Limbic encephalitis and type 1 diabetes with glutamic acid decarboxylase 65 (GAD65) autoimmunity: Improvement with high-dose intravenous immunoglobulin therapy

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Abstract

Glutamic acid decarboxylase antibodies (GAD-abs) are an immunological factor involved in type 1 diabetes and other diseases involving the central nervous system. This report is of a patient with type 1 diabetes and a rare case of non-paraneoplastic limbic encephalitis mediated by anti-GAD65 antibodies that improved with the use of immunosuppressive drugs.

Keywords: Type 1 diabetes; Glutamic acid decarboxylase 65 (GAD); Limbic encephalitis; Immunotherapy; Epilepsia

Résumé

Encéphalite limbique et diabète type 1 avec auto-immunité anti acide glutamique décarboxylase 65 (GAD) : traitement par immunoglobulines intraveineuses à forte dose.

Objectif. – Les anticorps anti-acide glutamic decarboxylase 65 (ac anti-GAD) sont des facteurs immunologiques déterminants dans la physiopathologie du diabète de type 1 mais également dans un certain nombre de maladies du système nerveux central. Nous rapportons le cas d’une patiente avec un diabète de type 1 associé à une encéphalite limbique non paranéoplasique aux anticorps anti GAD, traitée par immunothérapie.

Mots clés : Diabète type 1 ; Acide glutamique décarboxylase 65 (GAD) ; Encéphalite limbique ; Immunothérapie ; Épilepsie

1. Introduction

The 65-kDa-enzyme glutamic acid decarboxylase (GAD65) catalyzes the conversion of glutamic acid to gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter of the central nervous system (CNS). Two GAD isoforms (65 kDa and 67 kDa) are found in pancreatic β cells and GABAergic neurons, and in the liver, kidneys, testes and adrenal glands [1,2].

Antibodies to GAD65 (GAD65-abs) are considered markers in 80% of patients with autoimmune type 1 diabetes mellitus (T1DM), although GAD autoimmunity has been implicated in
other neurological diseases [1,3,4], such as limbic encephalitis (LE). LE is an inflammatory process involving the hippocampus, amygdala and, less frequently, the frontobasal and insular regions of the brain [3,5,6]. LE with autoantibodies against neuronal cell surface proteins [3,7–10] could represent paraneoplastic disease or, more frequently, is associated with other autoimmune disorders. A subtype of LE with autoantibodies against GABA has also been recently described [5,6,10,11].

The present report is of a young woman with LE, manifested by drug-resistant epilepsy and brittle T1DM associated with a high titre of GAD65-abs in serum and cerebrospinal fluid (CSF), but without the paraneoplastic syndrome, who was treated by intravenous immunoglobulin therapy (IgIV).

2. Case report

A 27-year-old woman was hospitalized for the 15th time within 5 years of follow-up for complex partial seizures and brittle diabetes. The genealogical tree of our patient showed a high level of consanguinity and several autoimmune diseases. Much of her past-history included uncontrolled T1DM with pos-

sitive GAD65-abs (diagnosed in 2000) and recurrent hospitalization for ketoacidosis or severe hypoglycaemia (10 episodes per month). Her mean level of glycated haemoglobin (HbA1c) was 8% in 2005. Since 1999, she presented with epilepsy, manifested by 8–10 seizures per month; symptoms initially related to “absence” occurred several times in spite of multiple lines of treatment. High-resolution video-electroencephalography (EEG) diagnosed complex partial epilepsy (CPE) with absences and automatisms. Psychiatric symptoms, such as personality changes, irritability and depression, were also observed. Neuropsychological tests demonstrated a significant decrease in intellectual capacity, attention-deficit disorder, episodic memory problems and thymus dysfunction.

2.1. Diagnostic approach

In June 2006, our patient was re-admitted for elevated glycaemia and several seizures. Treatment at the time included detemir, lispro, valproic acid, levetiracetam, topiramate, carba-
mazepine and clonazepam. A search of the literature (PubMed) uncovered a similar case with antiepileptic resistance due to high levels of anti-GAD-abs in CSF and in serum [12]. A lumbar puncture performed in our patient revealed high CSF is high, interactions between GAD-abs and onconeuronal antibodies 

abs led to immunotherapy being proposed [13,14].

The therapeutic protocol consisted of the human intravenous immune globulin Octagam® (Octapharma France, Boulogne, France) at 1 g/kg on two consecutive days, every 4 weeks, from February to September 2007 (8 months). Evaluation included measurements of HbA1c, antibody levels, video-EEG and neu-

ropsychological tests every 3 months throughout this time. No adverse effects were reported, although transient hypergly-

caeaemia during the infusion of immunoglobulin was observed. This Ig treatment proved to be effective for LE. In fact, complete remission of seizures was observed and documented by video-EEG, together with a reduction in antiepileptic ther-
apy from five to two drugs (topiramate and carbamazepine). Brain abnormalities on MRI disappeared and psychometric tests improved. Concomitantly, mean HbA1c decreased by 1.3%, with a reduction of insulin doses from 62 to 45 U/day.

3. Discussion

On the basis of controlled clinical trials, high-dose intravenous immunoglobulin has emerged as an effective therapy in the management of patients with various autoimmune disorders [13,14]. The present patient had T1DM and LE with high levels of GAD65-abs. While the latter are frequently seen in T1DM, their presence in CSF is rare [2]. However, resistant epilepsy with complex partial seizures, such as stiff-person syndrome (SPS) with absences, was the rationale behind our proposal for immunosuppressive therapy in this patient [4,13].

The role of anti-GAD antibodies in neurological diseases such as SPS and cerebellar ataxia remains elusive due to a lack of experimental animal models. It has been postulated that the humoral immune response to GAD-abs could lead to functional impairment of GABAergic neuron synaptic transmission possibly due to the reduction of GABA synthesis by anti-GAD-

abs and/or interference with the exocytosis of GABA. Such autoimmunity against GAD may also, in part, contribute to the development of drug-resistant epilepsy and explain refractory epilepsy [2–4,7]. However, when the level of GAD65-abs in CSF is high, interactions between GAD-abs and onconeural antibodies [9] could limit the interpretation of immunological tests, and lead to false-positive results for onconeural antibodies (by courtesy of Dr Didelot). Nevertheless, LE with GAD-abs has been previously described in association with and without another autoimmune disease [5,6,10,11].

Our present report has demonstrated the efficacy of immunosuppressive therapy for autoimmune GAD-abs diseases: T1DM was evaluated by HbA1c levels, while LE was assessed by the number of CPE episodes and the results of cognitive tests.
Treatment appeared to be associated with improvement of metabolic control, as reflected by a decrease in HbA1c (by 1.3%), and by better control of epileptic manifestations. However, our case report has limitations that merit consideration. The association between immunosuppressive therapy and the patient’s improvement may have only been coincidental. Also, the repeated hospitalizations (every 4 weeks) may have had non-specific beneficial effects on both the diabetes and neurological disease in this fragile patient. Furthermore, no correlation was observed between the decrease in the number of seizures and the immunosuppressive therapy and serum/CSF GAD-abs titres.

4. Conclusion

This patient with brittle T1DM and a rare case of non-paraneoplastic LE mediated by anti-GAD65-abs showed improvement after 8 months of immunosuppressive drug therapy targeted against the intrathecal synthesis of antibodies. However, whether or not this observation is relevant to other cases of brittle diabetes associated with epilepsy and/or other neurological symptoms requires further consideration.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References