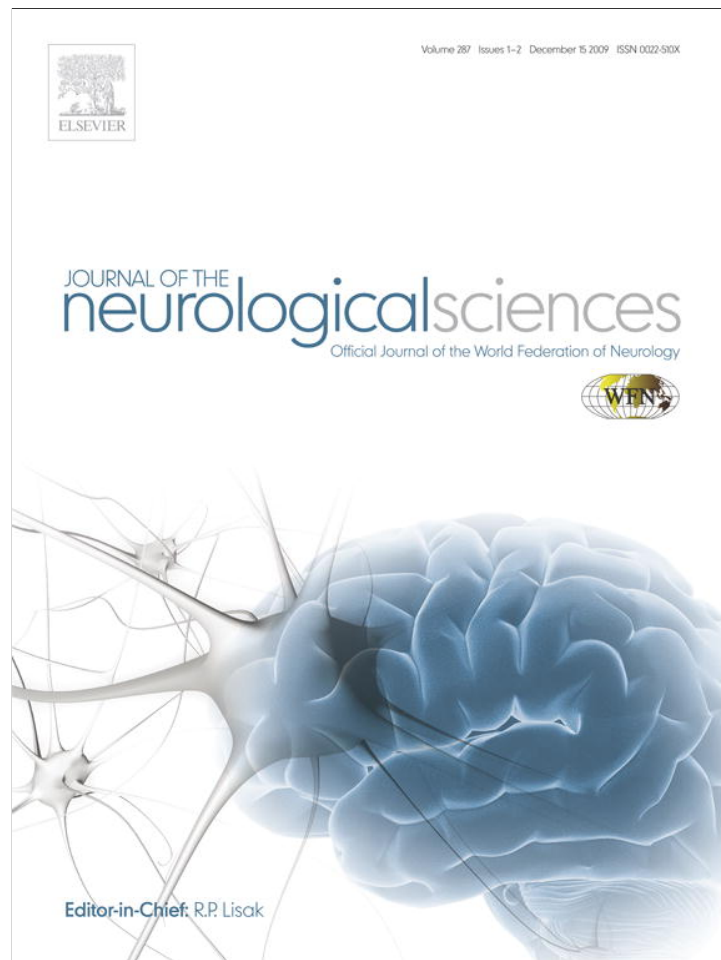


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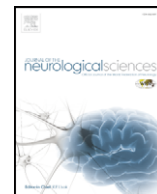
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Acute limbic encephalitis and glutamic acid decarboxylase antibodies: A reality?

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ABSTRACT

Limbic encephalitis (LE) associated with glutamic acid decarboxylase antibodies (GAD-Ab) is rare. We describe a 30-year-old male with acute LE and GAD-Ab, with follow-up during 2 years of cognitive status including verbal episodic memory, number of seizures recorded by high-resolution video-EEG, brain MRI, 2-[18F]-fluoro-2-deoxyglucose PET and GAD-Ab titres. Treatment with corticosteroids, IV immunoglobulins, immunosuppressors and antiepileptic drugs resulted in improved memory status, disappearance of seizures and decreased GAD-Ab titres. Review of the other cases of literature and this case is in favour of the existence of autoimmune LE associated with GAD-Ab and supports the link between memory, temporal seizures and possibly GAD-Ab titres.

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1. Introduction

Limbic encephalitis (LE) is an association of subacute anterograde amnesia, seizures and psychiatric symptoms such as personality changes, irritability and depression [1]. The pathogenesis of LE is related to inflammation of the medial temporal lobe and can be either viral, paraneoplastic or autoimmune in origin [1]. Different specific antibodies to intraneuronal antigens including anti-Hu can be detected in paraneoplastic LE [2]. Seventy-eight percent non-viral LE cases are paraneoplastic and antineuronal antibodies are present in 60% [1,3].

