CASE REPORTS

Case reports of unexplained weight loss in autoimmune central neurological syndromes with anti-GAD antibodies

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ABSTRACT

Glutamic acid decarboxylase (GAD) is becoming increasingly recognised as an antigenic target in autoimmune disorders of the central nervous system. There are currently no reports of weight loss being a manifestation in such disorders. We describe two cases of anti-GAD associated neurological disorders with profound and otherwise unexplained weight loss. Both patients had incomplete response to immunotherapy, as is becoming typical of these disorders. The variable disease associations of anti-GAD antibodies is incompletely understood, and leads us to question whether weight loss in these patients could possibly be immune-mediated.

Key Words: Glutamic acid decarboxylase, GAD, Encephalitis, Weight loss

1. INTRODUCTION

Antibodies directed against glutamic acid decarboxylase 65 (GAD65) are seen in a number of neurological and non-neurological conditions. Specifically, it has been well characterised as a marker of autoimmune conditions of the endocrine system, including type 1 diabetes and autoimmune thyroid disease.[1,2] In clinical neurology it has been identified in stiff person syndrome, cerebellar ataxia, progressive encephalomyelitis with rigidity and myoclonus (PERM) and limbic encephalitis.[3–5] Low titers of anti-GAD65 antibodies can be found in well defined syndromes, such as anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis,[6] anti-γ-amino butyric acid receptor B (GABAb) encephalitis[7] or other neurological disorders.[2,8] In these circumstances the significance of the antibody is undetermined, and may simply be a bystander representing immune activation and neuroinflammation. However, there are emerging case reports of non-paraneoplastic autoimmune encephalitis with very high titers of anti-GAD antibodies in isolation.[9–12] Part of the challenge in describing such a presentation as a unique clinical entity is that many of these reports depict patients with co-existing autoimmune diabetes.[13–15] While anti-GAD65 titers are frequently higher in cases with an immune mediated neurological syndrome,[2,4] this finding is certainly not ubiquitous.[4] Therefore a major interest in characterizing anti-GAD encephalitis is to examine cases without type 1 diabetes mellitus.

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Weight loss has never before been identified in the literature as a symptom of anti-GAD autoimmune encephalitis. While it could potentially be a manifestation of poorly managed type 1 diabetes mellitus, overt autoimmune thyroid disease or underlying malignancy, in cases without these comorbidities it remains unexplained. Herein we illustrate two non-paraneoplastic cases of autoimmune neurological disorders with high titer anti-GAD65 antibodies. Both cases describe significant unexplained weight loss either shortly before or at the onset of their neurological syndrome. While both patients developed diabetes mellitus during the course of their respective illnesses, the diagnosis seemed unrelated to the weight problem. These cases were identified in a cohort of retrospective cases of autoimmune encephalitis. Among the seven patients in this cohort with high titer anti-GAD antibodies (> 1,000 U/ml), these were the only two with significant weight loss. This study was approved by Melbourne Health Human Research and Ethics Committee.

2. CASE PRESENTATIONS

2.1 Case 1: Anti-GAD cerebellar syndrome

A 36-year-old female presented with sudden onset of vertical diplopia, oscillopsia, multi-directional rotational nystagmus, disequilibrium, myoclonic jerks and truncal ataxia on a background of 6 months of mild dysarthria. Aside from some minor previous surgical complaints, she was otherwise well, had no family history of autoimmune disease and took no regular medications. Regarding her investigations, an magnetic resonance imaging (MRI) scan of her brain identified an incidental 4 mm left cavernous internal carotid artery aneurysm and an arachnoid cyst of the posterior fossa, but otherwise no abnormalities. Cerebrospinal fluid (CSF) analysis revealed a lymphocyte count of 99 cells/mm^3 and protein concentration 0.34 g/L. Her anti-neuronal and myaesthenic (anti-acetylcholine receptor and anti-muscle specific tyrosine kinase) antibodies were both negative. However, she had detectable serum anti-GAD65 antibodies with a titer > 1,483 U/ml, and a CSF that demonstrated anti-GAD-like staining but with insufficient sample for an immunoblot. She went on to have a repeat CSF which again demonstrated anti-GAD-like staining, but this time the immunoblot could be performed and was negative. This was likely due to the fact this assay was not designed for CSF analysis, and the volume required necessitated dilution of CSF thereby reducing the sensitivity (see Figure 1).

