Autoimmune encephalitis associated with voltage-gated potassium channels-complex and leucine-rich glioma-inactivated 1 antibodies – a national cohort study


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Background and purpose: The aim of this study was to describe clinical and para-clinical characteristics of all Danish patients who tested positive for anti-voltage-gated potassium channels (VGKC)-complex, anti-leucine-rich glioma-inactivated 1 (LGI1) and anti-contactin-associated protein-2 antibodies in the serum/cerebrospinal fluid between 2009 and 2013 with follow-up interviews in 2015 and 2016.

Methods: We evaluated antibody status, symptoms leading to testing, course of disease, suspected diagnosis and time of admission as well as diagnosis and treatment. All magnetic resonance imaging, electroencephalography and 18F-fluorodeoxyglucose positron emission tomography scans were re-evaluated by experts in the field.

Results: A total of 28/192 patients tested positive for VGKC-complex antibodies by radioimmunoassay and indirect immunofluorescence; 17 had antibodies to LGI1 and 6/7 of the available cerebrospinal fluids from these patients were seropositive. These 17 patients all had a clinical phenotype appropriate to LGI1 antibodies. The remaining 11 were LGI1 negative (n = 4) or not tested (n = 7). Of these, two had a phenotype consistent with limbic encephalitis. The remaining phenotypes were Guillain–Barré syndrome, Creutzfeldt–Jakob disease, neuromyotonia and anti-N-methyl-D-aspartate receptor encephalitis. Magnetic resonance imaging abnormalities were demonstrated in 69% of the LGI1-positive patients. Two patients with normal magnetic resonance imaging demonstrated temporal lobe hypermetabolism using 18F-fluorodeoxyglucose positron emission tomography. Abnormal electroencephalography recordings were found in 86% of the patients. Upon follow-up (median 3.2 years), the median modified Rankin Scale score of anti-LGI1-positive patients was 2 and only two patients reported seizures in the past year.

Conclusions: Patients diagnosed with anti-LGI1 autoimmune encephalitis increased significantly from 2009 to 2014, probably due to increased awareness. In contrast to seropositive anti-VGKC-complex patients, all anti-LGI1-positive patients presented with a classical limbic encephalitis. The majority of patients recovered well.
Introduction

Autoimmune encephalitis (AIE) is a generic term for a heterogeneous group of disorders characterized by specific autoantibodies against neuronal antigens, which results in distinct neurological and psychiatric symptoms. The cell surface antigens most frequently involved are N-methyl-D-aspartate receptors and the voltage-gated potassium channels (VGKC) complex [1–3]. Recent advances have shown that the binding of pathological antibodies are the associated proteins leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-2 (Caspr2) [1,4]. Although AIE may be associated with antibodies that exclusively bind to the VGKC complex [5], the role of VGKC-complex antibodies is controversial. Recent data suggest that cases with negative LGI1 or Caspr2 antibodies (‘double negative’) most often represent different phenotypes [6–10]. Anti-LGI1 antibodies are associated with limbic encephalitis, faciobrachial dystonic seizures (FBDS), hyponatremia and epileptic seizures, whereas Caspr2 antibodies can be associated with limbic encephalitis but typically lead to Morvan’s syndrome and neuromyotonia [1,9]. Definite diagnosis of AIE is based on the detection of antibodies in the cerebrospinal fluid (CSF) and/or serum in a patient with a clinical history suggestive of AIE. Structural magnetic resonance imaging (MRI), functional imaging with positron emission tomography (PET) and electroencephalography (EEG) are often helpful and form parts of the recently published consensus criteria [11].

In this study we identified all Danish patients who tested positive for anti-VGKC-complex and anti-LGI1 antibodies in the serum/CSF in the period from 2009 to 2013. The aim was to describe diagnostic workup, clinical features, treatment responses and long-term outcomes.

Materials and methods

Ethics

All procedures were performed according to the Declaration of Helsinki and with permission from The Danish Health and Medicines Authority (2013-41-2482).

Patients

Data on antibody status were obtained from Statens Serum Institute, Copenhagen, the national referral center for antibody testing that receives all blood and CSF samples from patients with suspected encephalitis in Denmark. We assessed all samples from January 2009 to December 2013. Patients with positive anti-VGKC-complex, anti-LGI1 and anti-Caspr2 titer status were included in this study. Anti-VGKC-complex antibodies were determined in the CSF and/or serum by 125I radioimmunoassay, and considered positive if present at a concentration of >100 pmol/L. Anti-LGI1 and anti-Caspr2 antibodies were evaluated in the CSF and/or serum by indirect immunofluorescence using the kit from Euroimmun (Lübeck, Germany) and graded from negative to mildly, moderately and strongly positive.