In immune-mediated LE, antibodies to novel cell-membrane antigens, voltage-gated potassium channels (VGKC), *N*-methyl-D-aspartate receptors and AMPA (Glu-R1 and R2) have been described [3–5]. The prognosis of non-viral LE is poor. However, the prognosis of non-paraneoplastic immune-related LE is improved with immunotherapy [6]. Few patients have been described with LE and glutamic acid decarboxylase antibodies (GAD-Ab) [3,7–12]. We report a case of immune-mediated LE associated with anti-GAD65-Ab that partially responded to immunotherapy. Other cases of GAD-Ab associated LE are discussed.

2. Case report

A 30-year-old African male, with no previous medical history, was admitted in December 2006 for acute short-term memory loss. Memory tests revealed a massive anterograde episodic memory disorder. Performance on verbal memory was deficient with no cueing effects. Copy of the Rey Complex Figure was correct, but recall was nil. Digit span forward was low average, while Digit span backward was deficient. His Mini Mental State Test was 24/30. General and neurological examinations were normal. Brain MRI demonstrated hyperintensity without contrast enhancement in both medial temporal lobes and amygdalae on T2 and FLAIR sequences (Fig. 1a). Brain 2-[18F]-fluoro-2-deoxyglucose (FDG)-PET showed hypermetabolism in both medial temporal lobes (Fig. 1b). Whole body FDG-PET and CT-scans completed by abdominal MRI and gastroscopy revealed no sign of neoplasm; diffuse enlargement of the pancreas was observed without FDG enhancement. Negative biological tests (lipase, amylase, carbonic anhydrase I and II, and lactoferrin antibodies) eliminated autoimmune pancreatitis. Routine haematological and biochemical analyzes were normal. A cerebrospinal fluid sample revealed oligoclonal IgG bands (table). PCR for herpes virus was negative and serum tumour markers were negative. Alpha fetoprotein was elevated to 13.3 µg/l ($N < 7$). Immunological tests for intraneuronal antibodies, by immunochemistry and immunoblot including anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, anti-CV2, anti-Ta and Ma1, were unremarkable. VGKC-Ab were negative (courtesy of Dr. Angela Vincent).

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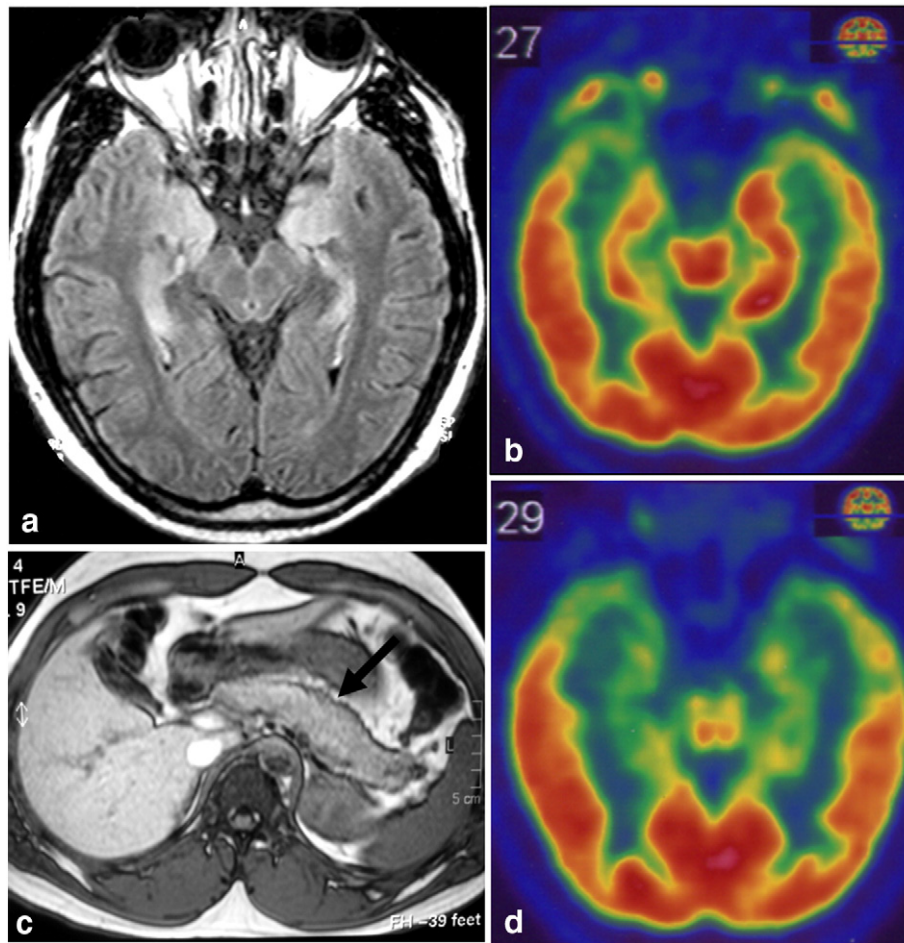


