## Acknowledgements

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# Rapidly progressing cerebellar ataxia associated with anti-GAD antibodies☆,☆☆

## Ataxia cerebelosa rápidamente progresiva asociada a anticuerpos anti-GAD

*Dear Editor:*

The aetiology of sporadic acute ataxia in adults includes toxic and immune-mediated factors; vitamin deficiencies; and infectious, degenerative, and genetic diseases.[1] The literature includes reports of sporadic subacute ataxia mediated by anti-glutamic acid decarboxylase (anti-GAD) autoantibodies, with neurological symptoms responding partially to immunosuppressive therapy. We present the case of a patient who developed symptoms of subacute ataxia, and laboratory results compatible with ataxia associated with anti-GAD antibodies. The patient had no other associated autoimmune diseases, and symptoms fully resolved following immunosuppressive therapy.

The patient was a 52-year-old man who smoked 20 cigarettes a day, with no further relevant personal or family medical history. The patient presented with vertigo, mild dysarthria, and truncal ataxia; symptoms had begun upon waking. Suspecting vascular aetiology, we activated the code stroke protocol and performed a multi-parameter cerebral computed tomography (CT) scan with perfusion and angiography sequences; this revealed no abnormalities. We also performed a brain magnetic resonance imaging (MRI) scan with FLAIR, T2-weighted, and diffusion-weighted sequences, which returned normal results. We therefore ruled out intravenous fibrinolysis. The patient's clinical condition worsened rapidly in the first 72 hours following

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☆☆ This clinical case was presented as an oral communication at the 67th Annual Meeting of the Spanish Society of Neurology under the title ''Rapidly progressing cerebellar ataxia associated with anti-GAD antibodies with complete remission after plasmapheresis''.

onset, with bilateral dysmetria developing, and dysarthria progressing to anarthria. The patient's condition was not associated with constitutional symptoms, fever, infection, or ingestion of toxic substances prior to symptom onset.

A blood test found no evidence of leucocytosis, increased acute-phase reactant levels, vitamin deficiencies, or ion imbalance. A lumbar puncture detected mirrored oligoclonal bands (banding detected in both serum and cerebrospinal fluid [CSF]). The remaining biochemical, cytological, and microbiological parameters were in the normal range.

In the light of the CSF findings and clinical suspicion of an autoimmune process,[2] we administered IV methylprednisolone 1 g for 5 days, with symptoms partially improving. However, despite maintaining methylprednisolone at 1 mg/kg/day (oral administration), the patient's clinical condition deteriorated. We therefore decided to test for adult-onset acute cerebellar ataxia. We performed MRI scans to obtain images for all sequences not previously run, as well as cervical/thoracic/abdominal CT scans, electroencephalography, and testicular ultrasound; and ordered serology tests for tumour markers, analysis of 14-3-3 protein in the CSF, and autoantibody screening (for antinuclear, antithyroid, onconeuronal, antiganglioside, antigliadin, and anti-GAD antibodies).[1,3] While awaiting the results, and given the patient's rapid clinical deterioration and our suspicion of underlying inflammatory pathology, we began plasmapheresis, performing a total of 7 exchanges on alternating days.

All the complementary tests yielded normal results, with the exception of the results for anti-GAD-65 antibodies, with serum levels of 17 U/mL and CSF levels of 71 U/mL (threshold for positivity: $\geq$5 U/mL). Baseline glycaemia was normal at all times, with Hb1Ac levels of 5.5%; results were negative for all other autoimmune markers (including antithyroid antibodies and coeliac disease screening).

The patient's symptoms resolved fully one month after discharge. We performed a systemic study to detect any concealed neoplasm, including a PET-CT scan, a mammography, and a breast ultrasound; all results were normal.

Non-paraneoplastic immune-mediated cerebellar ataxia is characterised by positive results for antibodies in the serum or CSF, with no presence of tumour, and MRI results showing signs of early cerebellar atrophy.[4,5] Immunotherapy may at least partially improve symptoms.[6] There are 3 classic forms of the syndrome, depending on the type of antibody detected: (1) cerebellar ataxia associated with antithyroid antibodies (cerebellar variant of Hashimoto encephalopathy); (2) cerebellar ataxia associated with coeliac disease; and (3) cerebellar ataxia associated with anti-GAD antibodies. More recently, Jarius and Wildemann[7] performed a review on the aetiology of autoimmune ataxia, observing that other antibodies associated with cerebellar ataxia (anti-GluR$\delta$2, anti-Nb/AP3B2/beta-NAP, anti-LGI1, anti-MOG, anti-AQP4, anti-$\gamma$-enolase, anti-pericentrin, anti-ninein, anti-PCM1, anti-Mob1, anticentriole, anti-triosephosphate isomerase, and anti-20S proteasome antibodies) have not to date been described in connection with any underlying neoplasm.

