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Exploring the diverse phenotypes of anti-GAD 65 encephalitis, diagnosis and treatment challenges

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ABSTRACT

Objectives. To present two cases of anti-glutamic acid decarboxylase 65 (anti-GAD65) antibody encephalitis with different clinical phenotypes.

Introduction. Anti-glutamic acid decarboxylase 65 antibody encephalitis (GAD-65 AE) is a rare pathology with a high potential for severity, having multiple forms of presentation and multiple differential diagnoses. This presentation aims to exemplify the strong clinical heterogeneity that is associated with this clinical entity by putting forth two cases that were treated in our clinic, each representing a separate clinical phenotype of this pathology.

Material and methods. We analyzed two cases from our clinic of autoimmune encephalitis with positive anti-GAD65 antibodies and compared the cases with the data from the literature regarding clinical presentation, differential diagnosis, treatment, and evolution.

Content. The first case presented is a woman aged 71 (66 at onset) presenting with progressive cerebellar ataxia. She was diagnosed with GAD-65 AE based on clinical presentation and positive anti-GAD65 antibodies titer. She was initially treated with methylprednisolone pulse therapy and received four such courses in the first year after diagnosis, resulting in a slowing of the progression of the neurological deficit. During the COVID19 pandemic, treatment was paused and her neurological status resumed its decline, and she also developed insulin-dependent diabetes mellitus. Starting in 2021, treatment was continued, having received one course of IVIg and one course of plasma exchange in our clinic. Eventually, the treatment was switched to Mycophenolate mofetil but her status continues to decline.
The second case is about a 32 years old woman, with a history of recurrent seizures and progressive memory decline that started at 28 years. She was diagnosed 11 months after the onset with limbic encephalitis with anti-GAD65 antibodies, left temporal focal epilepsy with nocturnal seizures and mild cognitive decline. She was treated with corticotherapy and IgG. She was discharged home with antiepileptic treatment with no recurring seizures, but a slow cognitive decline. She had two relapses at distance from the onset, the first one with status epilepticus and the second one with focal seizures and a generalized seizure. She developed type I diabetes with positive anti-pancreatic islet antibodies. After the first relapse, immunosuppressive therapy with Mycophenolate mofetil was initiated. The evolution was good and under immunosuppression she had only one episode of seizures in the context of a COVID-19 infection.

Conclusions. Autoimmune encephalitis with positive GAD antibodies presents a very diverse clinical picture, as we can see in the presented cases.

Keywords: brain metastases, diagnosis, duration, lung cancer

INTRODUCTION

Autoimmune encephalitis (AE) is a rare pathology with a high potential for severity, having multiple forms of presentation and multiple differential diagnoses.

Clinical symptoms can begin in a subacute manner (symptom onset in less than 3 months, as seen in autoimmune encephalitis with anti-NMDAR antibodies and most paraneoplastic limbic encephalitis) or, on the contrary, the symptoms can appear pro-

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gressively, sometimes mimicking the onset of a neurodegenerative disease (especially in encephalitis with anti-LGI1, IgLON5, or CASPR2 antibodies) [1].

The symptomatology varies greatly depending on the associated antibody. If there is limbic involvement, the symptoms are often classic and indicate: anterograde amnesia, temporal epilepsy, and behavioral changes (Table 1) [1,2].

DIAGNOSIS

For the diagnosis, the presence of several elements is necessary: a specific neurological syndrome (limbic encephalitis, encephalomyelitis, rapidly progressive cerebellar ataxia, etc.), a circulating antibody targeting a neuronal or glial antigen and a triggering mechanism (paraneoplastic, post-infectious, or autoimmune context) [1].

The diagnosis is mostly based on clinical findings, supported by brain imaging and cerebrospinal fluid analysis.

In recent years, two types of encephalitis have been differentiated based on the intracellular or extracellular localization of the antigen recognized by the patient's autoantibodies.