Fig. 1. Limbic encephalitis and pancreas enlargement. (1a) Axial T2-FLAIR-weighted brain MRI showing intense signal in the amygdalae and hippocampi. (1b) Axial 2-[18F]-fluoro-2-deoxyglucose brain PET showing hippocampal hypermetabolism at the start of encephalitis, predominating on the left side. (1c) Axial T1-weighted abdominal MRI showing diffuse pancreas enlargement. (1d) Axial brain PET in March 2007 when the patient's memory had improved showing hypometabolism of the hippocampi and temporal poles.

Serum anti-GAD65-Ab level was 463 000 U/ml (<5 U/ml) (using biotinylated GAD65 in a commercial kit (RSR,Cardif,UK)) (Fig. 2). Furthermore they reacted strongly in the Dot assay (DTEK,Mons,B).

Anti-IA2 antibodies were negative. Initial EEG showed a theta focus involving the left temporal region. High-resolution 24-h video-EEG showed 25 bilateral temporal seizures, mostly on the left side. No obvious

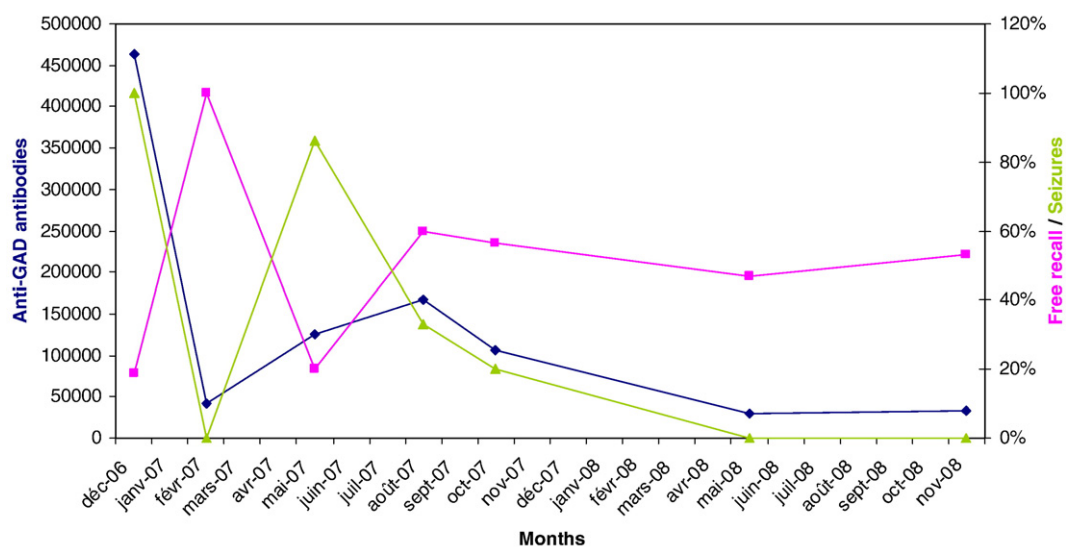


Fig. 2. Outcome of verbal memory tests, number of seizures and GAD-Ab titres. GAD65-Ab titres are expressed as U/ml (blue line). Verbal memory performance (purple line) is expressed as the ratio between delayed free recall and maximal score (Grober and Buschke test, 5 words test, Rey Auditory-Verbal learning test). Number of seizures is expressed as a percentage of the maximum number of seizures on 24-h high-resolution EEG (25 seizures/day in December 2006). GAD-Ab seems to be directly correlated with number of seizures and inversely with delayed free recall. A small increase in GAD-Ab in May 2007 was sufficient to alter memory and initiate seizures, probably because the hippocampi were more sensitive. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