Evaluation of patient records

We retrospectively assessed the medical history of the event leading to antibody testing by evaluating all relevant electronic patient records. Registration of the following data was performed: (i) initial symptoms, (ii) time from symptom to hospitalization, (iii) working and final diagnosis, (iv) symptoms throughout disease course including FBDS, (v) immunosuppressive treatment, and (vi) treatment with antiepileptic drugs. Based on the clinical presentation, patients were divided into clinical phenotypes with either classical limbic encephalitis phenotype (LGI1 phenotype, with subacute short-term memory deficit and neuropsychiatric disturbances with/without evidence of epileptic seizures) or other phenotypes (see Fig. 1).

Evaluation of magnetic resonance imaging, electroencephalography and positron emission tomography scans

All MRI images collected throughout the disease course were re-evaluated by a senior neuroradiologist (C.T.). Changes were grouped into bilateral mesial temporal lobe hyperintensity, unilateral mesial temporal lobe hyperintensity or unspecific changes. Clinical description of other pathologies was also provided. EEG performed during/after admission was re-evaluated (S.B.) and assessed for ictal activity, interictal discharges and focal or global slowing.

The majority of patients underwent 18F-fluorodeoxyglucose (FDG) PET scans during the initial clinical evaluation. These scans were also re-evaluated by a senior specialist (L.M.). Changes were grouped into bilateral hippocampal hypermetabolism, unilateral hippocampal hypermetabolism or focal hypometabolism.

Assessment of treatment and outcome

Treatment with high-dose steroids, intravenous immunoglobulin (ivIg) and/or plasma exchange was considered as first-line therapy, whereas treatment with azothioprine was considered as second-line...
therapy. Clinical outcome was determined by modified Rankin Scale (mRS) and Mini Mental Status Examination assessed on admission and at a minimum of 1 year after start of treatment. Seizure freedom was defined as the absence of all seizures with or without antiepileptic drugs.

**Results**

**Antibody status and clinical phenotype**

In the period between 2009 and 2013, sera from 192 patients and corresponding CSF samples from 67/192 patients were assessed for neuronal antibodies. Of these, 28 (14.5%) sera were positive for anti-VGKC-complex and/or anti-LGI1 antibodies, 6/28 were positive for both anti-VGKC complex and anti-LGI1, whereas 11 were positive for anti-LGI1 but not tested for anti-VGKC complex. Details are presented in Fig. 1. Seven CSF samples were available for 17 patients who were seropositive for LGI1 antibodies and six contained LGI1 antibodies. Only one of these patients shows signs of intrathecal antibody synthesis with raised IgG index. None of the seronegative samples tested CSF positive.

**Demographic data and clinical symptoms of leucine-rich glioma-inactivated 1 antibody-positive patients**

Of the 17 LGI1-positive patients, data were available for 16. Nine of these were male (56%). The median age of disease onset was 62 (range 29–84) years (Table 1). The most frequent initial symptom was short-term memory loss \((n = 7; 44\%)\), closely followed by epileptic seizures \((n = 6; 38\%)\). Other less common initial symptoms were abnormal movements \((n = 1; 6.3\%)\), mood disorder \((n = 1; 6.3\%)\) and dizziness \((n = 1; 6.3\%)\) (Table 1). The working diagnoses at admission were diverse, ranging from psychiatric disorder (20%) to pyrexia of unknown origin (7%). Only two patients (13%) were suspected of having limbic encephalitis (Table 1). Based upon review of the medical history, symptoms noted throughout the disease course were more diverse than the presenting symptoms (Table 2). All patients had loss of short-term memory and seizures were observed in 12 patients (75%). Four patients had FBDS (25%), but in one patient this was not noted until re-evaluation of the video-EEG. Other features were changes in personality (25%), mood disorder (25%), hallucinations (25%), anxiety (19%) delusions (12%) and insomnia (12%). Nineteen percent of the patients had headache. Autonomic features were noted in 25% of the patients. Nine patients (56%) had hyponatriemia at the time of diagnosis (Table 2).

The time from initial symptoms to medical consultation was a median of 22 (range 0–188) days. A definite diagnosis (positive antibody titer) was obtained after a median of 168 (range 32–327) days from symptom onset. Immunosuppressive treatment was initiated after a median of 168 (range 10–328) days and at a median of 0 days from diagnosis (range 1–79 days...
and a mean of 14 days before definite diagnosis) (Table 1).

