Clinical commentary

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Acute amnesia and seizures in a young female

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ABSTRACT – Limbic encephalitis is a condition characterised by an acute or sub-acute onset of memory disorder, associated with seizures and psychiatric manifestations. Investigations such as brain MRI usually reveal a high intensity signal in the medial temporal lobe and cerebrospinal fluid analysis shows mild pleocytosis and oligoclonal bands. It may occur in association with cancer, infection, or as an isolated clinical condition, often accompanying autoimmune disorders. Immune-mediated limbic encephalitis is now subclassified according to the presence and type of autoantibodies, which has significant consequences regarding the effectiveness of treatment and prognosis. Glutamic acid decarboxylase (GAD) is an enzyme that catalyses glutamic acid into gamma aminobutyric acid. Anti-GAD antibodies are associated with different neurological and non-neurological disorders, but only a few cases of limbic encephalitis associated with anti-GAD antibodies have been reported in the literature, most of them non-paraneoplastic. Here, we report the case of a young female patient with a medical history of psoriasis who developed an acute onset and chronic evolution of anterograde amnesia, associated with drug-resistant epilepsy. Brain MRI showed hyperintensity in the medial temporal lobes and the biochemical studies revealed intrathecal synthesis of anti-GAD antibodies. Screening tests for tumours were negative. Despite antiepileptic drugs, intravenous immunoglobulins and immunosuppressive treatment, the patient did not show clinical improvement and one year later, she continues to present refractory temporal epilepsy and cognitive deficits.

Key words: limbic encephalitis, glutamic acid decarboxylase, paraneoplastic antibody, immunotherapy

Limbic encephalitis (LE) is a clinico-pathological entity characterised by an acute to sub-acute onset of seizures, short-term memory deficits, and behavioural changes or other psychiatric symptoms (Vincent *et al*., 2011).

The pathogenesis of LE is related to inflammation of the medial temporal lobe and may be considered as infectious (herpes simplex virus [HSV] and human herpesvirus 6) paraneoplastic, or non-paraneoplastic, based on immune-mediated processes (Matà *et al*., 2008). Currently, the diagnosis of most typical LEs may be obtained through the information provided

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by the combination of clinical, EEG, MRI, and routine CSF studies, and it is no longer necessary to demonstrate an inflammatory infiltrate in the temporal lobe (Tüzün and Dalmau, 2007). Taking into account the type of antibody found, autoimmune LE has been classified into two broad categories. The first one, *paraneoplastic LE*, includes patients with antibodies (Abs) directed against intracellular antigens such as Hu, Yo, CV2, Ri, and Ma2. These Abs are associated with cytotoxic T cell mechanisms, which are considered the main pathogenic effectors. Due to these Abs being highly specific to cancer, an exhaustive evaluation is necessary to exclude tumour.

The second category, *non-paraneoplastic limbic encephalitis* (NPLE), includes patients with Abs directed to cell membrane antigens such as voltage-gated potassium channel (VGKC), N-Methyl-D-aspartate receptor (NMDAR), or the group referred to as "novel neuropil Abs". These patients have better clinical and neuroimaging response to immunotherapy than patients with paraneoplastic LE, except when the Abs are directed against intraneuronal antigens, as is the case for anti-GAD Abs (Malter *et al*., 2010). Association with other autoimmune diseases (ocular myasthenia and psoriasis) is common (Bien and Scheffer, 2011).

Anti-GAD Abs are a type of intracellular Ab directed against GAD. They were initially described in a patient affected by stiff-person syndrome (Solimena *et al*., 1988) and subsequently they have been reported in other diseases such as type 1 diabetes, chronic cerebellar ataxia, drug-resistant epilepsy, myoclonus, and LE (Saiz *et al*., 2008). Anti-GAD Ab-associated LE is a rare condition and no more than a few cases have been reported in the literature (Marchiori *et al*., 2001; Vincent *et al*., 2011).

We report a case of NPLE associated with anti-GAD Abs with no response to immunotherapy and severe consequences, such as memory loss and refractory temporal lobe epilepsy.

