequent (three patients each). However, an initial diagnosis of suspected encephalitis was only reached in 16 patients (32.0%), nine (18.0) of which were suspected to have infectious encephalitis, and seven (14.0%) patients were suspected to have AE. In 34 patients (68.0%), a diagnosis other than encephalitis was considered, (e.g., epilepsy, psychiatric diseases, transient ischemic attack, dementia, meningitis, and cerebellitis).

Conclusions These data show the broad spectrum of initial symptoms of AE; the correct initial diagnosis of AE is often missed or delayed. Hence, clinicians in neurological and psychiatric hospitals should consider AE in the differential diagnosis of cases with atypical clinical presentations.

Keywords Autoimmune encephalitis · Admission diagnosis · Manifestation symptoms

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Background

Autoimmune encephalitis (AE) comprises a broad spectrum of rare disorders. The most common subtype is AE with *N*-methyl-D-aspartat receptor (NMDAR) antibodies, which usually has a typical disease course, beginning with flu-like symptoms, followed by psychiatric symptoms, amnesia, dyskinesia, autonomic instability, catatonia, mutism, and a decreased level of consciousness. Seizures can occur at every stage [1, 2]. Patients with classical limbic encephalitis (LE) show a more limited clinical picture with symptoms such as seizures, psychiatric symptoms, and working memory deficits. The most common AE presenting as classical LE is associated with surface antibodies against leucine-rich glioma inactivated-1 (LGI1), previously categorized together with the rare AE with antibodies against contactin-associated protein 2 (CASPR2) as AE associated with voltage-gated potassium channel complex (VGKC) antibodies [1]. More than 20 other rare antineuronal antibodies associated with distinct clinical presentations of AE have been described [3–5]. AE can also present with atypical manifestations such as chronic pain, nystagmus, or cerebellar ataxia [6–9]. In these cases, the diagnosis can be missed initially or delayed and strongly depends on antibody test results. Early diagnosis is critical as rapid treatment initiation is associated with a better clinical outcome [10–13]. AE can also occur as a paraneoplastic neurological syndrome and might indicate an underlying tumour, thus enabling the earlier diagnosis and better prognosis of the tumour [1]. The aim of this study was to describe the spectrum of initial symptoms and the admission diagnoses of AE according to diagnostic criteria consensus suggestions [1] at first clinical presentation.

Methods

In this retrospective study, we collected clinical data from patients with AE from five university hospitals in Germany and Austria who were diagnosed between April 2007 and February 2016. Patients had been originally recruited for the analysis of cerebral [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) data. Inclusion criteria were (1) at least one typical symptom of AE (i.e., subacute memory deficits, personality changes, psychiatric symptoms, or at least one seizure [2, 10]), (2) serum or cerebrospinal fluid (CSF) antibodies against neuronal surface antigens (i.e., LGI1, CASPR2, and VGKC-complex without specificity, as well as NMDAR, γ-aminobutyric-acid receptor ($GABA_BR$), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic-acid receptor (AMPAR), and metabotropic-glutamate-receptor 5 (mGluR5), and (3) the exclusion of alternative causes. Antibody analysis was conducted via indirect immunofluorescence on a biochip mosaic with fixed transfected HEK293 cells (Euroimmun, Luebeck, Germany) using a starting dilution of 1:10 in serum and 1:1 in CSF and radioimmunoassay for VGKC (Weatherall Institute of Molecular Medicine, Oxford). In a subgroup of patients, serum or CSF was also tested for antibodies against glutamic acid decarboxylase (GAD). Quantitative immunofluorescence titres were not available in all cases. Participating centres retrospectively assessed initial symptoms, admission diagnoses, as well as the clinical course of the disease, antibody status, and elapsed time between the first symptoms and a final diagnosis of AE.

Graus et al. published diagnostic criteria for AE in 2016, in which, antibody diagnostic did not play the key role in the diagnosis [1]. In this algorithm, patients are investigated for possible AE in the first step. In some cases, patients can be diagnosed as definite LE of autoimmune origin only on the basis of clinical data. For patients who did not fulfil these criteria, there are criteria for probable AE, which is defined as 'probable AE without antibodies'. These criteria should only be used in patients who did not fulfil criteria for definite AE. There are further criteria for NMDAR encephalitis that categorize the diagnosis into two groups, probable or definite NMDAR encephalitis. The diagnosis of definite NMDAR encephalitis can only be made with positive antibody findings [1].