Notably she was also being investigated for unexplained weight loss, which commenced 12 months prior to the onset of dysarthria. Her weight declined over the subsequent 18 months, starting from 66 kg and reaching a nadir of 47 kg (BMI 16.5). She had no symptoms of dysphagia, anorexia or diarrhoea that might explain this. A history of family trauma coincided with the onset of this symptom, and consequently a provisional diagnosis of an eating disorder was made. However, detailed psychiatric input failed to identify any clear evidence of such a diagnosis and the patient's weight remained at 52 kg (BMI 18.3) despite high calorie nasogastric feeding and dietician involvement. A comprehensive series of investigations failed to elicit a cause, including celiac and non-neural (anti-nuclear and anti-neutrophil cytoplasmic) antibodies, thyroid function, short synacthen test, serology for latent viral infections (human immunodeficiency virus, Hepatitis B and C), serum angiotensin converting enzyme level, various tumour markers and stool culture. She also went on to have an MRI small bowel, and both upper and lower endoscopy with histological samples, all of which were normal. A whole body PET/CT (positron emission tomography/computed tomography) scan did demonstrate mild splenomegaly and low grade axial marrow activity, but a bone marrow biopsy was normal and the haematological opinion was that the marrow change was related to weight loss and malnutrition. Importantly, her tests for diabetes were normal at this time.

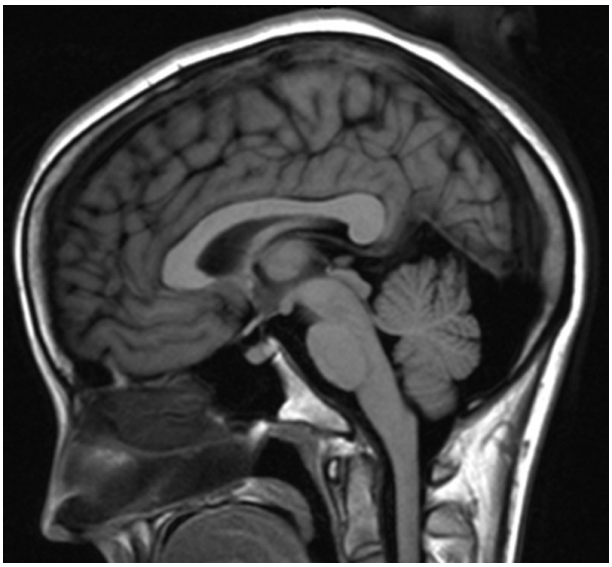

Figure 1. Magnetic resonance imaging findings for case 1. Sagittal T1-weighted sequence demonstrating that the brainstem and cerebellar vermis have normal appearances. An arachnoid cyst is incidentally seen in the posterior fossa.

She had a short course of corticosteroids at a peripheral hospital on initial presentation treating a presumed vestibular neuronitis, but formal immunosuppression did not commence for three months. She was given a trial of induction intravenous immunoglobulin (IVIg) at 0.4 g/kg over 5 days, which was continued as maintenance treatment for several months. Due to poor response she was then given 4 treatments of

plasma exchange followed by another course of 1 g daily methylprednisolone with a weaning oral tail of prednisolone. In the 3 months after commencing immunotherapy, it was noted that her weight appeared to improve, increasing to 56 kg. Notably this did coincide with the commencement of corticosteroid treatment. Her weight continued to fluctuate over the coming months, declining again to 52 kg, but ultimately increased to 59.5 kg and stabilized there. It was around this time she was diagnosed with type 1 diabetes mellitus. Over a year after presenting she was ultimately commenced on an induction dose of rituximab (375 mg) for four weeks with maintenance doses (1 g) 6-monthly and oral prednisolone 10mg daily thereafter. She gradually improved with this treatment, noting reduced symptoms of ataxia and oscillopsia although never completely disappearing. Low grade cervical intra-epithelial neoplasia and human papilloma virus changes were found on a routine pap smear one year later, requiring loop excision, but no systemic malignancy was ever detected on surveillance imaging. Three years after the onset of her cerebellar syndrome, the patient had stable neurological symptoms, and was able to return to work and start driving again.