Case study

A 29-year-old female was admitted to the emergency care unit with a three-hour history of disorientation and short-term memory loss. Her medical history was unremarkable except for mild cutaneous psoriasis. Furthermore, her mother endured Hashimoto's thyroiditis and vitiligo, while her brother and one of her cousins presented with multiple sclerosis and another cousin was epileptic.

On admission, the patient presented disorientation, severe anterograde amnesia, and several episodes of *déjà-vu* and *déjà-connu* feeling. No other abnormalities were found in the neurological or physical examinations. The blood test and cranial CT were normal. The CSF analysis showed mild pleocytosis with normal levels of glucose and protein. Owing to the main symptoms of the patient being partial seizures and anterograde amnesia, a medial temporal lobe involvement was suspected. At that time, intravenous acyclovir (600 mg/8 hours) was initiated to treat a suspected case of herpetic encephalitis and antiepileptic drugs for acute symptomatic seizures (levetiracetam at 2,000 mg/day and carbamazepine at 600 mg/day).

One day later, and in spite of the treatment, the patient continued to have partial seizures consisting of abdominal aura, oral automatisms, and *déjà-vu* and *déjà-connu* feeling, with or without impairment of consciousness. These episodes lasted from several seconds to 2-3 minutes. Several antiepileptic drugs (levetiracetam at 3,500 mg/day, carbamazepine at 800 mg/day, and phenytoin at 300 mg/day) were necessary in order to control the seizures.

Routine haematological and biochemical analyses were normal. Serological testing for HIV, syphilis, cytomegalovirus, HSV-1, and HSV-2 were negative. A serological panel for autoimmune disorders was negative including: anti-nuclear, anti-double-stranded DNA, anti-SS-A, and anti-SS-B, anti-cardiolipin, anti-thyroglobulin, and anti-thyroid peroxidase antibodies. The antibodies to intracellular antigens associated with paraneoplastic encephalitis (anti-Hu, anti-Yo, anti-amphipysin, anti-Ri, anti-Ma2, and anti-CV2) and those against cell surface antigens (anti-NMDA, anti-AMPA, anti-GABA, and anti-VGKC complex, including anti-LGI 1 and CASPR2) were negative. The anti-GAD Abs showed high levels, both in serum and CSF, with a CSF/serum index of 7.8 indicating intrathecal synthesis. Oligoclonal bands were positive.

Initial brain MRI was carried out 48 hours after the onset of the symptoms and did not show any abnormalities. A second MRI investigation was performed 20 days later and axial T2 and fluid attenuation inversion recovery (FLAIR) sequences revealed a hyperintense signal in both of the mesial temporal lobes (milder in the right temporal lobe), suggesting LE (*figure 1*). An ovarian ultrasound, whole-body CT, and PET-FDG were unremarkable. A 24-hour video-EEG showed interictal epileptiform activity in both anterior temporal lobes, but mainly in the left side. Several typical seizures were recorded showing a left temporal ictal onset with subsequent propagation to the contralateral side several seconds later (*figure 2*).

The neuropsychological assessment revealed temporal disorientation, a mild dysexecutive syndrome with difficulties in planning and decision-making, and a Mini Mental State Test score of 24/30. Digit span

