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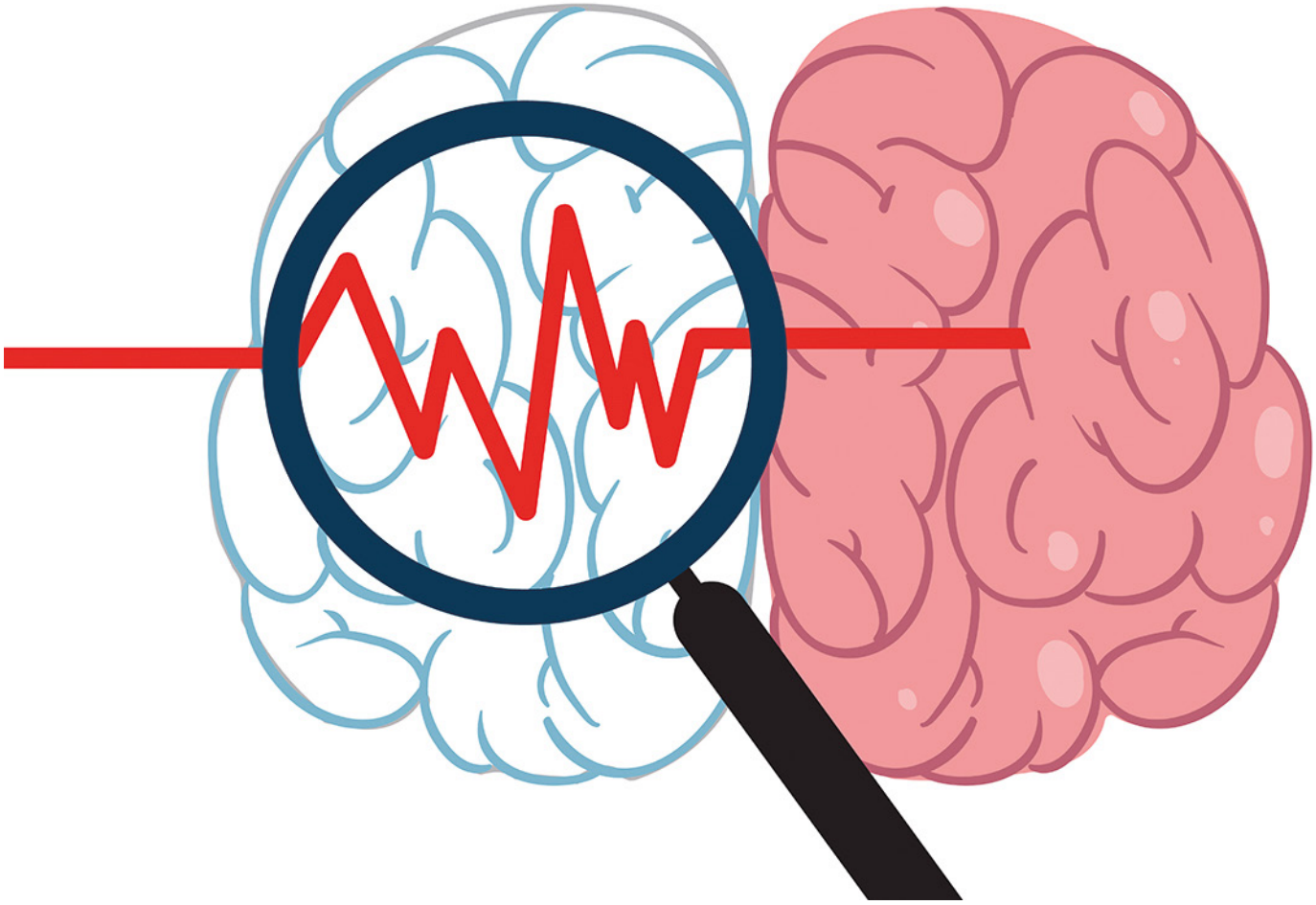

Autoimmune encephalitis and type 1 diabetes mellitus

Epilepsy is 4-6 times more prevalent in patients with type 1 diabetes mellitus (T1DM) than in the general population, and patients with epilepsy have a 4 times higher prevalence of DM than the general population (1). Patients with T1DM may present with seizures of metabolic cause such as hypoglycemia and non-ketotic hyperglycemia (NKH). Autoimmune etiology is a less known cause and is the one we will focus on in this article.

AUTOIMMUNE EPILEPSIES

The autoimmune etiology is increasingly recognized as a cause of epilepsy with acute onset and chronic epilepsies.