We retrospectively investigated patients with positive antibodies without considering the antibody results. We wanted to evaluate how often Graus' criteria are fulfilled in our cohort and, hence, how often it is possible to make the diagnosis of AE before antibody test results are available. It is important to mention that special criteria for 'definite NMDAR-E (NMDAR encephalitis)' cannot be diagnosed without antibody results. Hence, we could not make this diagnosis because we did not consider antibody results. We also used criteria for definite AE for NMDAR patients.

We grouped patients as follows:

1. Patients fulfilling criteria for possible and subsequently definite autoimmune LE.
2. Patients fulfilling criteria for possible AE and subsequently 'probable AE without antibodies' or probable NMDAR but not fulfilling the criteria for definite AE. This definition is not completely in accordance with Graus' criteria because one possible criterium is based on brain biopsy. We could not consider this criterium because none of our patients were biopsied.
3. Patients fulfilling criteria for possible AE, but not fulfilling criteria for 'probable AE without antibodies'/probable NMDAR encephalitis or definite autoimmune LE.

4. Patients who did not fulfil criteria for possible autoimmune LE.

In the group 4 patients, we further investigated whether patients could still fulfil criteria for probable NMDAR encephalitis or definite autoimmune LE. Thus, in these patients, we skipped the first step of the diagnostic algorithm and began at step 2. It should be noted that strict adherence to the diagnostic algorithm suggested by Graus is only possible when assuming that the criteria of possible AE have a sensitivity of 100%. In our approach, a lack of sensitivity of the screening criteria for possible AE will be documented by the proportion of patients ending up in group 4.

Ethics

The local ethics committee approved the study.

Statistical analysis

We used SPSS Statistics 20.0 for statistical analysis. The Chi-square test and Mann–Whitney *U* test were performed for comparisons between different groups. For correlation analyses, we used a Chi-quadrat test. p values of < 0.05 were considered statistically significant.

Results

A total of 50 patients with AE were included in this study comprising 24 females and 26 males, who were diagnosed between April 2007 and February 2016. Twenty-five patients were recruited from Freiburg, eight patients each from Innsbruck and Hamburg, five patients from Berlin and four patients from Ulm. The median age was 49.5 years (range 15–84 years). Twenty-four (8.0%) patients had antibodies against NMDAR (19 tested in serum and CSF and six tested in serum only). Two of these 24 patients also had antibodies against glutamic acid decarboxylase (GAD) and VGKC (RIA 164 pmol/ml). In the serum of seven patients (14.0%), VGKC antibodies without subspecificity for LGI1 and CASPR2 were detectable, although they were tested for both. Twelve (24.0%) patients had LGI1 antibodies, and five patients (10.0%) had CASPR2 antibodies; both groups were positive for VGKC-antibodies. One patient (2.0%) had $GABA_BR$ antibodies, and one patient (2.0%) had mGluR5 antibodies. In seven patients (14.0%), a tumour was found. In four of these patients, the tumour was already known at the first manifestation of AE (prostate carcinoma associated with LGI1 antibodies; breast cancer, ovarian teratoma, and testis carcinoma; each of the latter three were associated with NMDAR antibodies). In three additional patients, the tumour was diagnosed after AE manifestation (ovarian teratomas were diagnosed in two patients, and renal lymphoma was diagnosed in one patient, each associated with NMDAR antibodies). We further describe two patients with Morvan syndrome (one from Freiburg and one from Ulm), a rare neurological condition characterized by confusion, agitation, neuromyotonia, and vegetative symptoms [12]. These disorders were excluded by Graus et al., nevertheless, they are caused by a similar pathogenesis, namely an encephalitis caused by CASPR2 antibodies. We did not include these patients into statistical analyses. Both of these patients were male; one was 63 years and one 65 years old. Both had CASPR2 antibodies. In the 63-year-old patient a tumour was found (thymoma) after the diagnosis of Morvan syndrome. The clinical data are summarized in Table 1.