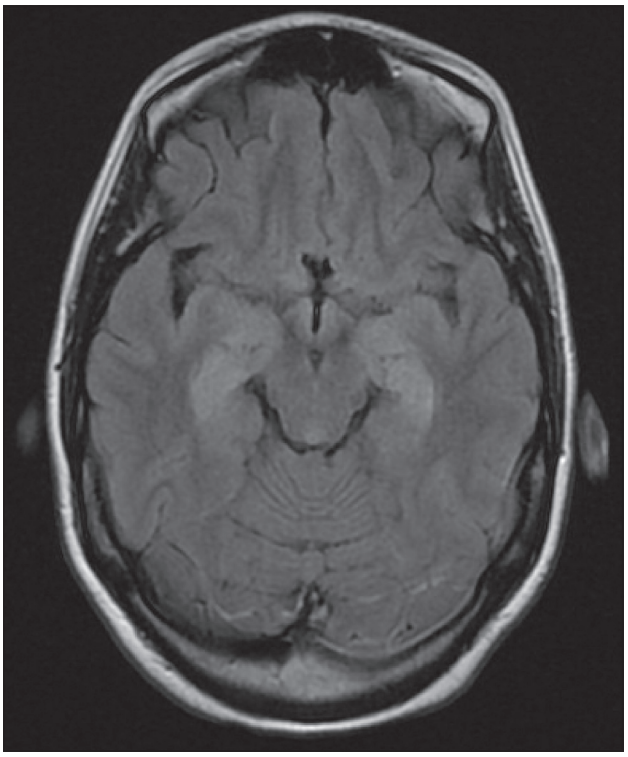

Figure 1. Axial FLAIR-weighted brain MRI showing a hyperintense signal in both medial temporal lobes.

forward was almost average and digit span backward was deficient. Memory tests showed a severe anterograde memory deficit (immediate free recall after distraction and delayed free recall) with no improvement after being given clues. The Rey Complex Figure test also revealed a visual memory deficit.

The patient was treated with two cycles of intravenous immunoglobulins (400 mg/kg/24 hours, five days per cycle) resulting in a decrease in the seizure frequency. Due to this improvement, we decided to continue with immunoglobulins (one cycle) instead of using steroids or plasmapheresis and to start immunosuppressive treatment. The patient was discharged with intravenous rituximab (0.5 g/week), cyclophosphamide (200 mg/day for five days), and AEDs (lacosamide at 300 mg/day and levetiracetam at 3,500 mg/day). Four days later, she returned to the emergency unit with abdominal pain. Blood tests showed liver toxicity, therefore immunotherapy was discontinued, and when the transaminases were normal, azathioprine was initiated without any side effects. One year after the onset of the clinical symptoms, and in spite of the different treatments, the patient continues to present with refractory epilepsy and cognitive deficits. The neuropsychological reassessment showed only a slight improvement in visual memory and executive dysfunction and no changes in verbal memory test results. Subsequent brain MRI revealed bilateral hippocampal atrophy (*figure 3*) while control whole-body CT and FDG-PET were normal.

Discussion

We present the case of a young female with anti-GAD Ab-associated NPLE, which is a very uncommon type of LE and only a few cases have been reported in the literature.

LE is a well-recognised condition characterised by subacute development of short-term memory loss, behavioural change, and seizures involving the temporomedial lobes. The initial differential diagnosis may be challenging due to the myriad of clinical presentations and lack of symptom specificity. Viral infections, autoimmune disorders, and paraneoplastic syndromes are some of the possible aetiologies. As HSV encephalitis is a possible cause, most patients with subacute LE are prescribed acyclovir. In the case of herpetic encephalitis, the presence of fever, an accelerated presentation of symptoms, a significant mass effect on T2-weighted sequences, or evidence of haemorrhagic encephalitis based on MRI or CSF are more frequent (Gultekin *et al*., 2000).

Given that our patient was a young female and after ruling out infectious aetiology, we considered anti-NMDAR Ab-associated LE as the most probable diagnosis. Nevertheless, immunological tests for Abs directed against cell membrane antigens or against intracellular antigens were negative except the anti-GAD Abs, which showed high titres in both serum and CSF. Because anti-GAD Abs in serum may be found in other diseases (DM1 or other endocrine autoimmune disorders), the demonstration of positive intrathecal synthesis of these Abs could indicate that the GAD autoimmunity is related to the neurological syndrome (Liimatainen *et al*., 2010).

Although the pathogenic role is unclear, it has been proposed that anti-GAD Abs could impair GABAergic synaptic transmission by reducing GABA synthesis and/or interfering with exocytosis of GABA, leading to increased excitability and lower seizure threshold (Vianello *et al*., 2002). However, the correlation between disease activity, serum Ab titres, and immunotherapy in anti-GAD Ab-associated LE is otherwise unknown. A reduction in Ab titre with immunotherapy in some reported cases was paralleled with disease stabilisation (Blanc *et al*., 2009) while in others cases, the titres did not fall substantially (Malter *et al*., 2010). Considering this, we decided not to determine levels of anti-GAD Abs again and guide treatment based on the severity of the symptoms.

