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Encephalopathy and adrenal insufficiency secondary to anti-glutamic acid decarboxylase antibodies☆

Encefalopatía e insuficiencia suprarrenal secundaria a anticuerpos antiácido glutamil decarboxilasa

Dear Editor:

Although autoimmune encephalopathies are frequently described,[1] encephalopathies associated with autoimmune polyglandular syndromes with antibodies targeting glutamic acid decarboxylase (anti-GAD) are much rarer.[2] We present a case of encephalopathy associated with anti-GAD antibodies and adrenal insufficiency manifesting with akinetic mutism and non-convulsive status epilepticus.

Our patient was an 82-year-old woman with history of hypothyroidism. She was admitted due to a one-month history of unsteady gait, hyporexia, and weight loss. The week before admission, she presented disorientation and bradypsychia. Laboratory analysis detected hyponatraemia (118 mEq/L). Despite slow correction of sodium levels (123 mEq/L at 24 hours), she presented hallucinations, confusion, and finally severe akinetic mutism within hours. She also presented oropharyngeal candidiasis.

Contrast brain MRI and head CT scans showed no relevant alterations. A CSF analysis yielded no abnormal results. Subsequent follow-up blood analyses revealed no significant improvement in sodium levels, with concentrations ranging from 125 to 128 mEq/L despite restriction of water intake and administration of hypertonic saline. Osmolality was low in the serum (255 mOsm/kg) and normal in urine (550 mOsm/kg). Chest, abdomen, and pelvis CT and PET/CT scans revealed no abnormalities. EEG revealed non-convulsive status epilepticus. We started treatment with lacosamide and subsequently intravenous valproate, which improved EEG activity; akinetic mutism persisted, however. Suspecting autoimmune encephalopathy, we requested an immunological study including tests for antibodies associated with the disease, and started empirical treatment with intravenous methylprednisolone 1 g/day for 5 days. The patient showed a partial improvement, with fluctuation of the symptoms, and we subsequently started treatment with intravenous immunoglobulins dosed at 0.4 g/kg/day for 5 days, achieving significant improvements in her clinical status. Adrenal insufficiency, hypoglycaemia, and hyponatraemia improved after administration of hydrocortisone. The immunological study revealed high anti-GAD antibody titres (119; normal range, <10); vitamin B_{12} deficiency (192 ng/L) and presence of anti—gastric parietal cell antibodies (titre of 1/80) were also detected. Gastroscopy revealed atrophic gastritis. Treatment led to clinical, electrophysiological, and EEG improvements; the patient continued to present disorientation and slightly decreased speech fluency. We administered 2 additional cycles of intravenous immunoglobulins; the patient has presented no further relapses after 6 months of follow-up.

Glutamic acid decarboxylase is expressed in the pancreatic islets and the central nervous system.[3] One of its functions is to convert glutamate into gamma-aminobutyric acid (GABA). The neurotransmitter GABA has an inhibitory function in the central nervous system. Anti-GAD antibodies act mainly on the GAD65 isoform, which is directly involved in neurotransmission, inhibiting the conversion of gluta-

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mate into GABA.[4] Anti-GAD antibodies have been associated with cerebellar ataxia, limbic encephalitis, stiff person syndrome, movement disorders, autoimmune epilepsy, and oculomotor alterations.[5–9] From an endocrinology viewpoint, anti-GAD antibodies have been associated with type 1 diabetes mellitus and autoimmune polyglandular syndromes. The exact mechanism by which a single antibody is involved in such a wide range of syndromes remains a mystery.[4]

Our patient presented autoimmune encephalitis, nonconvulsive status epilepticus, and endocrine disorders compatible with a polyglandular syndrome: she presented oropharyngeal candidiasis and adrenal insufficiency, 2 of the diagnostic criteria for autoimmune polyglandular syndrome type 1, as well as mild pernicious anaemia.[9] Although anti-GAD antibodies are most clearly associated with type 1 diabetes mellitus, our patient's episodes of hypoglycaemia were attributed to adrenal insufficiency. Presence of anti-GAD antibodies has been reported in 41% of patients with autoimmune polyglandular syndrome type 1,[10] and in only 12%-18% of patients with type 1 diabetes mellitus, but is not included as a diagnostic criterion of the syndrome.[11] In our case, mycosis may also have been caused by the systemic disorder our patient presented during the month before admission. In this scenario, presence of adrenal insufficiency and pernicious anaemia should be considered symptoms of autoimmune polyglandular syndrome type 4, which includes other autoimmune endocrine disorders not meeting diagnostic criteria for other autoimmune polyglandular syndromes; the literature also includes cases of autoimmune polyglandular syndrome type 4 associated with anti-GAD antibodies.[9]

Early diagnosis and treatment of autoimmune encephalitis is essential. According to the criteria established by Graus et al.,[12] diagnosis may be established in the absence of pathological brain MRI or CSF analysis findings if the patient presents compatible symptoms and epileptic seizures not explained by history of epilepsy, and once other causes have been ruled out. Diagnosis may be confirmed by slow or epileptiform EEG activity in both temporal lobes and presence of antineuronal antibodies.[12]

Presence of anti-GAD antibodies is sometimes the result of paraneoplastic processes.[13,14] In our patient, a thorough examination ruled out presence of tumours. Given the strong suspicion of autoimmune encephalopathy (with compatible clinical and electrophysiological signs) and having ruled out other causes, we started empirical treatment; diagnosis was subsequently confirmed by presence of high anti-GAD antibody titres.