The first group consists of encephalitis associated with autoantibodies directed against intracellular antigens, mainly including paraneoplastic encephalitis (e.g. Ac anti ANNA1/HU, Ac anti ANNA2/Ri, Ac anti CV2/CRMP5); The associated autoantibodies, also called anti-onconeural antibodies, are excellent markers for the presence of an underlying cancer, often still occult [2].

The second group consists of encephalitis associated with autoantibodies directed against antigens expressed on the surface of neurons and particularly at the synapse, the association with cancer is less common (Table 1). Unlike anti-onconeural antibodies, antibodies directed against surface antigens potentially have a pathogenic effect and can disrupt synaptic transmission, reversibly and with little or no cell death [3,4]. The reversibility of the antibody effect explains that, despite sometimes very severe initial signs, patients are likely to recover completely.

CSF analysis is fundamental to demonstrate the presence of inflammation in the central nervous system and may show high protein and pleocytosis, but usually moderate (less than 100 cells/mm3); A normal CSF analysis does not rule out the diagnosis of autoimmune encephalitis [2].

Neuroimaging - A cerebral MRI should be performed on all patients suspected of autoimmune encephalitis, for both positive diagnosis and differential diagnosis. However, a normal MRI does not rule out the diagnosis; for example, 70% of patients with anti-NMDAR encephalitis have an MRI [2].

TREATMENT

First-line treatment (in the acute phase) we have 3 options [1]:

- High-dose corticosteroid therapy (initially IV then PO);
- IV immunoglobulins - 2 g/kg for 3-5 days;
- Plasmapheresis - 5-10 sessions every other day.

Second-line treatment is considered if after 2-3 weeks of initiating first-line therapy, there is no response or if the initial symptoms are severe.

- ***Cyclophosphamide*** – 1 g IV, monthly pulses for 3–6 months - alkylating agent that inhibits cell proliferation - has a global immunosuppressive action, acting on both cellular and humoral immunity and is more effective in cases of cell-mediated autoimmune encephalitis, but also presents a significant risk of toxicity which limits the duration of treatment [1,5].
- ***Rituximab*** - induction - 1 g IV, at intervals of 15 days; maintenance 1 g IV every 6 months; Selective immunosuppressive action on humoral immunity, especially on CD20+ B lymphocytes, which makes it useful in the treatment of autoimmune encephalitis with anti-membrane antibodies [1,5].
- ***Tocilizumab*** – 8 mg/kg IV monthly – is a monoclonal antibody that targets interleukin 6 receptors, presenting a rapid immunosuppressive effect on both cellular and humoral immunity [1].
- ***Bortezomib*** - proteasome inhibitor that reduces plasma cell production – subcutaneous injections 0.3 mg/m2 with 20 mg IV dexamethasone, twice weekly for 2 weeks (days 1, 4, 8, and 11), followed by a 10-day rest [1,5].
- ***Azathioprine*** – antagonist of purine synthesis, mode of administration: initially 1–1.5 mg/kg once daily or divided twice daily, target 2–3 mg/kg/day [5].
- ***Mycophenolate mofetil*** – 500 mg twice daily, target 1,000 mg twice daily – inhibitor of purine metabolism, mainly acting on lymphocytes [5]

CASE 1 - CEREBELLAR ATAXIA

First, we present the case of a 71-year-old woman, with prior history of autoimmune pathology (vitiligo), who, starting in late 2018, at the age of 66, developed a progressive cerebellar syndrome manifested as disturbance of balance and vertigo. The patient's family history is worth mentioning, her father having been diagnosed with type II diabetes mellitus and vitiligo and her brother with an ophthalmic neoplasm.