Paraclinical examinations during initial evaluation of leucine-rich glioma-inactivated 1 antibody-positive patients

All patients underwent MRI during initial evaluation (Table 1). Of these, 11 (69%) had medial temporal T2 weighted/fluid attenuation inversion recovery (T2/FLAIR) hyperintensity, bilateral in 9 (56%) and unilateral in 2 (13%) cases. Five patients (31%) had a normal MRI or unspecific white-matter lesions. Nine patients underwent brain FDG-PET. Seven patients had either bilateral (45%) or unilateral (33%) hippocampal hypermetabolism, whereas one patient had unilateral hippocampal hypometabolism. One patient had no abnormalities on FDG-PET (Table 1). Among five patients with normal MRI, two underwent FDG-PET and were found to have unilateral hippocampal hypermetabolism (not shown).

Twelve patients (86%) had abnormal EEG recordings (Table 1). The most frequent EEG abnormalities were interictal epileptiform discharges, which were present in nine patients (64%). The interictal
epileptiform discharges were in the temporal region in seven patients and in the frontal region in two patients. Focal slowing in the temporal region was observed in six patients (43%) and, in one patient, frontal intermittent rhythm delta activity occurred. Diffuse slowing was seen in six patients (43%) and in one patient the only abnormality was the decreased frequency of the posterior dominant rhythm (6–8 Hz).

Seizure occurred during the EEG recording in five patients (36%). Two patients had myoclonic jerks (unilateral perioral myoclonus in one patient and jaw myoclonus in another patient). Two patients had complex focal (temporal lobe) seizures. One patient had FBDS. One patient had simple partial seizures and one patient had electrographic seizure. The most common ictal EEG pattern was rhythmic ictal activity in the temporal region (four patients). In one patient the rhythmic ictal activity started in the frontal region and then propagated to the temporal region.

**Treatment and follow-up of leucine-rich glioma-inactivated 1 antibody-positive patients**

Median follow-up for the LGI1-positive patients was 3.2 (range 2.2–6.4) years. Patients were all treated with high-dose intravenous steroid and/or ivlg (n = 7; 44%) or plasma exchange (n = 5; 31%). One patient received both ivlg and plasma exchange in addition to steroid. Five patients (31%) continued treatment with azathioprine (Table 2).

Of 16 patients, 12 had follow-up MRI at a median of 360 (range 133–797) days from initial diagnosis. Eight of these (67%) had sustained bilateral temporal lesions, whereas one patient (8%) had a unilateral temporal lesion. MRI remained normal in three patients, whereas one with an initial normal MRI developed first unilateral and then bilateral temporal lesions (Table 2).

Only three patients had a follow-up brain FDG-PET. All showed improvement towards normalization of metabolism, but slight changes were still noted in the hippocampus bilaterally in one patient and unilaterally in two patients (Table 2). These patients all had persistent MRI changes bilaterally.

One patient was found to have an underlying tumor. This was pathologically confirmed to be ductal carcinoma of the breast (Table 2).

Clinical follow-up and interviews of all patients revealed a median mRS score of 2 (range 0–6). Only one patient died during follow-up. This was an 84-year-old female with substantial co-morbidity. She died 6 months after her discharge from the hospital and the cause of death is not known. The cognitive profile assessed on Mini Mental Status Examination had increased from a median of 23.5/30 (range 10–29) to 30/30 (range 21–30). Six patients were still on antiepileptic drugs, but only two patients reported any seizure activity during the last year (Table 2).

**Discussion**

We report on 28 patients who tested positive for anti-VGKC-complex antibodies in Denmark from 2009 to 2013. Of these, 17 had anti-LGI1 antibodies, which translates into an incidence of 0.63 per million per year. This incidence is similar to the recently described Dutch annual incidence of 0.83 per million [12], but is probably underestimated due to the limited awareness of the condition in the period studied. This is supported by the fact that only one patient was diagnosed in 2009, whereas nine were diagnosed in 2013, giving an annual incidence in 2013 of 1.8 per million.