Glucocorticoids and immunoglobulins constitute the treatment of choice for neurological disorders associated with anti-GAD antibodies[3]; in cases of high index of suspicion, administration should start before laboratory results are returned.

In conclusion, co-presence of heterogeneous neurological and endocrine symptoms may point to autoimmune disorders associated with anti-GAD antibodies. Early diagnosis and treatment with immune therapy greatly determine prognosis.

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Progressive multifocal leukoencephalopathy in a patient with systemic lupus erythematosus: Could CD4+ lymphopenia be the main risk factor?

Leucoencefalopatía multifocal progresiva en paciente con lupus eritematoso sistémico: ¿podría ser la linfocitopenia-CD4+ el principal factor de riesgo?

Dear Editor:

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by reactivation of a latent infection with JC virus. We report the case of a patient diagnosed with systemic lupus erythematosus (SLE) and receiving low-dose prednisone.

Our patient was an 83-year-old man with hypertension and no other relevant medical history, who since the age of 81 years had been under follow-up by the rheumatology department due to symptoms of arthritis and probable SLE (antinuclear antibodies, lymphopaenia, thrombocytopaenia). Prednisone at a maximum dose of 10 mg/day achieved satisfactory control of the articular symptoms, but lymphopaenia persisted.

The patient visited the emergency department due to left hemiparesis. A head CT scan revealed a hypodense lesion in the right frontoparietal area (Fig. 1A), of probable ischaemic origin; antiplatelet treatment was started. He returned a week later due to symptom progression; the examination revealed visual extinction in the left visual hemifield and left hemiplegia and hemihypaesthesia. A further head CT scan (Fig. 1B and C) revealed extension of the previously detected lesion.

The patient was admitted for further testing. A brain MRI scan revealed a lesion in the right frontoparietal region, which was hypointense on T1-weighted sequences and hyperintense on T2-weighted sequences, with no contrast uptake (Fig. 1D-F). An emergency biochemical and cytological analysis of a CSF sample showed no pathological findings. We suspected inflammatory aetiology due to the chronology of the symptoms and our patient's history, and started empirical treatment with methylprednisolone at 1 g/day while we awaited laboratory results.

Our patient worsened, presenting bulbar symptoms and a low level of consciousness. An additional brain MRI scan revealed lesion growth, with meningeal involvement and contrast uptake in right cranial nerves IX and XI (Fig. 1G-I). Laboratory analyses revealed lymphopaenia, with 237 CD4 T cells/mm^3 and a high CD4/CD8 ratio. CSF findings were negative for oligoclonal bands and positive for JC virus, which led to diagnosis of PML. Active treatment was ruled out given the patient's age and clinical status, and he died 6 weeks after symptom onset.

The seroprevalence of JC virus is 65% among individuals older than 17 years, and even higher among those above the age of 70.[1] Virus reactivation in the form of PML has become more frequent in recent decades due to increased prevalence of HIV and the more widespread use of immunosuppressants. However, virus reactivation has also been described in patients with minimal immunosuppression[2] and even in immunocompetent individuals.[3] The risk of developing PML is greater in patients with SLE than in those with other rheumatic disorders.[4,5] Up to 40% of cases present in patients with minimal iatrogenic immunosuppression[2,6] and no other risk factors for PML.[5]

This gives rise to the hypothesis that SLE may increase the risk of developing PML, although the mechanisms are not fully understood. The striking increase in the incidence of PML during the HIV/AIDS epidemic and the presence of PML in patients with idiopathic CD4 lymphopaenia underscores the significant role of CD4 T cells in controlling JC virus infection.[7] In both scenarios, CD4 lymphopaenia is detected in the peripheral blood; CSF lymphocyte levels in these patients are not well documented, as in the case presented here.

It has recently been suggested that 2 forms of lymphopaenia may present in patients with SLE: the more frequent form is associated with the activity of SLE, and may improve with immunosuppressants, whereas the other form is more sustained, is not related to disease activity, and is associated with greater risk of infection, since it behaves as an immunodeficiency disorder.[8] Given the shortage of information on the immune status of patients with PML and their treatment history,[6] it may be interesting to analyse whether sustained CD4 lymphopaenia or its association with a specific drug[9] increases the risk of the infection. This may enable the development of management algorithms,[8] like those used with multiple sclerosis.[10]

In any case, PML is rare in patients with SLE, with an estimated prevalence of 4 cases per 100 000 patients (0.44% of all cases of PML),[5] although it is probably underdiagnosed. The condition should be suspected in patients with SLE

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