TABLE 1. Characteristics of the main antibodies associated with autoimmune encephalitis

Antibodies (serum/CSF)	Clinical presentation, particularities and evolution	Frequency of association with the presence of a tumoral mass	The most frequently associated tumors
NMDAR (CSF>Serum)	- psychiatric disorders; - cognitive and behavioral disorders; - speech disorders; - seizures - abnormal movements, especially orolingual and facial dyskinesias; - confusional states; - cardio-respiratory dysautonomia; It is associated with age and sex-dependent tumors (often presenting as paraneoplastic syndrome in cases of ovarian teratoma in young women or post-herpetic encephalitis in elderly males). Subacute evolution	40%	- ovarian teratoma; - carcinomas (in elderly patients)
LGI1 (Serum>CSF)	- limbic encephalitis; - facio-brachial dystonia; - sleep disorders; - hyponatremia Subacute or chronic evolution.	<10 %	- thymoma; - neuroendocrine tumors
GAD 65 (CSF>serum)	- stiff person syndrome; - cerebellar ataxia; - limbic encephalitis; - drug-resistant temporal lobe epilepsy Often chronic evolution	<10 %	- small cell lung carcinoma; - thymoma; - neuroendocrine tumors
IgLON 5 (CSF>serum)	- sleep disorders - REM and non-REM parasomnias; - respiratory disorders during sleep - stridor, sleep apnea syndrome; - bulbar symptoms; - cerebellar ataxia, - cognitive disorders Chronic, slowly progressive evolution	<10 %	- thymoma; - neuroendocrine tumors
CASPR 2 (serum>CSF)	- limbic encephalitis; - episodic or permanent cerebellar ataxia; - autoimmune neuromyotonia; - Morvan syndrome (neuromyotonia, peripheral nerve hyperexcitability, dysautonomia, sleep disorders) Subacute or chronic evolution.	<10 %	- thymoma;
GABABR (CSF>serum)	- limbic encephalitis; - rapidly progressive cognitive decline Subacute evolution.	50-80%	- small cell lung carcinoma;
ANNA1/HU (serum and CSF)	- limbic encephalitis; - acute disseminated encephalomyelitis; - sensory neuronopathy; - chronic gastrointestinal pseudo-obstruction. Subacute or chronic evolution.	85%	- small cell lung carcinoma; - non-small cell lung carcinoma; - neuroendocrine tumors
ANNA-2/Ri (serum and CSF)	- cerebellar ataxia; - opsoclonus/myoclonus; - abnormal movements; - limbic encephalitis.	80%	- breast cancer; - gynecological cancer; - gastrointestinal cancer
PCA1/YO (serum and CSF)	- cerebellar ataxia. Subacute or chronic evolution.	90%	- ovarian and breast cancer.
GFAP (CSF)	- meningoencephalitis; - acute disseminated encephalomyelitis Subacute evolution.	20 %	- ovarian teratoma;

In green AE with antibodies against intracellular antigens and in yellow AE with antibodies against surface antigens; Abbreviations: NMDAR - N-methyl-D-aspartate receptor; LGI1 - leucine-rich glioma inactivated protein, GAD - glutamic acid decarboxylase, IgLON 5 - antibodies against immunoglobulin-like cell adhesion molecule 5, CASPR2 - contactin-associated protein-like 2; GABABR - gamma-aminobutyric acid-b receptor; ANNA - antineuronal nuclear antibody; GFAP - anti-glial fibrillary acidic protein