clinical signs were noted during these seizures. Therapy was initiated with methylprednisolone (1 g/day for 3 days) and clobazam (15 mg/day). No improvement was observed on neuropsychological testing 1 week later and intravenous (IV) immunoglobulin (0.4 g/kg/day for 5 days every 6 weeks) was added. After 6 weeks, short-term memory had improved and brain PET revealed hypometabolism in the temporal lobes (Fig. 1d). Brain MRI remained unchanged and anti-GAD65-Ab decreased to 42 000 U/ml (Fig. 2).

Five months later, the patient was readmitted because of relapse of his memory disorder. Video-EEG showed a bilateral asynchronous temporal focus with several seizures involving the left temporal lobe. Anti-GAD65-Ab levels increased to 126 000 U/ml. Treatment with methylprednisolone (1 g/day for 3 days), associated with IV immunoglobulin (0.4 g/kg/day for 5 days) and mycophenolate mofetil (2000 mg/day) was administered. Antiepileptic therapy consisted of levetiracetam (3 g/day) and clobazam (15 mg/day). Verbal memory was improved (Fig. 2). Visual recall was satisfactory during the learning phase and flawless during recognition-delayed recall. The patient resumed normal life. However, epileptic partial seizures persisted on antiepileptic therapy. Prednisolone (1 mg/kg/day) and oxcarbamazepine (900 mg/day) were added.

In 2008, control whole body CT- and FDG-PET scans were normal and pancreas enlargement had disappeared on abdominal MRI. Under antiepileptic drugs, mycophenolate mofetil and corticosteroids, the outcome of the patient was stable for cognitive functions including memory, and seizures had disappeared (Fig. 2).

3. Discussion

Acute anterograde amnesia, associated with bilateral temporal involvement and temporal seizures, was consistent with the diagnosis of LE. LE was attributed to autoimmune GAD-Ab as there was no evidence of underlying paraneoplastic aetiology.

Ten cases of LE with GAD-Ab have been described previously [3,7,8,10–13]. However five of these also had other autoantibodies. Thus, the LE could have been attributed to other autoimmune aetiology such as anti-neuropil antibodies because GAD-Ab titres were unchanged during follow-up for one case [3], or steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) for another case [14]. In our case, we show a direct correlation between GAD-Ab titres and number of temporal seizures and inverse correlation between GAD-Ab and memory. GAD converts L-glutamic acid into the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Two GAD isoforms (65 and 67 kDa) are found in GABAergic neurons and pancreatic β -cells [15] and pathogenicity of GAD-Ab to the CNS has been confirmed in patients with neurological symptoms [15]. But GAD65-Ab have been detected previously in patients with many other neurological disorders such as stiff-man syndrome and cerebellar ataxia [16], and thus lacks specificity.

However, GAD65 is highly expressed in CA1 and the hippocampal dentate gyrus [17]. GAD65-Ab could impair GABAergic synaptic transmission by reducing GABA synthesis and/or interfering with exocytosis of GABA in stiff-man syndrome and cerebellar ataxia [18]. This mechanism may have been responsible for the focal seizures and hippocampal inflammation seen in our patient. Moreover, GAD-Ab are suspected to be involved in some cases of refractory epilepsy: status

epilepticus originating in the temporal lobes was described recently. GAD-Ab titres and seizures decreased after cyclophosphamide treatment [19].

In our case, the link between GAD-Ab and pancreas enlargement is unclear. Autoimmune pancreatitis was eliminated but an inflammatory process is possible because enlargement disappeared after immunosuppressor treatment.

This case is in favour of the occurrence of rare cases of non-paraneoplastic LE mediated by GAD-Ab. Improvement of memory and disappearance of seizures occur with diminution of GAD-Ab but a causal relationship between antibodies and the encephalitis remains to be demonstrated. Nevertheless, monitoring GAD-Ab titres could be an effective indicator to guide immunotherapy.

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