2.2 Case 2: Anti-GAD limbic encephalitis

A 44-year-old female initially presented to an overseas centre with a two month history of visual hallucinations. She also complained of one month of episodes of déjà vu, olfactory hallucinations, agitation, paranoia and depression. She was previously well and took no regular medications. An MRI brain performed during this overseas admission showed bilateral but asymmetrical signal hyperintensity in the medial temporal structures with associated swelling. Anti-GAD antibodies were detectable in both serum and CSF, and she was treated with plasmapheresis, which gave modest subjective improvement. She was started on sodium valproate 200 mg twice daily after developing a rash to oxcarbazepine. It was during the course of this admission that she was found to have type 2 diabetes mellitus, but only requiring dietary modification. Her father was identified as also having a diabetes diagnosis. Unfortunately we do not have any further reports of this admission. Over the subsequent weeks the patient experienced precipitous weight loss, declining from her baseline of 56 kg and stabilizing at 44 kg (BMI 16.2). This occurred despite no symptoms of anorexia or diarrhoea, and a normal oral intake. About a month after discharge she developed profound and progressive cognitive impairment. By the time she presented to our centre she had severe deficits in both short and long term memory, and scored 23/30 on mini-mental state examination. In repeating her investigations we found that both her serum and CSF GAD65 were > 2,000 U/ml. The remaining CSF was bland and acellular, her anti-neuronal, cell surface (NMDAR, GABAb, voltage-gated potassium channel complex, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) and non-neuronal (ANA, ANCA, extractable nuclear antigen, double stranded DNA) antibodies were all negative. Her thyroid function was normal, but low titer anti-thyroid antibodies were detected with anti-thyroglobulin and anti-thyroid peroxidase titers of 14.3 IU/ml and 42.6 IU/ml respectively. Her MRI brain demonstrated bilateral T2-weighted and FLAIR (fluid-attenuated inversion recovery) signal hyperintensity in the medial temporal structures (see Figures 2A-B) with associated shine-through on DWI (diffusion-weighted imaging) and ADC (apparent diffusion coefficient) sequences. She also had corresponding hypermetabolism on PET imaging of the brain (see Figures 2C-D). There were multiple events during video EEG monitoring, demonstrating ictal and inter-ictal epileptiform discharges originating from the temporal lobes bilaterally. A screen for malignancy with CT whole body identified a 2.1 cm low density lesion right adnexa that was radiographically benign, and a 1.7 cm $\times$ 1.3 cm hypodense lesion of left thyroid which was later found to have no suspicious sonographic features of malignancy.

At this time the patient was admitted for 5 days of 0.4 g/kg IVIg and started oral prednisolone 40 mg daily. She also underwent baseline neuropsychological assessment, which demonstrated marked difficulties with both verbal and non-verbal learning, and an overall cognitive performance below the 4th percentile. During this time she started a mixed insulin and metformin for her diabetes treatment, and the sodium valproate was increased to 500 mg twice daily. Within a week of this treatment she was already showing signs of improvement with regression of seizures and agitation, and demonstrable improvement in cognitive performance with a two point increment in MMSE (mini-mental state examination). She went on to have maintenance IVIg and continued the same dose of prednisolone.

Two months after starting treatment she was showing qualitative trends for improvement on repeat neuropsychological assessment, although these were not apparent on a statistical level. Both her seizures and hallucinations had stopped, although her depression and agitation persisted. At this time her weight had increased to 50 kg. Unfortunately, the patient was lost to follow-up thereafter.