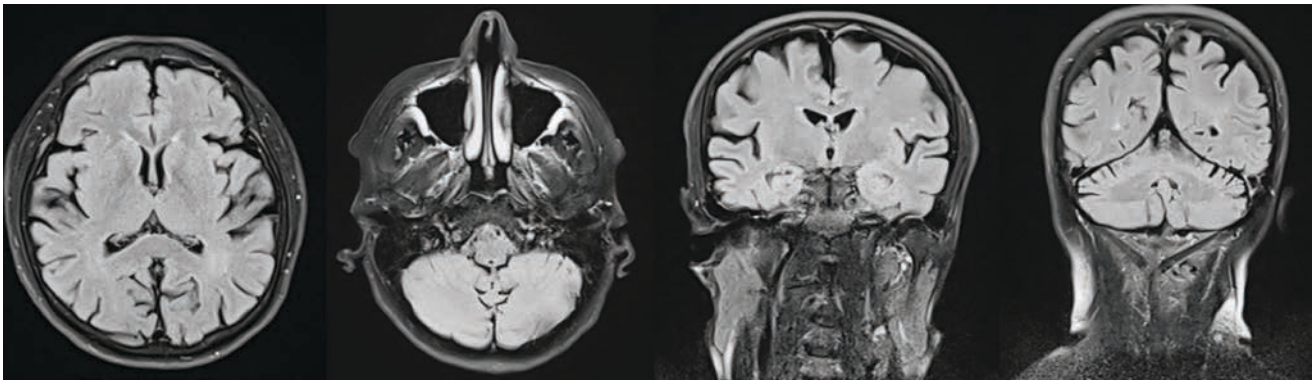

FIGURE 1. Brain MRI - FLAIR sequences showing a slight degree of cerebellar and cerebral atrophy

The neurological symptomatology gradually worsened by early 2019, having developed ataxia of the left limbs with associated disturbance of gait and diplopia. By July of 2019, the disturbance of gait had developed to such a degree that she required a walking frame in order to ambulate over short distances.

Initial presentation

The patient was initially referred to the Neurology department of another clinic in late July 2019. On admission, she presented with horizontal nystagmus in left lateral gaze, ataxia of the left limbs, ataxic gait, with ability to walk a few steps with bilateral support, and bilateral positive Babinski sign. Neurocognitive evaluation was unremarkable.

Investigations, diagnosis

Multiple diagnostic directions were pursued, resulting in the rapid exclusion of an infectious condition by serological testing. Immunological labs revealed weakly elevated anti-neuronal antibodies (23.9 UI/ml), negative onco-neuronal antibodies blot and negative usual tumoral markers (CEA, AFP, CA19-9, CA15-3, CA125). A lumbar puncture was performed, with CSF analysis revealing normal cell count but positive oligoclonal bands.

Suspecting a paraneoplastic syndrome, a full-body CT scan was performed. No notable anomalies were detected. This investigation was later augmented by full-body PET-CT that detected only minimal radiotracer enhancement in the bilateral hilar ganglia. Cerebral MRI found no abnormalities except for a few small T2 and FLAIR hyperintense lesions, characterized as microangiopathic, located in the right fronto-parietal and left posterior-parietal white matter and a slight degree of cerebellar and cerebral atrophy (Figure 1).

It was concluded that the neurological deficit was caused by idiopathic diffuse inflammation of the central nervous system, without being able to isolate a specific antibody. In late 2019, a very high seric titer of anti-GAD65 antibodies was found (>2,000 IE/mL, ref: <10 IE/mL) and thus the definitive diagnosis was established as autoimmune encephalitis with anti-GAD65 antibodies, the clinical picture being consistent with the cerebellar ataxia phenotype of this pathological entity.

Treatment

An initial course of corticosteroid therapy was followed during the first hospital stay, consisting of 40 mg of Dexamethasone over 5 days (8 mg per day) and 3 g of Methylprednisolone over 3 days (1 g per day). The treatment was well tolerated however the patient's state had not improved significantly.

Clinical course 2019 - 2022

Over the next two years (2019-2020), three other courses of corticosteroid pulse-therapy were administered, resulting in only mild amelioration of the neurological deficits. Since a paraneoplastic etiology could not be excluded, the patient was kept under oncologic observation and several other investigations were conducted, all inconclusive. The treatment was stopped in 2020 due to the COVID-19 pandemic and the gradual decline of her neurological status resumed.

In 2021, neurological examination during an admission at the same clinic additionally showed vertical nystagmus and a worsened limb ataxia affecting all limbs, indicating a slow but continued worsening of her condition. A course of IV immunoglobulins was administered (a total of 90 g) during an admission at the same clinic resulting in significant albeit temporary improvement. A cerebral MRI scan was performed, showing no change relative to 2019.

In 2022 the patient was diagnosed with diabetes mellitus for which insulin therapy was required from onset.

Course in our clinic

In early 2023, the patient was first referred to our clinic. On admission, a paraclinical reassessment was conducted. Cerebral MRI showed no change relative to 2019 or 2021. Seric anti-GAD65 antibody titer remained very high (>2,000 IE/mL). ENMG showed no abnormality. Full-body CT also showed no abnormalities. A colo-

noscopy was also performed, for oncological screening.