In 80% of the patients with LE, CSF studies show inflammatory changes with lymphocytic pleocytosis and

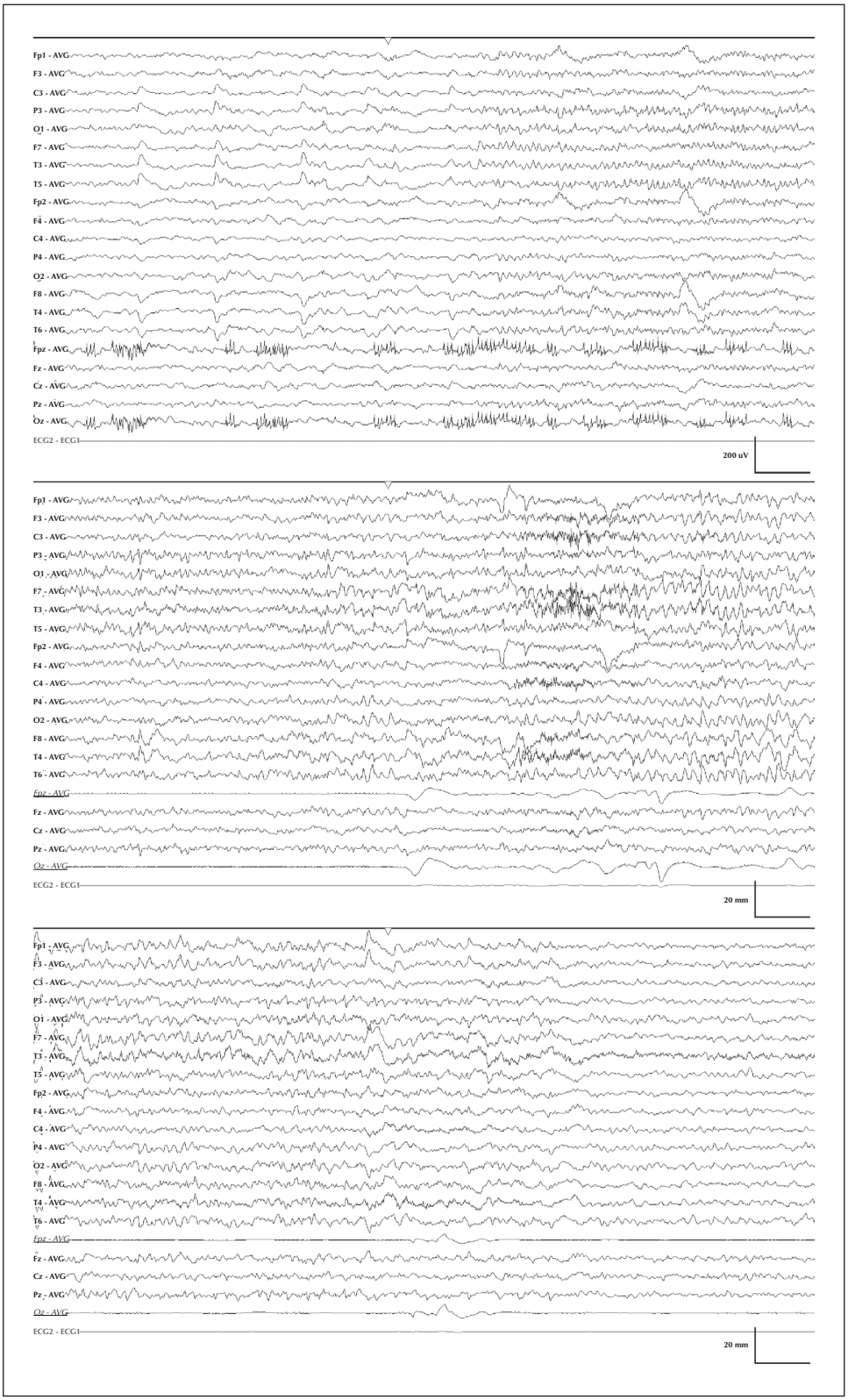

Figure 2. Ictal EEG recording showing a left temporal ictal onset, subsequently spreading to the contralateral side, concomitant with abdominal aura, oral automatisms, and an impression of *déjà-vu*.