On average, the mean time from first symptoms to the diagnosis of AE was 8.7 (± 10.6), showing a significant difference between NMDAR patients (mean: 11.8 ± 11.3 months) and all VGKC-complex patients (5.9 ± 7.5 months; LGI1 and CASPR2 antibody-positive patients included; Morvan syndrome excluded; $p = 0.003$). Seventeen patients (34.0%) were initially admitted to the psychiatry department. In 27 patients (54.0%), the disease progressed to a severity that demanded admission to an intensive care unit. The most common disease manifestations were seizures ($n = 17$, 34.0%), followed by psychiatric disturbances, including hypomania or mania, schizoaffective symptoms, or depression ($n = 9$, 18.0%), behavioural abnormalities ($n = 7$, 14.0%), and memory impairment ($n = 7$, 14.0%). Altogether, 80.0% of the patients presented with at least one typical AE sign or symptom.

In the two patients with Morvan syndrome, the time between disease onset and the diagnosis was 12 and 4 months. Both patients were admitted with atypical symptoms (paraparesis, myasthenic syndrome). One patient had to be treated on intensive care unit.

In patients with only an atypical disease manifestation ($n = 10$; 20.0%), cerebellar symptoms and isolated headache occurred most often ($n = 3$; 6.0%). Further initial symptoms included gait disorder, monocular visual loss, aphasia, and hypaesthesia (each: $n = 1$, 2.0%). Although headaches can occur in the course of flu-like symptoms in NMDAR encephalitis [14], it is seldom described as an isolated symptom when the disease manifests. Furthermore, it is very unspecific and does not point directly to AE and may delay the diagnosis. For this reason, we classified isolated headaches in the category of atypical symptoms. As already mentioned, both patients with Morvan syndrome presented with atypical symptoms (paraparesis, myasthenic syndrome).

Even if these symptoms were not typical, antibodies were assessed because of different reasons. In five of these patients, the further clinical course led to the suspected diagnosis (headache: three patients, cerebellar symptoms: one patient, hypaesthesia one patient). We found

Table 1 Summary of clinical data of all patients

Antibody	NMDAR	VGKC without subspecificity	LGI1	CASPR2	$GABA_BR$	mGluR5	Morvan
Number of patients	24 (48.0)	7 (14.0%)	12 (24.0%)	5 (10.0%)	1 (1.9%)	1 (1.9%)	2
Sex (m/f)	8/16	4/3	8/4	5/0	1/0	0/1	2/0
Median age (range)	29.5 (15–75)	33 (25–72)	70 (53–77)	67 (52–84)	73	30	64 (63–65)
Tumour	6 Ovarian teratoma: $n=3$ Breast cancer: $n=1$ Testis carcinoma: $n=1$ Renal lymphoma $n=1$	0	1 Prostate carcinoma	0	0	0	1 Thymoma
Psychiatric clinic	10	4	2	1	0	0	0
Intensive care unit	19	4	3	0	1	0	1
Mean duration from manifestation until diagnosis (months; mean ± standard deviation)	11.3 ± 11.6	3.3 ± 2.9	7.6 ± 8.8	3.8 ± 4.3	1.0	6.0	8.0 ± 5.66

Number of patients, in whom a tumour was diagnosed. Number of patients who were treated in a psychiatric clinic or on intensive care unit during the whole course of disease

NMDAR N-methyl-D-aspartate receptor, *VGKC* voltage-gated potassium channel complex, *LGI1* leucine rich glioma inactivated-1, *CASPR2* contactin associated protein 2, *$GABA_BR$* γ-aminobutyric-acid-B receptor, *mGluR5* metabotropic glutamate receptor 5, *m* male, *f* female

pathological findings in EEG in further two patients (cerebellar and aphasia) and in CSF in one patient (cerebellar). In one patient, cerebral MRI showed mesiotemporal hyperintensity (visual loss) and in one patient, breast cancer was already diagnosed, therefore, a paraneoplastic etiology was assumed. No significant differences were observed between patients with typical and atypical manifestations regarding the duration from onset to diagnosis (typical mean: 8.81 months; atypical mean: 8.95 months; $p=0.0738$). The association between clinical presentation and antibodies is presented in Table 2.