The decision was made to initiate a course of plasma exchange. Unfortunately, during the first admission, basic labs indicated a mild inflammatory syndrome associated with bacteriuria. The treatment was postponed and the patient was discharged and prescribed a course of antibiotics.

She returned a month later and underwent four plasma exchange sessions. Clinical evaluation after the procedure showed marked improvement of gait, no longer requiring bilateral support over short distances and moderate amelioration of limb ataxia. She was discharged with a chronic treatment plan of Methylprednisolone, 8 mg per day and gastric protection, aside from her usual diabetes treatment.

Clinical course 2023 - present

In late 2023, the treatment was switched to mycophenolate mofetil. Until now, evolution was mostly stagnant, with a continued progression and short periods of recovery adjacent to IVIg administration or plasmapheresis. Overall, the patient's state continues to trend downward, albeit at a diminished pace.

CASE 2 - LIMBIC ENCEPHALITIS

The second case is about a 32 years old woman with a history of recurrent seizures and progressive memory decline that started at 28 years (June 2020). Initially, she was investigated in another hospital, and was diagnosed 11 months after the onset, with limbic encephalitis with anti-GAD65 antibodies, left temporal focal epilepsy with nocturnal seizures and mild cognitive decline (MMSE 25/30, MoCA23/30). During hospitalization the patient received both corticotherapy and IgG. She was investigated for identifying a neoplasia, she had an ovarian cyst removal, considering that her family history included a grandmother who died at 56 from breast cancer. She was discharged home with only antiepileptic treatment (Levetiracetam 1750 mg/day and Lamotrigine 37.5 mg/day), with no following seizures, but a slow cognitive decline.

In June 2022, the patient had a convulsive status epilepticus which subsided after Diazepam and Phenytoin 20 mg/kg iv administered 3 hours after onset and arriving at our clinic.

At the moment of admission, the patient presented persistent bradylalia and bradypsychia, mild right-sided ataxic hemiparesis and marked bilateral horizontal nystagmus, difficulties standing, and able to walk only with unilateral aid.

Investigation in our clinic

An initial brain CT scan excluded acute cerebral lesions.

A first standard 20-minutes EEG revealed slowed background rhythm in the left hemisphere and bilateral frontal and temporal epileptiform discharges. A 3h video EEG (including sleep), was performed and indicated persistent subclinical seizures originating in the left temporal mesial during sleep, but a slight improvement in the frequency of frontal bilateral discharges and slowing in the right temporal lobe (Figure 2).

The cerebral MRI on day 3 showed signal abnormalities with cortical topography located at the level of both temporal lobes in the mesial portion, more important on the left side (Figure 3).

The lumbar puncture revealed high CSF protein levels with normal CSF cell count and normal glycae-

