

GAD65-Ab encephalitis and subtle focal status epilepticus

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ABSTRACT – Aims. To delineate common epilepsy features associated with the presence of glutamic acid decarboxylase autoantibodies (GAD65-Ab).

Methods. Three consecutive cases of GAD65-Ab encephalitis patients, followed in our neurological department, were investigated with regards to clinical semiology and EEG.

Results. These patients presented new-onset subtle ictal clinical features. Patients 1 and 2 described prolonged and transitory feelings of “*déjà vu* - *déjà vécu*” and a “*dreamy state*”. Patient 3 was admitted for subsequent transient aphasia events followed by paroxysmal behavioural disturbances. Epileptic origin of the symptoms was confirmed using either a standard EEG (observation of temporal status epilepticus in one case) or a prolonged EEG (focal epileptiform activity during an asymptomatic period for two patients). All patients suffered from clinical focal status epilepticus. Patients 1 and 2 presented with temporo-mesial seizures in agreement with the definition for limbic encephalitis, whereas Patient 3 presented with neocortical (lateral temporal and frontal lobe) seizures arguing for a non-limbic encephalitis. A high level of GAD65-Ab was found in cerebral spinal fluid, confirming a diagnosis of epilepsy associated with GAD65-Ab encephalitis.

Conclusion. Encephalitis seems to be a frequent neurological syndrome associated with GAD65-Ab disorders. Epilepsy may be more frequent and severe than currently suggested, as ictal semiology may be subtle for these outpatients in whom standard EEG is commonly falsely reassuring. Subtle focal status epilepticus is a particular semiology of the GAD65-Ab encephalitis spectrum.

Key words: GAD65 antibody, encephalitis, temporal lobe epilepsy

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The syndrome defined as limbic encephalitis (LE) is evolving rapidly (Graus *et al.*, 2016). Specific phenotype spectrums are progressively defined for each type of autoantibody (against cell surface membrane or intracellular antigen). Temporal lobe epilepsy (TLE) may be the main or the only initial feature in LE (Brenner *et al.*, 2013; Gaspard, 2016; Serafini *et al.*, 2016). LE associated with glutamic acid decarboxylase autoantibodies (GAD65-Ab) remains understudied, whereas other GAD65-Ab disorders such as stiff person syndrome and cerebellar ataxia are better characterized (Honnorat *et al.*, 2001; Saiz *et al.*, 2008). The encephalitis phenotype associated with GAD65-Ab seems, in fact, to be a major neurological syndrome associated with GAD65-Ab. LE and non-LE may be both observed (Najjar *et al.*, 2011). However, actual reports on encephalitic clinical pattern in patients with GAD65-Ab (epileptic disorders and associated features such as anxiety, mood disorder, and memory impairment) remain only general without accurate qualitative data (Najjar *et al.*, 2011; Gagnon and Savard, 2016; Daif *et al.*, 2018). The common effort of classification (based on clinical, paraclinical and prognostic features) is essential to optimize treatment and improve the functional outcome of these patients.

We report three consecutive cases of GAD65-Ab encephalitis patients followed in our neurological department for which we detail specific epilepsy features that seem to be particularly relevant to this disorder.

Case studies

Patient 1

A 33-year-old woman, with no medical issue, was first admitted to the emergency room for a first generalized tonic-clonic seizure in September 2016. After a detailed interview, she reported a “dreamy state” feeling with abdominal pain over a year. These episodes could last several hours to days without a clear start and end. The initial standard EEG performed during the asymptomatic period showed only intermittent theta activity with few left anterior temporal sharp waves. She received specific treatment with levetiracetam but was also treated for a few months with escitalopram and praxepam due to severe and subacute anxio-depressive disorder. During the neurological follow-up, the “dreamy state” was still persistent under antiepileptic drugs and she started to complain about her memory. The long-term video-EEG monitoring revealed a strong argument for left mesial TLE, with abundant left anterior temporal spikes occurring specifically during sleep (*figure 1A*).