The initial suspected diagnosis was encephalitis in only 16 patients (32.0%), of infectious origin in nine (18.0%), and of autoimmune origin in seven (14.0%); all 16 presented with typical symptoms (32.0% referred to the whole group). In the further 24 patients with typical symptoms, admission diagnoses were epilepsy ($n=10$, 20.0% of the whole patient group), psychiatric disorders ($n=8$, 16.0%), dementia ($n=2$; 4.0%; one of them was suspected of suffering from Lewy body dementia because of accompanying motor symptoms), transient ischemic attack, dissociative disorder, myoclonus of unknown origin, and acute disseminated encephalomyelitis (each $n=1$; 2.0%). In contrast, a presentation with atypical symptoms led to the correct diagnosis in only one patient ($n=1$; 2.0%). In these patients, further admission diagnoses were cerebellitis,, amyotrophic lateral sclerosis, psychiatric disease, normal pressure hydrocephalus, optic neuritis, transient global amnesia, transient ischemic attack,, and meningitis (each $n=1$; 2.0%). In the patients with Morvan syndrome, admission diagnoses were amytrophic lateral sclerosis and myasthenia gravis. The association between the admission diagnosis and antineuronal antibodies are shown in Table 3.

Using the diagnostic criteria suggested by Graus et al. [1], 43 patients (086.0%) fulfilled the diagnostic criteria for possible AE. Fourteen of these patients also fulfilled the criteria for definite autoimmune LE (group 1; 28.0% referred to the whole group). Six of these patients had NMDAR antibodies. Twenty-one patients (42.0%) were categorized into group 2 and, hence, were diagnosed as probable AE; 12 patients had NMDAR antibodies. Of these 12 NMDAR patients, all fulfilled the proposed criteria for probable NMDAR encephalitis and vice versa. Among the 43 patients with possible AE, eight patients (16.0%) fulfilled criteria for possible AE only but not those for either probable AE without antibodies, probable NMDAR encephalitis, or definite autoimmune LE (group 3). Furthermore, seven patients (14.0%) did not fulfil criteria for possible AE (group 4). This is possible because the diagnosis of possible AE can only be made with working memory deficits, an altered mental status, or psychiatric symptoms, whereas for the diagnosis of definite autoimmune AE seizures indicating affection of the limbic system can substitute for psychiatric or memory disturbances. Both patients with Morvan syndrome fulfilled the criteria for possible AE, but not those for definite AE (group 2).

The distribution of antibodies is presented in Table 4.

Five of these seven patients (71.4%) also failed to fulfil any of the other criteria of AE. Three patients had NMDAR antibodies, and two patients had VGKC antibodies. Both patients with VGKC antibodies, one male and one female, presented with psychiatric symptoms but without focal CNS findings, seizures, CSF pleocytosis, or pathologic

Table 2 Number of patients with different manifestation symptoms in relation to different antibodies

Initial signs or symptoms	NMDAR ($N=24$)	VGKC without specificity ($N=7$)	LGI1 ($N=12$)	CASPR2 total ($N=5$)	$GABA_BR$ ($N=1$)	mGluR5 ($N=1$)	Morvan ($N=2$)
Typical symptoms of AE							
Seizure	7 (29.2%)	1 (14.3%)	6 (50.0%)	3 (60.0)	0	0	0
Memory deficit	1 (4.2%)	0	4 (33.3%)	2 (40.0)	0	0	0
Personality change	4 (16.7%)	1 (14.3%)	0	0	1 (100%)	1 (100%)	0
Other psychiatric symptom							
Psychosis	4 (16.7%)	0	0	0	0	0	0
Hypomania/mania	0	3 (42.9%)	0	0	0	0	0
Depression	0	0	1 (8.3%)	0	0	0	0
Schizoaffective symptoms	1 (4.2%)	0	0	0	0	0	0
Total	17 (70.8%)	5 (71.4%)	11 (91.7%)	5 (100.0%)	1 (100.0%)	1 (100.0%)	0
Atypical symptoms of AE							
Cerebellar ataxia	2 (8.3%)	1 (14.3%)	0	0	0	0	0
Headache	3 (12.5%)	0	0	0	0	0	0
Gait disorder	0	1 (14.3%)	0	0	0	0	0
Visual loss	1 (4.2%)	0	0	0	0	0	0
Aphasia	0	0	1 (8.3%)	0	0	0	0
Hypaesthesia	1 (4.2%)	0	0	0	0	0	0
Myasthenic symptoms	0	0	0	0	0	0	1
Paraparesis	0	0	0	0	0	0	1
Total	7 (29.2%)	2 (28.6%)	1 (8.3%)	0 (0.0%)	0(0.0%)	0 (0.0%)	2