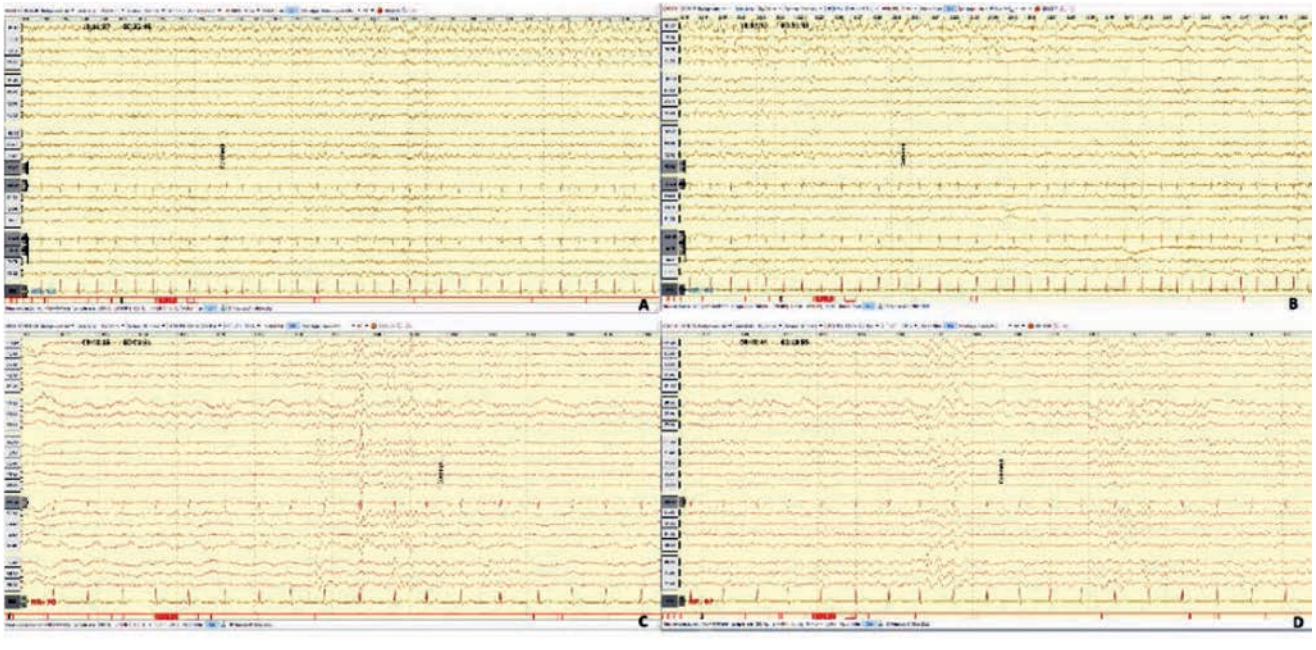

FIGURE 2. Video EEG on day 7 after admission with subclinical seizures starting from the left temporal area (A & B), bilateral frontal sharp waves (C), right temporal sharp theta activity (D)