Seizures of autoimmune etiology have been classified since 2020 as acute symptomatic seizures due to autoimmune encephalitis (patients have seizures during the acute phase of the disease, but most of them do not develop subsequent epilepsy) and epilepsy associated with autoimmune disease (patients have epilepsy chronically) (2). The antibodies associated with autoimmune epilepsy are divided into (2):

- Antibodies against neuronal surface and synaptic proteins (predominantly mediated by B cell immunity). Generally produce acute symptomatic seizures and, less frequently, autoimmune epilepsy.

- Antibodies against intracellular antigens (predominantly mediated by T cell immunity). They can produce autoimmune epilepsy as in the case of glutamic acid decarboxylase isoform 65 antibodies (GAD65), an enzyme involved in the synthesis of the inhibitory neurotransmitter GABA from glutamate. These epilepsies are more refractory and have a worse prognosis. Although many of these antibodies are associated with cancer, the paraneoplastic etiology in GAD65-mediated epilepsy is extremely rare.

COMMON DENOMINATOR: ANTI-GAD 65 ANTIBODIES

GAD65 antibodies produce autoimmune diseases of the central nervous system (CNS) and more commonly, non-neurological autoimmune diseases, with type 1 diabetes mellitus (T1DM), autoimmune thyroid disease, and pernicious anemia being the most frequently associated. Approximately 70% of patients with neurological involvement due to GAD65 present one or more of these disorders.

Anti-GAD65 antibodies reflect the autoimmune etiology of T1DM and can be detected in 80% of patients (1)(4), although only 0.8% have anti-GAD > 2000 U/mL, unlike patients with autoimmune neurological diseases mediated by these antibodies, in whom titers are high.

There are two isoforms of glutamic acid decarboxylase: GAD 65 and GAD67. GAD 65 is responsible for the synthesis of GABA, the main inhibitory neurotransmitter of the CNS. It is found predominantly in the inhibitory CNS (GABAergic) and in the islets of pancreatic β cells (3), which explains the association between T1DM and CNS conditions.

That is why antibodies against GAD65 can be associated with a wide spectrum of neurological syndromes, such as cerebellar ataxia, stiff-person syndrome, limbic encephalitis, and temporal lobe epilepsy. (1)

GAD65 IN AUTOIMMUNE EPILEPSY

There are 2 predominant clinical scenarios described in GAD65-mediated autoimmune epilepsy (2) (3)

- Autoimmune encephalitis: acute/ subacute onset of isolated seizures (including New Onset Refractory Status Epilepticus - NORSE) or accompanied by varying degrees of cognitive impairment, altered mental status, and psychiatric disorders due to inflammation of the mesial temporal region. There is a high risk of subsequent epilepsy and development of hippocampal sclerosis as a frequent sequelae.

- Epilepsy associated with autoimmune disease: chronic epilepsy with an indolent course, generally drug-resistant, without inflammatory findings on magnetic resonance imaging. The detection of anti-GAD65 antibodies occurs in 17% of limbic encephalitis cases, 1.7% - 12.5% of new-onset focal epilepsies in adults of undetermined etiology (epilepsy is the main and sometimes only symptom), and around 6% of refractory epilepsies of childhood (3).

Seizures are predominantly focal of temporal origin, frequent, and resistant to treatment. It is more common between the second and third decades of life, has a higher prevalence in women (70-80%), and is associated with other autoimmune diseases.

GAD 65 IS RESPONSIBLE FOR THE SYNTHESIS OF GABA, THE MAIN INHIBITORY NEUROTRANSMITTER OF THE CNS

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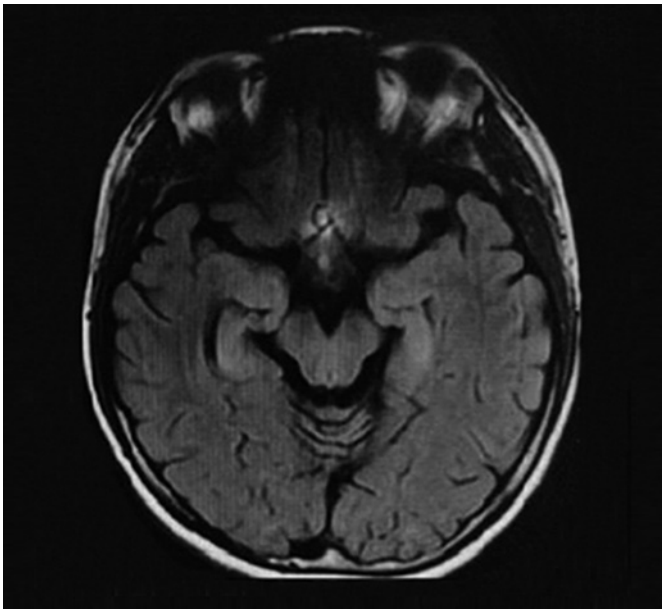

IMAGE.
T2 FLAIR hyperintensity of both medial temporal lobes, predominantly on the left, in a patient with limbic encephalitis due to GAD65 antibodies.