In brackets, the percentage of each patient group relating to the antibody type is given

NMDAR N-methyl-D-aspartate receptor, *VGKC* voltage-gated potassium channel complex, *LGI1* leucine rich glioma inactivated-1, *CASPR2* contactin associated protein 2, $GABA_BR$ γ-aminobutyric-acid-B receptor, *mGluR5* metabotropic glutamate receptor 5, *AE* autoimmune encephalitis

MRI findings. In one female patient, EEG and MRI results were normal. VGKC antibodies were positive in CSF (2295 pmol/l). Following plasmapheresis, her symptoms improved. The EEG of one male patient was pathologic with slow-wave activity, but cerebral MRI was normal. VGKC antibodies were positive in serum (170 pmol/l). After immunosuppressive treatment, considerable improvement of his symptoms and decreased VGKC antibodies were noted. In the following months, symptoms relapsed, VGKC antibodies again increased, and the patient had to be treated with another immunosuppressive treatment, leading again to an improvement while VGKC antibodies decreased.

The reason the three patients with NMDAR antibodies did not fulfil any of the criteria for AE was that they did not suffer from memory deficits, altered mental status, or psychiatric symptoms. One female patient (37 years) presented with visual symptoms and seizures. EEG, CSF, and MRI showed pathological findings (slow-wave activity, pleocytosis, and mesiotemporal hyperintensity). NMDAR antibodies were positive, and clinical symptoms, as well as pathological EEG, CSF, and MRI findings, improved considerably after treatment with corticosteroids. One other female patient (age 44) presented with headaches. There was intrathecal IgG synthesis, and MRI showed typical findings. One 49-year-old male patient presented with seizures. The CSF analysis revealed pleocytosis and intrathecal IgG-, IgM-, and IgA-synthesis; MRI was normal. Because the clinical picture was very atypical for NMDAR encephalitis in all three patients, they also did not fulfil the criteria for probable NMDAR encephalitis. All patients improved significantly after immunosuppressive treatment.

One patient in group 4 was positive for NMDAR antibodies and fulfilled the diagnostic criteria for probable AE. He also fulfilled the criteria for probable NMDAR encephalitis. However, this patient, presenting only with psychiatric abnormalities, did not fulfil the criteria for possible AE because no focal CNS findings, seizures, CSF pleocytosis, or pathologic MRI features were detected. Another patient in group 4 fulfilled the criteria for definite autoimmune LE. He suffered from seizures and myoclonus, but he did not show working memory deficits, altered mental status, or psychiatric symptoms. Nevertheless, cerebral MRI showed

Table 3 Number of patients with different admission diagnoses in relation to different antibodies

Admission diagnosis	NMDAR ($n=24$)	VGKC without specificity ($n=7$)	LGI1 ($n=12$)	CASPR2 total ($n=5$)	GABA-B ($n=1$)	mGluR5 ($n=1$)	Total ($n=50$)	Morvan ($n=2$)
Encephalitis (infectious/autoimmune)	7/3 (29.2%/12.5%)	1/0 (14.3%/0%)	0/1 (0/8.3%)	0/2 (0/ 40.0%)	0/1 (0%/100%)	1/0 (100%/0%)	16 (9/7) (32.0%)	0
Meningitis	2 (8.3%)	0	0	0	0	0	2 (4.0%)	0
Epilepsy	3 (12.5%)	2 (28.6%)	3 (25.0%)	2 (40.0%)	0	0	10 (20.0%)	0
Psychiatric disorder	3 (12.5%)	3 (42.9%)	3 (25.0%)	0	0	0	9 (18.0%)	0
TIA	1 (4.2%)	0	2 (16.7%)	0	0	0	3 (6.0%)	0
Dementia	0	0	2 (16.7%)	0	0	0	2 (4.0%)	0
Cerebellitis	2 (8.3%)	0	0	0	0	0	2 (4.0%)	0
Normal pressure hydrocephalus	0	1 (14.3%)	0	0	0	0	1 (2.0%)	0
Optic neuritis	1 (4.2%)	0	0	0	0	0	1 (2.0%)	0
TGA	0	0	0	1 (20.0%)	0	0	1 (2.0%)	0
ADEM	1 (4.2%)	0	0	0	0	0	0 (2.0)	0
Dissociative disorder	1 (4.2%)	0	0	0	0	0	1 (2.0%)	0
Myoclonus of unknown origin	0	0	1 (8.3%)	0	0	0	1 (2.0)	0
MND	0	0	0	0	0	0	0 0	1
Myasthenia gravis	0	0	0	0	0	0	0	1