Initial investigation of this new-onset TLE was normal: MRI, laboratory workup, and a cerebrospinal fluid (CSF) study (normal cell count and protein, no oligoclonal bands). Brain ¹⁸F-FDG PET, performed four months after the clinical onset, revealed left temporo-mesial hypometabolism (*figure 2B*). GAD65-Ab was positive at a rate of 1,215 UEIA/mL (ELISA IsletestTM-GAD ref 7009 BIOMERICA; normal <1,000 UEIA/mL) in the serum and higher than 250 IU/mL (ELISA Medipan; normal <5 IU/mL) in the CSF.

She received four cycles of intravenous immunoglobulins (IVIG), combined with antiepileptic drugs (levetiracetam then lamotrigine and benzodiazepine). Symptoms of anxiety and depression improved. Brief “*déjà-vu/déjà-vécu*” still remained but only once a month and for a few seconds. Due to pregnancy, IVIG was interrupted. Immunosuppressive treatment (rituximab) was initiated just after pregnancy. Currently, the situation remains stable with monthly focal seizures. There was no cerebellar ataxia or cognitive complaint. Neuropsychological testing could not be performed because of French language difficulties (her maternal language was Arabic from Comoros).

Patient 2

A 30-year-old woman, without medical history event, presented in August 2015 with two successive generalized tonic-clonic seizures. The medical interview revealed possible temporo-mesial seizures over several weeks, characterized by an ascending gastric discomfort, a feeling of anxiety, palpitations, sometimes unpleasant smells, and a “*déjà-vu/déjà-vécu*” feeling. This feeling was frequent and could last several hours, described as a “strange dreamy state”. She also reported paroxysmal awakening with anxiety during night-time. A depressive mood with deep sadness, unprovoked crying, and dark thoughts started quite abruptly at the beginning of the epilepsy. Type 1 diabetes requiring insulin therapy was diagnosed a few months after the onset of seizures. She complained about her memory with altered autobiographic memory (she could not remember the day her daughter was born). The neuropsychological evaluation revealed dysexecutive disorders and working memory impairment. Standard episodic memory evaluation was normal.

The initial standard EEG showed right anterior temporal intermittent theta activity. However, on long-term video-EEG recording, we noticed few right temporal spikes only during sleep (*figure 1B*), arguing for a right temporo-mesial epilepsy. On cerebral MRI, bi-hippocampal T2/Flair hyperintensity was observed (*figure 2D*). The CSF analysis was normal (normal cell count, normal protein, and no oligoclonal bands). GAD65-Ab was positive in serum (1,239 UEIA/mL)