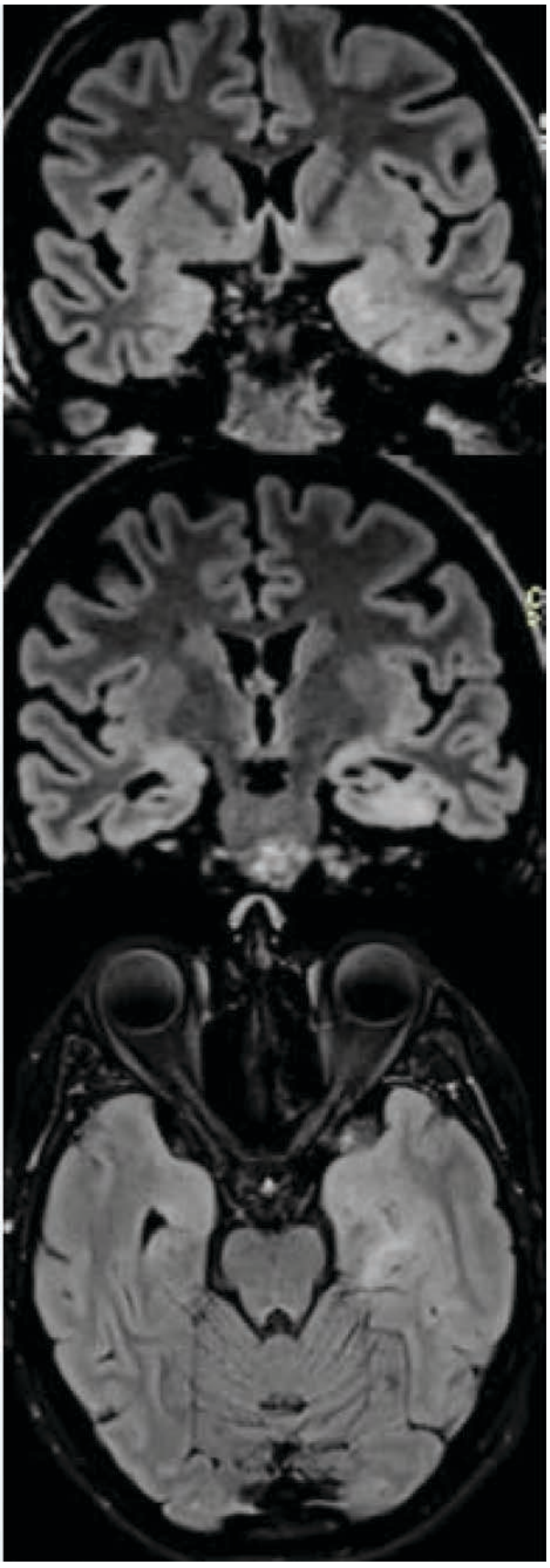

FIGURE 3. Brain MRI - FLAIR sequences with bilateral temporal hyperintensity left>right

mia. The serum and CSF antibodies panel revealed high titers of anti-GAD65 antibodies (>10,000) in both.

Considering that the patient presented with elevated blood glucose levels and an HbA1c of 5.8%, analysis of serum antibodies against ICA pancreatic islets, IA2, zinc transporter 8 was performed, and we found positive anti-pancreatic islet antibodies.

The neurocognitive evaluation indicated a mild cognitive decline (MMSE 24/30, MoCA 24/30), increased anxiety, difficulties with social interaction and mild depression.

To exclude a latent neoplasia, tumor markers were measured and a thoraco-abdomino-pelvine CT scan was performed - with normal results.

Treatment: The patient was started on Mycophenolate mofetil 1,000 mg/day in association with Levetiracetam 2,000 mg/day and Lamotrigine 150 mg/day, Vinpocetine 30 mg/day and tapered off Methylprednisolone. For diabetes, only a dietary regimen was prescribed.

At the moment of the discharge the patient was slightly disoriented in time and space, self-oriented, no cranial nerve disorders, mild right limb ataxia, fine bilateral upper limbs postural tremor, plantar reflexes in flexion, globally enhanced tendon reflexes, no major language disorders, executes simple and some complex commands, reduced emotional expression.

In December 2023, the patient returned to our clinic presenting with headache accompanied by a confusional state that began approximately 7 days prior to the presentation, as well as two focal seizures, followed by another focal seizure that evolved into a generalized tonic-clonic seizure one day prior to the presentation.

Neurological examination at the time of admission: the patient was alert, complaining of dizziness, partially oriented in time, space, showing bradyphrenia and short and long-term memory impairment. She correctly names objects and colors, follows simple commands, gets confused with some complex commands, without cranial nerve disturbances except for horizontal nystagmus on right lateral gaze, no motor deficit, mild ataxia in the lower limbs, postural tremor in the upper limbs bilaterally (right > left), no sensory disturbance, right plantar reflex in extension, and brisk osteotendinous reflexes globally.

An EEG examination was performed, which revealed structural changes in the left temporal region, intertwined with epileptiform discharges in the left temporal region, and a subclinical focal seizure originating from the left temporal region.

Under increased doses of antiepileptics and pulse therapy with Solumedrol 1g/day IV for 5 days, the patient did not experience further seizures, and her general condition, memory disturbance, and dizziness improved.

Later, because the patient presented with persistent rhinorrhea, she was tested for influenza and COVID, resulting in a positive COVID test. Therefore, Tamiflu 75 mg was added to the treatment regimen, which she tolerated well. The progress was favora-

ble, and the patient did not repeat the seizures during the hospitalization and she was discharged after a few more days with the following treatment plan: Levetiracetam 2,000 mg/day, Lamotrigine 300 mg/day, Clonazepam 0.5 mg 1-2 tablets in case of repeated focal seizures, Mycofenolat mofetil 2,000 mg/day and Tamiflu 150 mg/day for two more days.

So far, the patient has not experienced any further seizures, her cognitive function has slightly improved and the blood glucose levels are well controlled.

DISCUSSION

In this article we presented two female patients with different neurological manifestations of the anti-GAD65 autoimmunity spectrum, with onset at different ages, at 64 and 28 years old.