In brackets, percentage of each patient group relating to the antibody type is given. The percentage in the last row for each total patient group refers to the entire study cohort ($n=52$)

NMDAR N-methyl-D-aspartate receptor, *VGKC* voltage-gated potassium channel complex, *LGI1* leucine rich glioma inactivated-1, *CASPR2* contactin associated protein 2, *GABA-B* γ-aminobutyric-acid-B receptor, *mGluR5* metabotropic glutamate receptor 5, *TIA* transient ischaemic attack, *TGA* transient global amnesia, *MND* motor neuron disease, *ADEM* acute disseminated encephalomyelitis

Table 4 Number of patients of each diagnostic group in relation to antibody type

Diagnosis	NMDAR ($n=24$)	VGKC without specificity ($n=7$)	LGI1 ($n=12$)	CASPR2 total ($n=5$)	GABA-B ($n=1$)	mGluR5 ($n=1$)	Morvan ($n=2$)
Group 1	6 (25.0%)	1 (14.3%)	5 (41.7%)	1 (20.0%)	1 (100%)	0	0
Group 2	12 (50.0%)	3 (42.8%)	2 (16.7%)	3 (60.0%)	0	1 (100%)	2
NMDAR specific	12 (50.0%)	–	–	–	–	–	0
Group 3	2 (8.3%)	1 (14.3%)	4 (33.3%)	1 (20.0%)	0	0	0
Group 4	4 (16.6%)	2 (28.6%)	1 (8.3%)	0	0	0	0
(a)	3 (12.5%)	2 (28.6%)	0	–	–	–	0
(b)	1 (4.2%)	0	0	–	–	–	0
(c)	0	0	1 (8.3%)	–	–	–	0

In brackets, the percentage of each patient group relating to the antibody type is given

NMDAR N-methyl-D-aspartate receptor, *VGKC* voltage-gated potassium channel complex, *LGI1* leucine rich glioma inactivated-1, *CASPR2* contactin associated protein 2, *GABA$_B$R* γ-aminobutyric-acid-B receptor, *mGluR5* metabotropic glutamate receptor 5, *AE* autoimmune encephalitis

typical brain abnormalities, and EEG results were pathological, therefore, the criteria for definite autoimmune LE in the second step were met.

Table 5 Characteristics of patients who did not fulfil criteria for possible AE according to Graus et al. [1]

	Antibody	Age	Sex	Diagnostic certainty of AE	MRI*	CSF	EEG	Atypical onset?	Symptoms
Pat. 1	NMDAR	37	F	No	2	Yes	Yes	Yes	Scotoma, double vision
Pat.2	NMDAR	44	F	No	2	Yes	No	Yes	Headache, fever
Pat. 3	NMDAR	49	M	No	1	Yes	No	No	Seizure
Pat. 4	LGI1	73	M	Definite	1	No	Yes	No	Seizures, myoclonic movement disorder
Pat. 5	VGKC	33	F	No	0	No	No	No	Psychosis, mania, visual hallucinations, insomnia
Pat. 6	VGKC	49	M	No	0	No	Yes	No	Memory deficits, personality change, anxiety, panic attacks, irritability
Pat. 7	NMDAR	22	F	Probable—clinical NMDAR AE	0	No	Yes	No	Memory deficits, personality change, perseveration

0, normal MRI; 1, bilateral brain abnormalities on T2 fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobe (corresponding to the definition of definite AE by Graus et al.); 2, MRI demyelination (corresponding to probable AE by Graus et al.)

