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Short communication

Predictive value of high titer of GAD65 antibodies in a case of limbic encephalitis

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ABSTRACT

We report the case of a 42-year-old woman who presented with vertigo and migraine and rapidly developed cognitive decline and seizures. Both serum and cerebro-spinal fluid samples showed high titer of anti-glutamic acid decarboxylase (anti-GAD65) antibodies (998,881 IU/ml and 54,687 IU/ml respectively). Limbic encephalitis was diagnosed and high dose steroids treatment started. During one-year follow-up, without further immunomodulatory therapy, the patient became seizure free, and cognitive functions returned to normal. Serum anti-GAD65 antibodies titer decreased significantly but remained elevated (192,680 IU/ml). We discuss the prognostic and pathogenic value of high titer anti-GAD65 antibodies and its variations in a case of autoimmune limbic encephalitis.

1. Introduction

Anti-glutamic acid decarboxylase (anti-GAD65) antibodies are a rare cause of autoimmune encephalitis (Malter et al., 2010). Serum anti-GAD65 antibodies are present at low titers in 1% of healthy people and in 80% of type 1 diabetes mellitus patients (Meinck et al., 2001). Only serum anti-GAD65 antibodies at high titers are usually associated with autoimmune neurological disorders, such as limbic encephalitis (LE) (Nakajima et al., 2018). Neurological symptoms usually occur when the titers is 100–1000 times higher compared to those found in people with type I diabetes (Nakajima et al., 2018). Anti- GAD65 antibodies titers above 2000 IU/ml are detected in only 0.8% of analyzed patients with diabetes (Saiz et al., 2008). Seizures and memory impairment are considered cardinal symptoms of LE associated with anti-GAD65 antibodies, clinically comparable to other autoimmune LEs (Gagnon and Savard, 2016). We report and discuss the pathogenic and prognostic value of high antibody titer in patient with anti-GAD65 LE.

2. Case report

A 42-year-old right-handed woman experienced insomnia, vertigo and headache, associated with brief paroxysmal episodes of heart palpitations and sweats several times per day, for a period of four weeks before her first neurological evaluation. Following the appearance of two focal to bilateral seizures, memory complaints and blood pressure instability, she was admitted to an inpatient neurology unit. Family history was positive for multiple sclerosis of her sister. Personal history was positive for Hashimoto's thyroiditis. No febrile illness was reported before neurological clinical onset. Routine biological test was normal; neurological examination was normal except for a complaint of short term memory deficit; neuropsychological tests confirmed the presence of short- and long-term verbal and visual-spatial memory deficits, reduced semantic fluency. Brain MRI showed mild hyperintensity, without contrast enhancement, in both mesial temporal lobes and left insula on T2 and FLAIR sequences (Fig. 1, panel A). Cerebrospinal fluid (CSF) showed normal glucose and protein levels, increased cell count (156 lymphocytes per μl) and oligoclonal bands on CSF (type 2

Abbreviations: GAD65, Anti-glutamic acid decarboxylase 65; LE, limbic encephalitis; CSF, cerebrospinal fluid; FDG, 2-[18F]-fluoro-2-deoxyglucose; ELISA, Enzyme-linked immunosorbent assay; SMS, stiff-man syndrome

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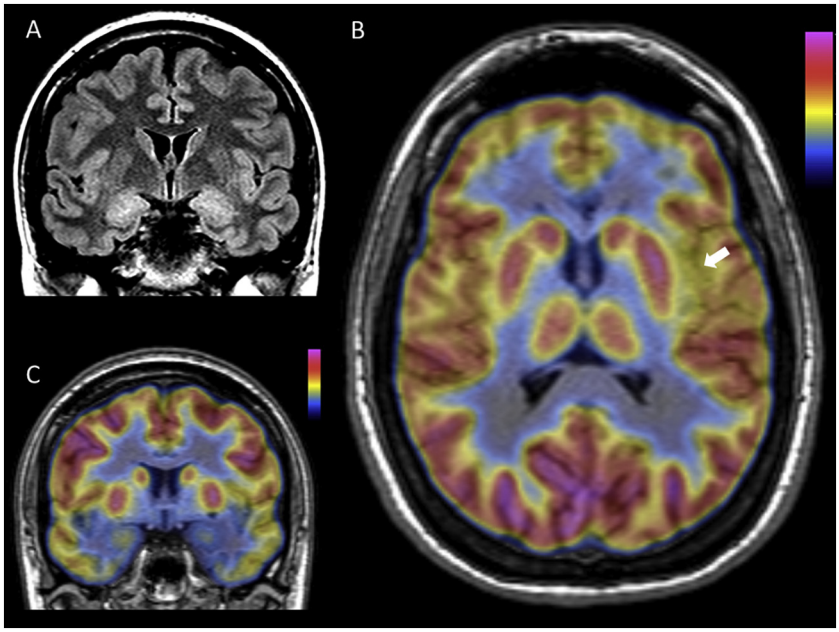