Glutamic acid decarboxylase (GAD) antibody-related encephalitis is an autoimmune disease associated with intracellular neuronal antigens [2,3]. GAD is an enzyme that produces the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and is mainly located in the brain and pancreas;

The onset is mostly subacute or chronic and aprimarily affects women of all ages.

In the literature it is cited that the disease usually manifests under the following phenotypes: stiff person syndrome, cerebellar ataxia, limbic encephalitis, drug-resistant temporal lobe epilepsy [6].

In case of limbic encephalitis among the involved symptoms we find anterograde amnesia, temporal epilepsy, and behavioral changes; on the other hand, cerebellar ataxia results from damage to the cerebellum or its connections, and manifests as poor muscle control and it can affect walking and balance, hand coordination, speech and swallowing, and eye movements.

In the acute phase of an autoimmune encephalitis, the treatment options described in literature are high-dose corticosteroid therapy, IV immunoglobulins plasmapheresis; as a secondary (or alternative) option, we have immunosuppressive therapy [5].

The symptomatology of the first patient is similar with the phenotype of cerebellar ataxia, meanwhile the second patient presented a progressive memory decline and recurrent seizures which lean towards limbic involvement. Persistent cognitive impairment, moderate or mild, depending on the evolution of the disease, was encountered in the second case.

In cases where autoimmune encephalitis is suspected, MRI brain imaging is necessary both for differential diagnosis and to highlight the existence of specific lesions [2].

MRI brain imaging revealed, for the patient with limbic encephalitis, signal abnormalities with cortical topography located at the level of both temporal lobes, more important on the left side (Figure 3). For the patient with cerebellar ataxia, repeated MRI examinations were normal except for a slight degree of cerebellar and cerebral atrophy (Figure 1).

The discovery of anti-GAD65 antibodies was not incidental, the specific antibody titration was performed, considering the clinical picture, at a distance of more than 8 months after the onset for both cases.

For the differential diagnosis, in both cases, detailed investigations were conducted to detect any possible neoplastic condition, tumor markers and repeated CT scans of the chest, abdomen, and pelvis yielded negative results. One of the patients underwent a colonoscopy with negative results, while the other had an ovarian cyst excised, but histopathological examination showed it to be benign.

An acute neurological pathology was excluded for each case, CSF analysis excluded a possible infectious source and the panel for autoimmune encephalitis was positive only for Ac anti-GAD65.

It is worth mentioning that in the first case genetic testing has not yet been performed to exclude other hereditary types of cerebellar ataxia.

It is also worth noting that the onset of diabetes mellitus coincided temporally with the progression of the encephalitis. As such, it is highly probable that it is a form of late autoimmune diabetes in adults (LADA) since they both fall under the anti-GAD65 autoimmunity spectrum [7,8]. Further tests specific to LADA need to be performed in order to elucidate this correlation. Glucocorticoid therapy could also have precipitated the onset of diabetes.

In the acute phase of the disease, patients received first-line therapy, as recommended in the specialized literature, represented either by high-dose corticosteroid therapy, IVIg or plasmapheresis. Plasmapheresis was not used in the second case.

The first patient was initiated on mycophenolate mofetil in late 2023, following a slow but constant decline of her neurological status punctuated by short periods of recovery following plasmapheresis and IVIg administration. In the future, considering that repeated IVIg administration is prohibitively expensive, if the patient's neurological status continues to decline, a course of treatment with Rituximab will be considered [1,5].

The young woman presented in the second case, had two relapses since the onset, the first one (two years after onset), status epilepticus requiring a dose increase of the antiepileptic treatment, at which point we decide it is opportune to initiate immunosuppressive treatment with Mycophenolate mofetil and the second one (two and a half years after onset), focal and generalized seizures in the context of a COVID infection.

The evolution of both patients under treatment is consistent with cases described in literature, showing some improvement but without complete recovery

[1,6]. In the first case, there were no evident relapses, but more a slow progression of symptoms.

Case particularities:

Different clinical manifestations in two patients with autoimmune encephalitis with positive anti-GAD antibodies; onset at different ages; without evidence of malignant pathologies associated; the onset of diabetes mellitus (most likely LADA) during the evolution of the disease.

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