The remaining 11 VGKC-complex antibody-positive patients were either negative or not tested for anti-LGI1 and/or anti-Caspr2 antibodies. Of these, only three had symptoms suggestive of limbic encephalitis (subacute onset of short-term memory deficit). None of these met the recently published criteria for possible AIE [11], however, as one patient probably had a metabolic encephalopathy and the other two had normal CSF and MRI. Based on the clinical picture and paraclinical investigations, we feel confident that these cases do not represent true AIE. Of the remaining eight VGKC-complex antibody-positive patients who were LGI1 antibody negative, six received a final diagnosis of another inflammatory disease such as Guillain Barré syndrome, neuromyotonia and N-methyl-D-aspartate receptor encephalitis. Following autopsy, two patients were diagnosed with Creutzfeldt-Jakob disease. VGKC-complex antibodies in Creutzfeldt-Jakob disease have been described previously [8,13]. VGKC-complex antibodies, moreover, have been described in children with Guillain Barré syndrome and N-methyl-D-aspartate receptor encephalitis [14]. Caspr2 antibodies were not tested in our two cases of neuromyotonia, which were positive for anti-VGKC-complex antibodies.

Our findings also suggest that the presence of VGKC-complex antibodies in the absence of anti-LGI1 and/or anti-Caspr2 is unlikely to be due to AIE. This finding corroborates results from a previous study [10].

The patients with LGI1 antibodies all had clinical features of limbic encephalitis with short-term memory problems and epileptic seizures as the most prominent symptoms. The average age was 61 years (nine diagnosed between the ages of 60 and 70 years) and 56% were male. Only one patient had FBDS as the predominant initial symptom. This patient had more than 120 daily episodes of FBDS, which
subsequently ceased following ivIg and high-dose steroid. It is of note that FBDS had been noted in only four patients during the entire course of the disease. This is probably because FBDS can be very subtle (and awareness of the condition was rather poor during the study period), as illustrated by one case in which FBDS were diagnosed only after re-evaluation of the video-EEG.

All patients with LG11 antibodies had clinical features of limbic encephalitis and developed short-term memory loss during the disease course, and 75% had frequent focal epileptic seizures. Moreover, 25% had features of autonomic dysfunction including bradycardia. We hypothesize that this might have been due to inflammatory changes of the insular cortex [15,16].

The median times from symptom onset to presentation at a medical facility and to final diagnosis were rather long (22 and 168 days, respectively). However, this was largely the result of two outlier cases where time from onset of symptoms to diagnosis exceeded 250 days. As noted above, limited awareness of AIE during the study period probably played a role. This delay is, however, of concern as fast initiation of immunotherapy is important to achieve good clinical outcome. However, relevant treatment was started early following referral to a specialist center (median 0 days, mean 14 days before final diagnosis) (Table 1).

The initial laboratory evaluation of LG11-positive patients revealed that 69% had a positive MRI with T2/FLAIR hyperintensities in the mesial temporal lobe. In most cases, inflammatory changes were bilateral as is common in limbic encephalitis [17]. We also found that a significant proportion of LG11-positive patients had a normal MRI (31%) even after re-evaluation by an experienced neuroradiologist. The patient with the longest time from symptom onset to diagnosis (340 days) had normal brain MRI even during follow-up. This probably contributed to the delay in diagnosis. Interestingly, two patients with normal MRI, who were evaluated with brain FDG-PET, had hypermetabolism of the hippocampus, emphasizing the importance of PET studies in MRI-negative patients for an early diagnosis [11,18].

Electroencephalography is also important as a supportive criterion for AIE [11,12]. In our cohort, the EEG abnormalities were heterogeneous, the most frequent abnormalities occurring in the temporal regions (interictal epileptiform discharges, slowing, rhythmic ictal activity).

Tumors in LG11-positive patients are rare [1,12]. We found only one malignancy, i.e. a pathologically verified ductal carcinoma of the breast. This was probably coincidental.

All patients received high-dose intravenous steroid in the acute/subacute phase, sometimes in combination with either ivIg or plasma exchange. This treatment paradigm is generally considered to be an appropriate first-line treatment of AIE [11,12]. Rituximab was not given, but five patients continued treatment with azathioprine.

On follow-up, clinical outcome was good despite the substantial delay in diagnosis and treatment in some patients. The median mRS score was 2 after a median follow-up of 3.2 years and 69% had a favorable outcome with an mRS score ≤ 2. The Mini Mental Status Examination score had increased from a median of 23.5/30 at diagnosis to 30/30 at follow-up. The patients did, however, often perform poorly on short-term memory testing. In accordance with this, there were still prominent temporal changes on follow-up MRI bilaterally in 66% and unilaterally in 8% of patients, consistent with mesial temporal sclerosis. Six patients were still on antiepileptic drugs, but only two had experienced seizures during the past year.

**Disclosure of conflicts of interest**

The authors declare no financial or other conflicts of interest.

**References**


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