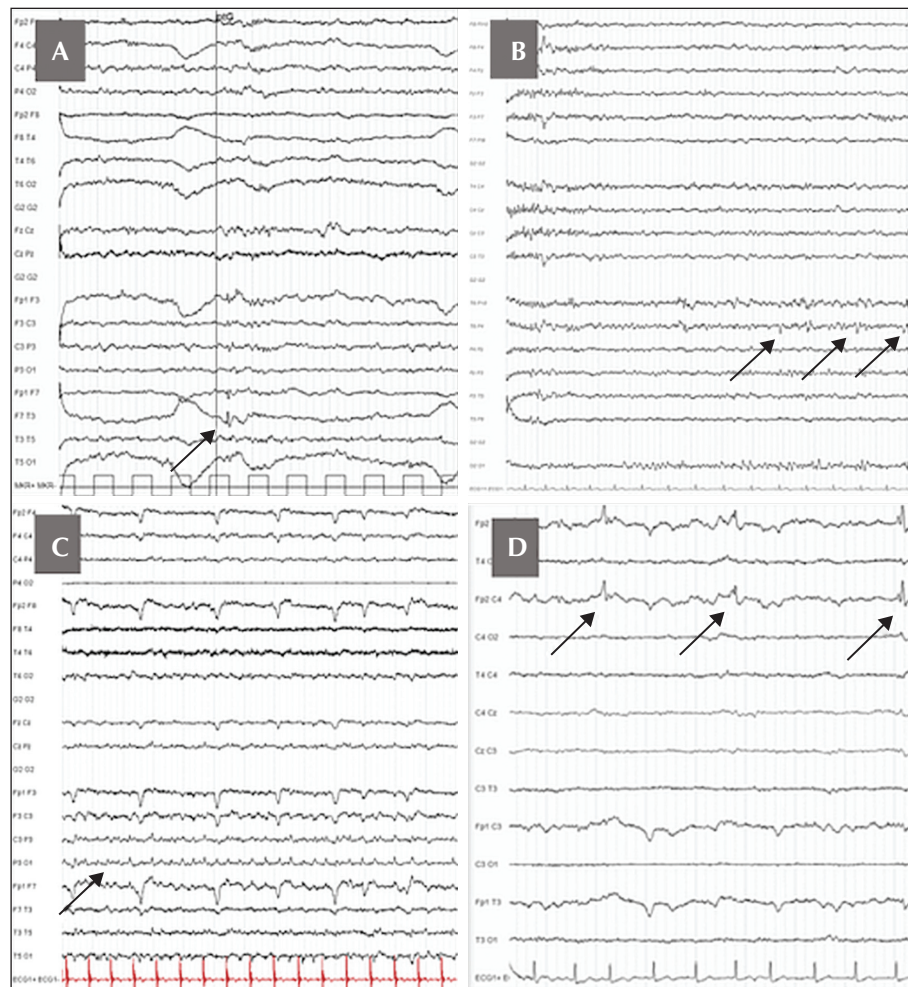


Figure 1. EEG features of GAD65-Ab encephalitis. (A) Patient 1: long-term video-EEG showing left anterior temporal spike. (B) Patient 2: long-term video-EEG showing right posterior temporal spikes. (C) Patient 3: initial EEG showing left temporo-parietal status epilepticus, with parietal rhythmic delta discharge, concomitant with aphasia. (D) Control EEG showing right frontal sharp wave and spikes.

and highly positive in CSF (DOT EUROIMMUN; normal <15). High IA2-Ab (4,000 IU/mL; ELISA EUROIMMUN; normal <10 IU/mL) and anti-insulin-Ab (49 U/mL; ELISA ORGENTEC; normal <10 U/mL) were identified. Brain ^{18}F -FDG PET, performed one year after the epilepsy onset, revealed diffuse bitemporal (internal and external) and left perisylvian hypometabolism (figure 2E).

Treatment with IVIG was initiated. Despite several trials of antiepileptic drugs (levetiracetam, lamotrigine, eslicarbazepine, carbamazepine, and benzodiazepine), her epilepsy became pharmacoresistant with weekly temporal seizures characterized by a brief “*déjà-vu/déjà-vécu*”. Mood disorders improved significantly with escitalopram. In parallel, control of type 1 diabetes improved and insulin could be reduced. Because of a desire for pregnancy, IVIG was pursued, avoiding immunosuppressive medication.

Patient 3

A 63-year-old woman was admitted in December 2015 for suspicion of stroke as an emergency secondary to three episodes of transient motor aphasia (lasting for less than one hour each). Several days before, she presented with five successive and transient stereotypic events, characterized by brief right ear tinnitus and motor aphasia, lasting 5-15 minutes. The initial standard EEG showed left lateral temporal status epilepticus (figure 1C). Levetiracetam was introduced. She was readmitted two months later for a confusional state, followed by generalized tonic-clonic seizure. Her husband also described paroxysmal behavioural disturbances with major anxiety, agitation, aggression, and screaming. A long-term EEG recording showed, during sleep, intermittent delta activity in the left temporo-parietal lobe and right