Fig. 1. Neuroimaging showed bilateral temporal and left insula involvement. Panel A. Brain magnetic resonance imaging fluid-attenuated inversion recovery coronal section: hyperintensity in both mesial temporal lobes and left insula. Panel B. Brain FDG-PET axial section: hypometabolism in the left insula (white arrow). Panel C. Brain FDG-PET coronal section: hypometabolism in the mesial temporal regions.

reaction) on isoelectric focusing suggestive of intrathecal IgG synthesis. Serum and CSF samples showed high titer of anti-GAD65 antibodies (998,881 IU/ml and 54,687 IU/ml respectively) using Enzyme-linked immunosorbent assay (ELISA - Medizym ®antiGAD cod 3802), in the absence of potential assay interference.

Screenings for HSV, EBV, VZV, CMV, HIV, West Nile, Enterovirus, Listeria, systemic autoimmunity and onconeural and surface antibodies (Amphiphysin, Hu, Yo, Ri, CV2 and Ma1–2, NMDAr, LGI1, Caspr2, AMPA1–2, GABAb) and antibodies for thyroperoxidase and thyroglobulin were negative. Whole body 2-[18F]-fluoro-2-deoxyglucose (FDG)-PET and CT-scans revealed no malignancy. EEG recordings showed bilateral parieto-occipital slow and epileptiform abnormalities.

Diagnosis of definite limbic encephalitis was achieved (Graus et al., 2016) and treatment with methylprednisolone, 1 g daily for 5 days, was started. Vertigo and headache promptly improved and seizures disappeared during the first week. Three months later, serum examination showed anti-GAD65 antibodies titer of 185,000 IU/ml and CSF examination 24.5 IU/ml. Without further immunomodulatory therapy, patient was seizure free and only mild memory and language disorders and blood pressure instability persisted.

After twelve months, brain-MRI remained unchanged, brain FDG-PET showed hypo-metabolism in left insula and bilaterally in mesial and polar temporal regions, with left prevalence (Fig. 1, panel B and C). The EEG was normal. Neuropsychological deficits completely recovered. Serum anti-GAD65 antibodies titer was 192,680 IU/ml at twelve months. Patient was asymptomatic without immunosuppressant or immunomodulatory treatment (Fig. 2).

3. Discussion

The correlation between the detection of anti-GAD65 antibodies and clinical symptoms is frequently discussed in the literature (Blanc et al., 2009; Najjar et al., 2011; Graus et al., 2016; Daif et al., 2018). The antibody titer depends on the technique used (Liimatainen et al., 2010; Daif et al., 2018) and may lack specificity since high values have been identified in patients with different neurological disorders such as LE, stiff-man syndrome (SMS), severe dysautonomia, chronic epilepsy and cerebellar ataxia (Honnorat et al., 2001; Ben Achour et al., 2018; Daif et al., 2018). Anti-GAD65 antibodies may impair GABAergic synaptic transmission by reducing GABA synthesis and by interfering with GABA exocytosis (Sloviter et al., 1996; Dinkel et al., 1998). Moreover, a down-regulation of GABA synthesis in basket-cell terminals, with a reduction of GABA release on postsynaptic Purkinje cells, has been demonstrated (Ishida et al., 1999; Mitoma et al., 2000; Takenoshita et al., 2001). GAD65 is highly expressed in CA1 and the hippocampal dentate gyrus, and pathogenicity of anti-GAD65 antibodies in CNS disorders has been considered in LE patients (Manto et al., 2007; Sloviter et al., 1996), but the hypothesis that anti-GAD65 antibodies invariably compromise inhibitory network function is controversial, as underlined by Stemmler et al. (Stemmler et al., 2015).

The clinical spectrum of anti-GAD65 is broad and it extends from asymptomatic patients to fulminant encephalitis with status epilepticus requiring aggressive immunosuppression (Triplett et al., 2018).

In our case, memory deficits, associated with CSF abnormalities, bilateral temporal involvement, and focal seizures, were consistent with the diagnosis of LE (Graus et al., 2016), which was attributed to high titer anti-GAD65 antibodies. Despite the presence of high titer anti-GAD65 antibodies, the pathogenic link between these antibodies and LE in our patient appears to be uncertain. Since she presented a high titer of serum and CSF antibodies at the onset of the encephalitis that remained within ranges defined as pathogenic by several authors (Graus et al., 2016; Naakajima et al., 2018; Saiz et al., 2008) during and after high-dose intravenous steroid therapy. The patient, however, became rapidly asymptomatic without the need of a chronic immunomodulatory treatment. Our results play against a pathogenic role of serum anti-GAD65 antibodies in our patient (cut-off of > 2000 IU/ml with Radioimmunoassay, > 1000 IU/ml with ELISA) (Nakajima et al., 2018; Saiz et al., 2008; Vianello et al., 2002). On the other hand, a further hypothesis was that the early intervention may have enabled good outcome in this otherwise chronic and hard-to-treat condition (Malter et al., 2015).