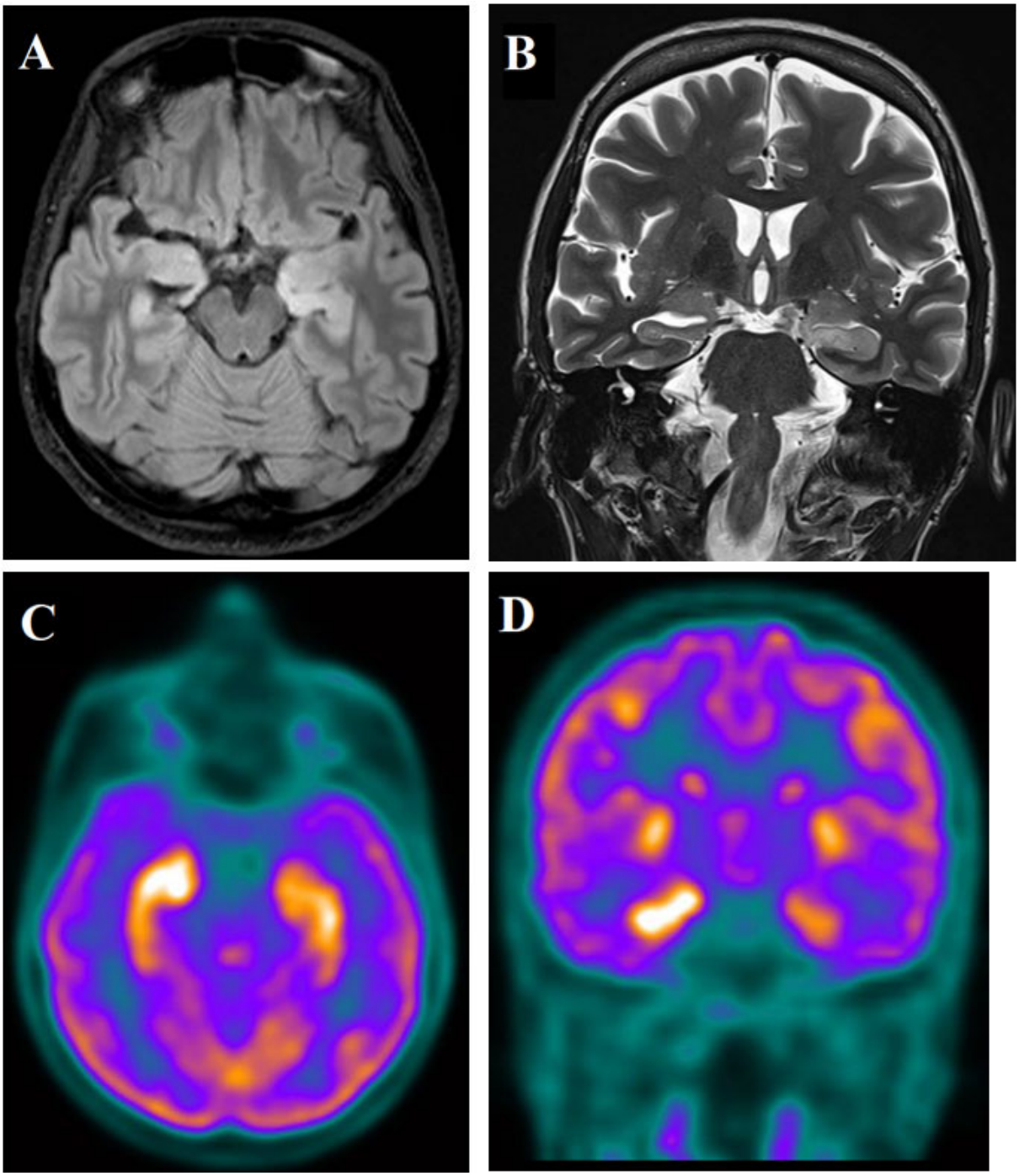

Figure 2. Neuroimaging findings for case 2. Axial FLAIR and coronal T2-weighted sequences on magnetic resonance imaging demonstrating signal hyperintensity in the medial temporal lobes (A, B). Hypermetabolism is demonstrated in the medial temporal lobes on fluorodeoxyglucose positron emission tomography (C, D).