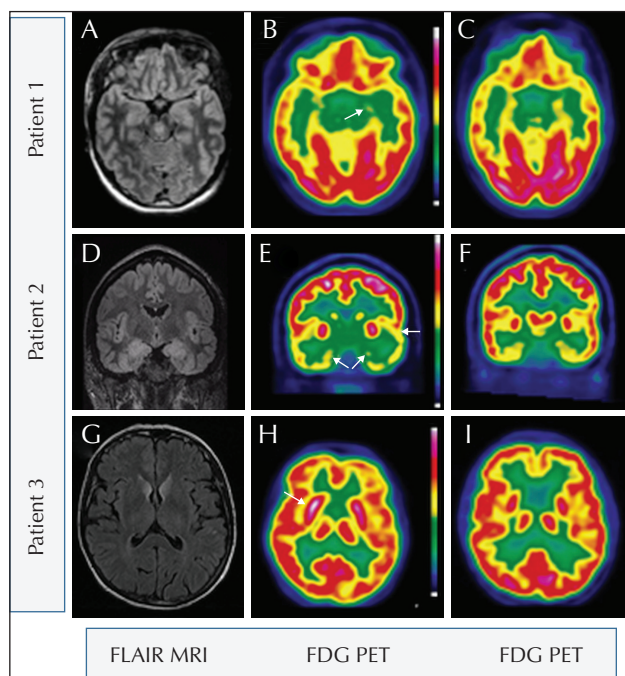


Figure 2. GAD65-Ab encephalitis: initial MRI and brain ^{18}F -FDG PET before and after specific treatment. (A-D) Patient 1: (A) brain MRI three months after epilepsy onset is normal; (B) brain ^{18}F -FDG PET, three months after epilepsy onset showing left temporal hypometabolism; (C) brain ^{18}F -FDG PET, two years after onset of treatment, showing partial reduction of left temporal hypometabolism. (D-F) Patient 2: (D) brain MRI showing bilateral mesial temporal FLAIR hyperintensity; (E) brain ^{18}F -FDG PET, one year after epilepsy onset and before immunoglobulin therapy, showing diffuse bitemporal and left insulo-opercular hypometabolism; (F) brain ^{18}F -FDG PET, three months after treatment, showing partial reduction of bitemporal hypometabolism. (G-I) Patient 3: (G) brain MRI, three months after epilepsy onset, showing FLAIR hyperintensity of the caudate nuclei; (H) brain ^{18}F -FDG PET, three months after epilepsy onset, showing hypermetabolism of the caudate nuclei; (I) brain ^{18}F -FDG PET, two years after onset of treatment, showing regression of the hypermetabolism.

frontal spikes (*figure 1D*). Paroxysmal behavioural disturbances, characterized by agitation, opposition, and aggression, were probably related to frontal epileptic seizures.

The initial MRI was normal. Three months later, the control MRI showed T2/Flair hyperintensity of the caudate nuclei and right anterior cingulum (*figure 2G*), corresponding to hypermetabolism on brain ^{18}F -FDG PET (*figure 2H*). CSF revealed $18/\text{mm}^3$ lymphocytes, CSF protein level was 0.53 g/L , with 11 oligoclonal bands. In the serum, GAD65-Ab was subnormal ($1,049 \text{ UEIA/mL}$), but more than 250 IU/mL in the CSF (ELISA Medipan; normal $<5 \text{ IU/mL}$).

The neuropsychological assessment revealed cognitive difficulties with dysexecutive impairment and

difficulty in lexical access. All clinical and paraclinical features argued for extra-LE.

She was treated with IVIG, cyclophosphamide, and then mycophenolate mofetil. Unusual anxiety with psychomotor acceleration still remains. She reports less than one seizure per month (mutism and loss of consciousness) under lamotrigine and eslicarbazepine. Control brain MRI showed atrophy evolution towards caudate nuclei, and brain ^{18}F -FDG PET regression of the hypermetabolism (*figure 2I*).

For all patients, other onconeural and cell-surface protein autoantibodies were negative based on negative immunofluorescence performed on brain sections. Scan TAP and whole-body ^{18}F -FDG PET revealed no neoplasia.

Discussion

GAD is an enzyme that allows the synthesis of GABA from glutamate, the main CNS inhibitory neurotransmitter. GAD65-Ab is commonly described in diabetes as well as three neurological disorders (Saiz *et al.*, 2008): stiff man syndrome (Chang *et al.*, 2013), encephalitis (Gagnon and Savard, 2016), and cerebellar ataxia (Honnorat *et al.*, 2001). The encephalitis phenotype associated with GAD65-Ab seems to be characterized by frequent and severe TLE (Falip *et al.*, 2012; Daif *et al.*, 2018). In a recent study, almost all patients with GAD65-Ab encephalitis had initial seizures, and a quarter displayed status epilepticus. Epilepsy remained intractable in half of the cases (Gagnon and Savard, 2016). GAD65-Ab encephalitis phenotype appears to differ from that associated with other antibodies with less cognitive and psychiatric impairment (Malter *et al.*, 2010; Daif *et al.*, 2018).