Cerebellar ataxia associated with anti-GAD antibodies is a relatively infrequent form of ataxia, representing around 2% of sporadic, adult-onset, progressive ataxias.[8] Serum and CSF anti-GAD antibody titres appear not to be correlated with the severity of the condition; increased intrathecal synthesis of the antibody is, however, thought to determine the appearance of neurological symptoms.[9] Our patient's serum antibody titres, while positive, were low in comparison to the values for the CSF; this demonstrates the importance of testing both media.[5,10]

These symptoms are most common in women (83%) and during the sixth decade of life, and are characterised by insidious onset of chronic or subacute ataxia, with a mean clinical progression time of 6 years. Neurological symptoms are associated with other autoimmune diseases in 72%-92% of cases (mainly insulin-dependent diabetes mellitus, thyroiditis, and pernicious anaemia).[5] Less frequently, it is associated with other neurological symptoms, such as stiff person syndrome, limbic encephalitis, epilepsy, progressive encephalomyelitis, or paraneoplastic syndromes, in rare cases.[6,11]

Although the literature considers cerebellar ataxia associated with anti-GAD antibodies to be a presentation of non-paraneoplastic autoimmune cerebellitis, equally rapidly progressive cases have been described in patients with tumours simultaneously or prior to the onset of anti-GAD antibody ataxia; some authors therefore recommend testing for an underlying tumour.[2,9,12,13] We attempted to detect a tumour in our patient (including with a mammography); all results were negative.[9,13]

The published case series in the literature report a partial clinical improvement in 35% of cases treated with immunomodulation.[6] A recent series of 3 patients treated with different immunosuppressive therapies (immunoglobulins, corticotherapy, and azathioprine) reported stabilisation of symptoms.[14]

The unusual aspect of our case is the rapid progression of the disease (2 weeks) and the complete clinical remission following corticotherapy and plasmapheresis. Such an excellent treatment response is exceptional in the literature[2,15]; however, several authors believe prognosis to be dependent on the speed with which treatment is initiated.[2,16]

Jones et al.[2] note that the response to immunosuppressive treatment is better in patients positive for anti-GAD antibodies, and when the period between symptom onset and treatment initiation is shorter. They therefore propose that all patients with autoimmune ataxia should receive sequential treatment with corticosteroids, plasmapheresis, and IV immunoglobulins. This would include patients with paraneoplastic ataxia, although a worse treatment response should be expected in these patients.

In our patient, the fact that we ruled out other aetiologies through complementary testing, as well as the clinical progression of the condition and the detection of oligoclonal banding in the CSF (which is present in 70% of cases of ataxia associated with anti-GAD antibodies[5,11]), supported our suspicion of autoimmune/inflammatory aetiology and enabled us to promptly begin empirical treatment without first receiving confirmation of the aetiology.

We therefore consider it important to include this condition in the differential diagnosis of rapidly progressive, acute cases of adult-onset ataxia. Although there is limited evidence regarding the treatment of these patients, it seems logical to begin early immunosuppressive therapy, which

may allow for the full remission of symptoms and prevent irreparable cerebellar damage.

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# Comments on the review article «Cerebral radiation necrosis: Diagnostic challenge and clinical management»☆

## Comentario al artículo de revisión «Necrosis cerebral por radiación: desafío diagnóstico y tratamiento clínico»

*Dear Editor:*

I read with great interest the review article by Eisele and Dietrich[1] on the exciting, little-understood subject of cerebral radiation necrosis secondary to surgical treatment for brain tumours.

The mechanisms involved in the physiopathogenesis of the condition are largely unknown; they may even vary with respect to the factors cited by authors as determinants: type of radiation, dose, treatment volume, and fractionation schedule. I would also like to add the type of supplementary treatment administered, which is normally chemotherapy, as mentioned in the review article.

The adjuvant chemotherapy used was different in each of the various studies establishing neuroradiological criteria over the past 3 decades.[2—4] It is therefore admirable that other authors[5] have attempted to compare the degree of correlation or concordance according to these criteria, in order to assess the type of progression, and suggest adding hyperintensity to FLAIR sequences to make contrast-enhanced sequences even more useful for assessing subsequent clinical worsening. We should also highlight that they compare treatments with the same adjuvant chemotherapy, in this case bevacizumab + irinotecan, which confers validity to the study and its results. Their main

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