3. DISCUSSION

We present two cases of profound weight loss in the setting of an anti-GAD65 related neurological illness. Both of these cases describe weight loss that remains unexplained aside from their temporal relationship with the onset of an anti-GAD mediated neurological syndrome. While each patient was found to develop diabetes mellitus, the severity and timing was insufficient to cause this symptom. We note that the second case was described as having type 2 diabetes mellitus, which would therefore have a non-autoimmune origin. It is possible, however, that this patient in fact has latent autoimmune diabetes of adults (LADA) and that over the

course of her limited follow-up this diagnosis was yet to reveal itself. This is especially important considering dysglycaemia was occurring irrespective of her weight. Another limitation for this patient is that she was never tested for adrenal insufficiency; an essential constituent of autoimmune polyendocrine disease. While her typical blood pressure was low but not unusual for a thin lady at around 100/65, she had no postural recordings. Factors against this diagnosis included normal serum sodium and potassium, and a lack of blood pressure increment with glucocorticoid use. On that note, it was also interesting to observe that the weight of both patients was improving with immunotherapy. It is impossible to determine whether this was a result of effective treatment against an immune-mediated phenomenon or simply a side effect of corticosteroid use. Identifying cases that were not treated with corticosteroids would be important in answering this question. One study documented the course of a patient with high titer anti-GAD antibodies who developed immunotherapy-responsive limbic encephalitis 18 years after the antibodies were first identified.[10] It is possible that the detectable antibody was a manifestation of underlying autoimmune thyroiditis and the patient simply had seronegative autoimmune encephalitis, but the authors propose that the neurological syndrome was anti-GAD mediated. This raises an interesting question that anti-GAD autoimmunity may be latent for months or even years prior to the onset of a clear neurological syndrome. In our first patient, this latent period may have manifest as weight loss.

Glutamic acid decarboxylase is an enzyme that converts L-glutamate to GABA. It exists in two isoforms, GAD65 and GAD67, each described based on its molecular mass in kDA (kilo-Daltons). While the latter is widespread in the body, GAD65 exists only in nerve cells. Specifically, it is present in the nerve terminals and functions to produce GABA for neurotransmission.[2] It is unclear how antibodies directed against GAD65 can be associated with such a diverse range of neurological and non-neurological conditions. Studies in other antibodies associated with autoimmune encephalitis suggest that while antibodies to targets on the neuronal cell surface may be directly pathogenic, cases with intracellular antigens are likely mediated by T-cell mediated immunity.[5] The neuropathology of anti-GAD65 antibodies also appears to involve T-lymphocytes, thereby likening to other typical intracellular antibodies.[5] However, other studies demonstrate that histological specimens of anti-GAD limbic encephalitis have reduced inflammation and a dissimilar lymphocyte picture compared to cases with classic intracellular targets such as Ma2 and Hu.[16] It is possible that an as yet unidentified antibody or antibodies are causative of the observed syndromes, and high-titer anti-GAD antibodies are simply a bystander here too. Regardless, anti-GAD associated limbic encephalitis appears unique in that outcomes seem quite poor when compared to similar cases with neuronal cell surface antibodies,[11] or even intracellular antibodies.[17]

4. Conclusion

Weight loss may be yet another autoimmune manifestation associated with anti-GAD65 antibodies. We propose that in situations of unexplained loss of weight and central neurological syndromes, clinicians should be vigilant in searching for anti-GAD65 antibodies. It is feasible that treatment of the underlying autoimmune disease may alleviate the degree of weight loss. Future studies are required to analyse this phenomenon further.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

References

[1] Gagnon MM, Savard M. Limbic Encephalitis Associated With GAD65 Antibodies: Brief Review of the Relevant literature. Can J Neurol Sci. 2016; (43): 486-493. PMid:27030381. https://doi.org/10.1017/cjn.2016.13

[2] McKeon A, Tracy JA. GAD65 neurological autoimmunity. Muscle Nerve. 2017; (56): 15-27. PMid:28063151. https://doi.org/10.1002/mus.25565