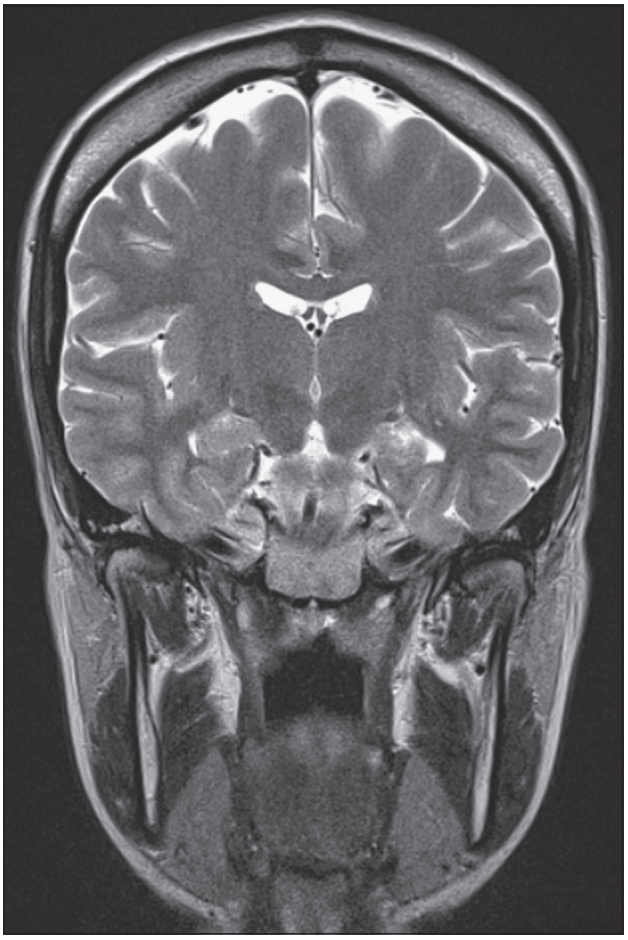

Figure 3. Coronal T2-weighted brain MRI (during follow-up) showing atrophy of both medial temporal lobes, mainly in the left hippocampus.

positive oligoclonal bands, although some patients (particularly those with anti-VGKC Abs) may have normal CSF or only oligoclonal bands (Tüzün and Dalmau, 2007). Video-EEG may show non-specific generalised or focal slowing, occasionally with epileptiform activity and clinical seizures.

Initial brain MRI was normal and it was not until the second MRI investigation that a signal hyperintensity in the medial temporal lobes was observed (after 20 days). This case report confirms, as do other articles, that early diagnosis of LE may be considered in patients with multiple daily temporal seizures and amnesia, even in the absence of early typical MRI abnormalities (Saiz *et al*., 2008). Subsequent brain MRI (performed 12 months later) revealed atrophy of both mediotemporal lobes.

There is a trend towards a worse clinical prognosis in LE associated with anti-GAD Abs compared to LE associated with anti-VGKC Abs. The cause of therapeutic failure is unclear and although one proposed hypothesis is the appearance of fixed morphological changes on brain MRI, this is considered doubtful as structural abnormalities on brain MRI have been found in equal proportions in patients with either anti-GAD Abs or anti-VGKC Abs (Malter *et al*., 2010).

Conclusion

Although anti-GAD Ab-associated LE is a rare condition, physicians should consider it in patients with unexplained acute onset of seizures and amnesia in the absence of data on infection and after ruling out other more common autoimmune LE. Currently, data suggest that it is a disease relatively resistant to immunotherapy, with a chronic course and poor outcome. □

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