We report three patients with confirmed GAD65-Ab encephalitis (positive antibodies in CSF). For all, the initial symptom was new-onset focal status epilepticus. Patient 1 and 2 reported an intense and prolonged dysmnestic experience (over several hours) without clear paroxysmal events. Neuropsychiatric comorbidities, a lack of initial standard EEG, and resistance to antiepileptic drugs made the interpretation of these subtle events complex. Prolonged EEG performed during the asymptomatic period provided an additional argument for an epileptic disorder, only during sleep. Retrospectively, the duration of these episodes (several hours) was clearly in favour of recurrent temporo-mesial status epilepticus. Semiology was more obvious for Patient 3, who started with recurrent prolonged atypical aphasic disorder. In this case, EEG during the symptomatic period showed direct evidence for lateral temporal status epilepticus. Neuropsychiatric comorbidities (mood disorders and

mnesic or dysexecutive impairment) were frequent and possibility linked to status epilepticus.

The semiology described here appears to be different from that of other auto-immune encephalitis, such as LGI1, CASPR2, AMPAR, and GlyR, with a more insidious and subtle semiology. Epilepsy is a core symptom of GAD65-Ab encephalitis (Daif *et al.*, 2018; Vinke *et al.*, 2018). Additional epileptic symptoms (psychiatric and cognitive) exist, but may be misdiagnosed without careful interview. For two of our patients, epilepsy diagnosis was not obvious and long-term video-EEG was essential to correlate this exclusive subjective semiology to recurrent temporal lobe status epilepticus. In the literature, the description of seizures is limited, but intense subjective impairment (such as dysgeusia and dysosmia) has previously been reported in a review (Gagnon and Savard, 2016). The two first patients presented with LE semiology with temporo-mesial seizures, whereas the third patient clearly presented with lateral temporal and frontal seizures arguing for non-LE. Neocortical and deep grey structure hyperintensity on MRI was in agreement with this encephalitic pattern. Two similar cases have been reported in the recent literature (Najjar *et al.*, 2011). GAD-Ab encephalitis appears to involve either limbic or extra-limbic structures, however, focal status epilepticus seems to reveal the pathology in all cases.

Taken together, our observations and the data from the literature suggest that GAD65-Ab should be screened in the CSF of patients with unexplained new-onset focal status epilepticus, especially when there is predominant subjective semiology. Careful anamnesis and paraclinical examination with a long-term EEG recording are essential to determine the diagnosis of epilepsy mediated by GAD65-Ab. In accordance with our three cases, pharmacoresistant epilepsy appears to be the main neurological problem in the clinical follow-up of GAD65-Ab encephalitis patients, even under optimized immunosuppressive treatment (Falip *et al.*, 2012; Gagnon and Savard, 2016; Daif *et al.*, 2018). Cognitive and psychiatric disorders, although less predominant, should be followed to better characterize the clinical outcome for this encephalitis. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.

None of the authors have any conflict of interest to declare.

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TEST YOURSELF



(1) What is the main symptom associated with GAD65-Ab encephalitis?

- A. Mood disorder
- B. Temporal lobe epilepsy
- C. Impaired vigilance
- D. Movement disorder
- E. Behavioural change

(2) An exclusive subjective semiology, as a recurrent feeling of a “dreamy state”:

- A. May require long-term video-EEG monitoring if standard EEG is normal
- B. Can be difficult to interpret in cases of mood disorder
- C. Can be a focal status epilepticus
- D. All of the above
- E. None of the above; not relevant to epilepsy

(3) Which of the following is correct regarding paraclinical features of GAD65-Ab encephalitis:

- A. Temporal lobe hyperintensity on brain MRI is always present
- B. The diagnosis is only confirmed by GAD65-Ab in CSF (intrathecal synthesis of Ab)
- C. Hyponatraemia is present in 60% of cases
- D. Cerebellar atrophy on brain MRI reinforces the diagnosis
- E. The absence of CSF inflammation excludes the diagnosis

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section “The EpiCentre”.