GIVEN THAT IT IS AN AUTOIMMUNE DISEASE, FOR ITS TREATMENT, IT IS NECESSARY TO REDUCE THE DEFENSES TO CONTROL THE ATTACK ON THE NERVOUS SYSTEM

» HOW IS IT DIAGNOSED

The fundamental tests include:

- **Brain magnetic resonance imaging:** may be normal or show hyperintensity in FLAIR/T2 of the temporal lobes (image 1). In late stages, hippocampal atrophy may be observed (5, 6).
- **Electroencephalogram:** more than 85% of patients show slow activity and/or epileptiform discharges in temporal regions (5).
- **Blood tests:** serum GAD65 antibody levels should be elevated (>2000 U/mL). Of note, patients with T1DM usually have GAD65 antibodies in serum at low titers, which does not imply that they will develop this disease. Furthermore, 2-8% of the healthy population presents low titers of these antibodies.
- **Lumbar puncture:** It is essential to analyze a sample of cerebrospinal fluid (CSF). Sometimes inflammatory data are found (lymphocytic pleocytosis, presence of oligoclonal bands), although it is often normal (3). It is indispensable for diagnosis to detect GAD65 antibodies in CSF in sufficient quantity to demonstrate intrathecal synthesis (within the central nervous system).

HOW IS IT TREATED

Treatment is based on immunomodulation. Since it is an autoimmune disease, for its treatment, it is necessary to reduce the defenses to control the attack on the nervous system. For this, high-dose corticosteroids are used as first-line (with caution in diabetes as it can decompensate glycemic control), immunoglobulins (better response in patients with stiff-person syndrome), and plasmapheresis. Cyclophosphamide is usually used as second-line, although there are described cases of patients treated with rituximab, natalizumab, or basiliximab (7).

From a symptomatic point of view, epilepsy should also be treated with anti-seizure drugs, although this treatment is usually insufficient for its control. Isolated cases of epilepsy surgery (temporal lobe resection) with partial and insufficient long-term responses have been described. Neuromodulation devices have also been used with a reduction of > 50% in seizures (only 4 cases described in the literature) (8). In general, the response to treatment is poor, and epilepsy is difficult to control. D

AUTOIMMUNE EPILEPSIES (SUMMARY)

	Acute Symptomatic Seizures Secondary to Autoimmune Encephalitis	Epilepsy Associated with Autoimmune Diseases
Involved Antibodies	Neural surface antigen antibodies (NMDAR, LGI1, GABABR, GABAAR)	Intracellular antigen antibodies (Anti-GAD and onconeural antibodies)
Pathogenesis	Antibodies against synaptic proteins Disruption of synaptic transmission due to downregulation of receptors	Cytotoxic T-cell mediated immunity Persistent immune activity damaging brain parenchyma or a combination of both
Clinical Presentation	Variable: combination of seizures, psychiatric symptoms, memory impairment, movement and sleep disorders, dysautonomia	Chronic drug-resistant focal epilepsy. Often epilepsy is the only symptom.
Diagnosis	Brain MRI: FLAIR/T2 hyperintensity mainly in the temporal lobes EEG: often slow activity and/or epileptiform activity in temporal lobes Blood tests: presence of specific antibodies CSF: inflammatory + detection of specific antibody	
Treatment/Prognosis	Immunotherapy. Good response. Anti-seizure drugs (ASDs)	Immunotherapy. Poor response. Drug resistance to ASDs. Epilepsy surgery rarely effective

CONCLUSIONS

Epilepsy in the context of autoimmune encephalitis due to GAD65 antibodies has a higher incidence in patients with T1DM. However, the presence of these antibodies does not imply that they will develop the disease. It is typically drug-resistant, and its diagnosis is based on elevated titers of GAD65 antibodies in CSF (intrathecal synthesis). Treatment with immunomodulators and antiepileptic drugs has a limited response. Identifying the disease early can help optimize therapeutic management and improve patients' quality of life.

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