[3] Tohid H. Anti-glutamic acid decarboxylase antibody positive neurological syndromes. Neurosciences (Riyadh). 2016; (21): 215-222. PMid:27356651. https://doi.org/10.17712/nsj.2016.3.20150596

[4] Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. J Neurol. 2010; (257): 509-517. PMid:20035430. https://doi.org/10.1007/s00415-009-5431-9

[5] Gresa-Arribas N, Arino H, Martinez-Hernandez E, et al. Antibodies to inhibitory synaptic proteins in neurological syndromes associated with glutamic acid decarboxylase autoimmunity. PLoS One. 2015; (10): e0121364. PMid:25774787. https://doi.org/10.1371/journal.pone.0121364

[6] Lu J, Samson S, Kass J, et al. Acute psychosis in a pregnant patient with Graves' hyperthyroidism and anti-NMDA receptor encephalitis. BMJ Case Rep. 2015; 22. PMid:25903201. https://doi.org/10.1136/bcr-2014-208052

[7] Lancaster E, Lai M, Peng X, et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. The Lancet Neurology. 2010; (9): 67-76. https://doi.org/10.1016/S1474-4422(09)70324-2

[8] Sunwoo JS, Chu K, Byun JI, et al. Intrathecal-specific glutamic acid decarboxylase antibodies at low titers in autoimmune neurological

disorders. J Neuroimmunol. 2016; (290): 15-21. PMid:26711563. https://doi.org/10.1016/j.jneuroim.2015.11.012

[9] Ben AN, Ben YT, Rebai I, et al. Severe dysautonomia as a main feature of anti-GAD encephalitis: Report of a paediatric case and literature review. Eur J Paediatr Neurol. 2018; (22): 548-551. PMid:29370977. https://doi.org/10.1016/j.ejpn.2018.01.004

[10] Fauser S, Uttner I, Arino H, et al. Long latency between GAD-antibody detection and development of limbic encephalitis - a case report. BMC Neurol. 2015; 15 (1) (no pagination).

[11] Malter MP, Helmstaedter C, Urbach H, et al. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol. 2010; (67): 470-478. PMid:20437582. https://doi.org/10.1002/ana.21917

[12] Markakis I, Alexopoulos H, Poulopoulou C, et al. Immunotherapy-responsive limbic encephalitis with antibodies to glutamic acid decarboxylase. J Neurol Sci. 2014; (343): 192-194. PMid:24950904. https://doi.org/10.1016/j.jns.2014.05.032

[13] Lopez-Sublet M, Bihan H, Reach G, et al. Limbic encephalitis and type 1 diabetes with glutamic acid decarboxylase 65 (GAD65) autoimmunity: improvement with high-dose intravenous immunoglobulin therapy. Diabetes Metab. 2012; (38): 273-275. PMid:22463975. https://doi.org/10.1016/j.diabet.2012.02.005

[14] Marchiori GC, Vaglia A, Vianello M, et al. Encephalitis associated with glutamic acid decarboxylase autoantibodies. Neurology. 2001; (56): 814. PMid:11274329. https://doi.org/10.1212/WNL.56.6.814

[15] M'Zahem A, Meziani A, Taghane N, et al. Limbic encephalitis associated with glutamic acid decarboxylase antibodies in a young adolescent. Rev Neurol. (Paris). 2016; (172): 327-328. PMid:27117742. https://doi.org/10.1016/j.neurol.2016.02.012

[16] Bien CG, Vincent A, Barnett MH, et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. Brain. 2012; (135): 1622-1638. PMid:22539258. https://doi.org/10.1093/brain/aws082

[17] Hansen N, Widman G, Witt JA, et al. Seizure control and cognitive improvement via immunotherapy in late onset epilepsy patients with paraneoplastic versus GAD65 autoantibody-associated limbic encephalitis. Epilepsy Behav. 2016; (65):18-24. PMid:27855355. https://doi.org/10.1016/j.yebeh.2016.10.016