CSF pleocytosis in CSF, according to diagnostic criteria, *EEG* epileptic or slow-wave activity involving the temporal lobes

The distribution of diagnostic criteria in patients with different antibodies is presented in Table 4. Table 5 shows the characteristics and symptoms of the seven patients who did not fulfil the criteria for possible AE.

Discussion

Although there are well-known diagnostically relevant clinical signs and symptoms of AE, patients may also present with a plethora of atypical initial signs and symptoms, which may lead to misdiagnosis, delay the diagnosis of AE, and, thus, the time until immunosuppressive treatment is initiated. In our retrospectively analysed cohort of patients with AE, only about one-third (34.0%) were admitted to the hospital with a suspected diagnosis of encephalitis. Only 14.0% were initially thought to suffer from AE.

The recently proposed diagnostic criteria for possible AE, probable NMDAR encephalitis (NMDAR-E), probable AE, and definitive autoimmune LE are primarily based on clinical presentation, cerebral MRI, CSF, and EEG findings; thus information that is available within a short time frame [1]. In our total cohort, almost 15% did not meet the criteria for possible AE at first presentation. In case this category is used as a trigger for antibody testing, these criteria will need revision as otherwise, diagnoses of other categories will be missed. Of the patients with NMDAR-E, almost 17% failed to fulfil the diagnostic criteria for possible AE, and 25% did not meet the criteria for probable NMDAR-E.

Eight patients could be diagnosed as possible AE; nevertheless, they did not fulfil criteria for probable AE or definite autoimmune LE (group 3). These patients did not show the bilateral mesiotemporal T2-hypertintensities required for the diagnosis of definite autoimmune LE but had a normal MRI, therefore, they did not fulfil these criteria. Furthermore, in the absence of a brain biopsy, which is a rare procedure that is not routinely performed, probable AE con only be diagnosed if the CSF and MRI are both typical for AE. However, in these eight patients, the CSF and MRI were both normal.

In contrast to the criteria of possible AE, our inclusion criteria considered seizures a typical clinical sign that could replace altered mental state, memory deficits, or psychiatric symptoms, whereas Graus et al. classified seizures in the same category as pathologic MRI features, CSF pleocytosis, and new focal deficits. Thus, patients who suffered from seizures and focal CNS findings but not psychiatric symptoms or memory deficits are not recognised by Graus' criteria. Nevertheless, in the diagnostic criteria for definite AE, seizures are classified in the same category as typical clinical symptoms. Thus, patients could be diagnosed as definite AE without fulfilling the criteria for possible AE if they suffer from seizures but not from other typical clinical findings when skipping the first algorithm step. In accordance with this, our group 4 patients, who fulfilled the criteria for definite AE but not possible AE, suffered from seizures.

We still believe that all patients in groups 3 and 4 are correctly diagnosed because they suffered from at least one typical symptom, which was defined as memory deficits, psychiatric symptom, and personality changes, as well as seizures and positive antibodies, and all patients improved after immunosuppressive treatment. Furthermore, alternative causes were excluded. As previously mentioned, we considered seizures in our inclusion criteria. Seizures are described in 58–76% as a typical symptom of AE [15]. In accordance with that, our findings show the importance of seizures in the clinical picture of AE.

In our cohort, atypical signs and symptoms occurred quite frequently at presentation. Cerebellar ataxia was the first clinical sign of the disease in > 5% of our patients and presented as an initial abnormality in > 8% of our patients with NMDAR-E. In a large cohort of 501 NMDAR-E patients, cerebellar ataxia has been reported to occur in ~ 3% [16],

which is compatible with our results. The other patient with cerebellar ataxia had VGKC antibodies but was negative for CASPR2 and LGI1 antibodies.

Three of 24 patients with NMDAR-E presented with isolated headache as the initial symptom, which did not occur in any of the 26 patients with other types of AE. NMDAR-E is characterized by a prodromal phase with unspecific signs and symptoms including flu-like symptoms and headache [2]. Although, due to the limited number of patients, the frequency of headaches as the presenting symptom in NMDAR-E patients was not significantly different from the non-NMDAR-E cohort. However, our data demonstrate that headaches associated with the frequently occurring prodrome can be severe enough to lead to a neurological admission. As all three patients showed CSF pleocytosis, the most likely diagnosis would be probable viral meningitis. Further investigations are needed to determine whether testing for NMDAR antibodies in patients with probable viral meningitis will improve the early detection and treatment of prodromal NMDAR-E. Moreover, including the prodrome into the diagnostic criteria of probable NMDAR-E might improve the specificity and sensitivity of this algorithm.