Usually, treatment options are based on immunotherapy with steroids, intravenous immunoglobulin, or plasma exchange in the acute phase of the disease. The need for long-term treatment with immunomodulatory/immunosuppressants drugs (Daif et al., 2018) is more controversial, given the burden of possible severe adverse events. Based on our observation anti-GAD65 antibodies titers may not be an effective indicator to guide long-term immunotherapy, which should be considered with caution and strictly related to the clinical picture. In the previous studies, persistently high anti-GAD65 antibodies titers are often associated with poor clinical response and reduced titers are often observed in patients who clinically respond to treatment, but the level

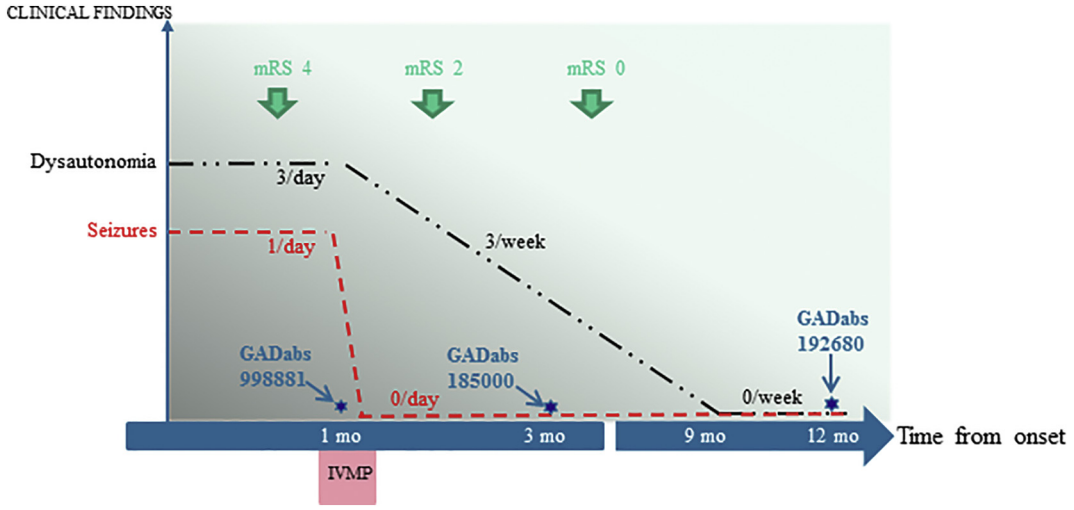

Fig. 2. Clinical course in relationship with antibodies titers and treatment. The panel indicated the time-course of clinical findings based on the modified Rankin Scale (mRS) score, dysautonomia and seizure episodes and serum antibodies titers course. GAD abs: serum anti-GAD65 antibodies; IVMP: intravenous methylprednisolone.

can decline or persist and rarely disappear in response to immunotherapy (Kwan et al., 2000; Errichiello et al., 2009). We propose that the clinical response and the 'relative' trend of the antibodies' titer over time rather than the 'absolute' value should be used to guide treatment decision.

Kim et al. demonstrated that anti-GAD65 antibodies in type I diabetes are predominantly directed to conformational epitopes of NH2-terminal of GAD65, while all SMS patients immunoprecipitated native GAD65 resulting in different pathogenicity (Kim et al., 1994). In addition, the authors hypothesized that the greater magnitude of antibodies in SMS reflected a biased involvement of the Th2 subset of CD4 + T cells, whereas diabetes was likely mediated by the Thl subset of CD4 + T cells and cytotoxic T cell responses (Kim et al., 1994). Therefore, an additional hypothesis, which cannot be excluded without further in vitro and in vivo studies, is that different involvement of epitopes of GAD65 and subset of CD4+ T cells are responsible for dissimilar pathogenicity of anti-GAD65 antibodies in different patients.

4. Conclusion

Anti-GAD65 associated LE should be considered in patients presenting with focal seizures, memory deficit and dysautonomia. This case further expands the knowledge about the role of anti-GAD65 in LE and its value in guiding long-term immunomodulatory treatment in such a severe neurologic condition. The work underlines the difficulty in the therapeutic management of these patients and highlights the relevance of early treatment and close clinical and laboratory follow-up.

Declaration of Competing Interest

None.

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