Almost 10% of our patients with NMDAR-E encephalitis presented with symptoms resulting from focal demyelination, for example, visual loss or hemihypaesthesia, but not in other forms of AE. Symptoms due to focal demyelination have been reported to occur simultaneously in ~2% of patients in a large NMDAR-E cohort [17]. Thus, signs or symptoms of focal demyelination associated with those more typical for AE require immediate testing for NMDAR antibodies.

We found a significant difference in the elapsed time between symptom onset and diagnosis of AE between patients with NMDAR antibodies and patients with VGKC complex antibodies, with a longer duration in patients positive for NMDAR antibodies. This could possibly be due to the disease manifesting in some of our patients before 2008, only a short time after the first reports on NMDAR-E were published. Similar findings are described by Herken and Prüss [18], who found a significant difference in the time from first symptoms to diagnosis prior to and after 2012 in NMDAR encephalitis [19]. We also found a trend towards a shorter time to diagnosis over the past few years, especially in NMDAR encephalitis without statistical significance. It must be noted that the patients of this study were recruited for an evaluation of cerebral FDG-PET. As performing a cerebral FDG-PET is a consequence of diagnostic uncertainties, our patients might have an atypical presentation or complicated disease course.

It has been recently reported that elevated VGKC antibodies without antibodies against LGI1 or CASPR2 lack diagnostic specificity [20]. Our cohort contained seven patients with this antibody finding. Of note, 5/7 (71.4%) fulfilled the criteria for possible AE. When categorizing these as negative antibody findings, 1/7 (14.3%) fulfilled the criteria for definitive AE and 3/7 (42.8%) for probable AE without the detection of antibodies.

One disadvantage of our study is the small number of patients in all but the NMDAR and LGI1 antibody patients. Hence, it is not possible to draw conclusions about the total incidence of the described symptoms, nevertheless, we included all these patients to show the wide—although rare—range of manifestation symptoms. For this reason, we waved statistical analyses.

Our data demonstrate that the initial signs and symptoms of AE vary remarkably. Hence, it is important to still consider AE as an alternative diagnosis when the presentation is atypical or unspecific. Thus, antibody testing should not be limited to patients with typical clinical signs but should also be performed in patients with rapidly progressive psychiatric diseases and neurological symptoms that are not in accordance with a common neurological disease. Furthermore, mentioning signs and symptoms compatible with the diagnosis of NMDAR-E, such as headaches or cerebellar ataxia, might lead to further improvement of the diagnostic criteria for NMDAR-E. The same applies to seizures, which should be considered as a symptom for possible AE with the same importance as working memory deficits, altered mental status, or psychiatric symptoms. Rigorous prospective validation and, when needed, subsequent modification of the criteria proposed for possible AE may provide clinicians with a reliable algorithm for deciding when to proceed to antibody testing.

Compliance with ethical standards

Conflicts of interest S.R. received consulting and lecture fees, grant and research support from Bayer Vital GmbH, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis and Teva. He is a founding member of ravo Diagnostika GmbH, Freiburg. F.L. disclosures receiving speakers honoraria from Grifols, Teva, Biogen, Merck, Roche and Fresenius. He is employed by an academic institution offering commercial antibody testing. H.H. has participated in meetings sponsored by received speaker honoraria or travel funding from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, Teva, and received honoraria for acting as consultant for Teva. J.L. has received honoraria for speaking and travel grants from Bayer, TEVA, CHDI and the Movement Disorders Society. F.D. has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Biogen Idec, Celgene, Genzyme-Sanofi, Merck, Novartis Pharma, Roche, and TEVA ratiopharm. His institution has received research grants from Biogen and Genzyme Sanofi. He is section editor of the MSARD Journal (Multiple Sclerosis and Related Disorders). A.B., T.H., F.U., H.P. and O.S. report no conflicts of interest with this study. None of the authors has any financial or personal relationships with individuals or organisations that could inappropriately influence this submission.

Ethical standard The authors confirm that the study is in accordance with ethical standards. The local ethics committee approved the study.

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