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Probable Paraneoplastic Cerebellar Degeneration With Anti-Zic And Anti-Gad Autoantibodies: Case Report

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Abstract:
Cerebellar ataxia can be antibody- mediated, and this can occur in the setting of paraneoplastic syndrome or in the absence of an ongoing malignancy. Interestingly, the detection of specific types of autoantibodies has been found to be statistically linked to different etiologies. Anti-Yo, -Zic, -CARPVIII, -Tr, -Ri, -Hu, -Ma, -CRMP-5, -ANNA-3, -PCA-2, -VGCC, and -mGluR antibodies were more commonly associated with paraneoplastic processes, while anti-GAD, -thyroid, and -gliadin were usually non-paraneoplastic. We present a case of ataxia due to both anti-glutamic acid decarboxylase (GAD) antibodies and anti- ZIC4 (Zinc-finger protein 4) not associated with malignancy.

Keywords: *Cerebellar ataxia, Anti GAD, Anti ZIC4*

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I. Introduction

Cerebellar ataxia associated with anti-glutamic acid decarboxylase (GAD) antibodies is a rare, but increasingly detected, autoimmune neurological disease characterized by the clinical presence of a cerebellar syndrome concomitant with elevated levels of anti-glutamic acid decarboxylase (GAD) antibodies GAD in serum and cerebrospinal fluid (CSF) [1]. Recent studies have linked anti-GAD cerebellar ataxia with type 1 diabetes mellitus, other autoimmune endocrine disorders, and sometimes even paraneoplastic etiologies [2].

Furthermore, patients with isolated ZIC4 (Zinc-finger protein 4) antibodies generally have paraneoplastic cerebellar degeneration and small cell lung cancer (SCLC), but their frequency is unknown [3].We report a case of probable paraneoplastic cerebellar degeneration with anti-ZIC4 and anti-GAD antibodies.

II. Observation

A 74-year-old man, with no particular pathological history, has been complaining for 15 months of instability when walking and slow speech. All symptoms were characterized by a subacute onset with progression to worsening.

The neurological examination revealed a static and kinetic cerebellar syndrome with ataxia and dysmetria of the upper and lower extremities, as well as dysarthria and vivid osteotendinous reflexes in all 4 limbs.

The neuropsychological evaluation did not reveal any significant cognitive deficit.

Brain MRI showed cerebellar atrophy (Figs 1-2).

Routine laboratory test results were only remarkable for a mild elevation of the erythrocyte sedimentation rate. Infectious diseases or vitamin or mineral deficiencies in the differential diagnosis, which in this specific setting would be highly considered, were ruled out.

He subsequently underwent a lumbar puncture, which showed a normal opening pressure and was negative for oligoclonal bands.

The immunological assessment revealed the presence of a high level of anti-GAD and anti-Zic4 autoantibodies in the serum. The rest of the biological assessment was normal. Cytochemical and immunological analysis of the CSF was normal.

The patient was put on steroid treatment, leading to an improvement in gait and balance disorders as well as dysmetria and dysarthria.

The diagnosis of anti-GAD cerebellar ataxia was established on the basis of subacute onset, a high titer of anti-GAD antibodies and, a response to immunotherapy.

As the detection of anti-GAD antibodies and anti-Zic antibodies can sometimes indicate a paraneoplastic etiology [4], we performed a PET scan called "positron emission tomography", returning without abnormalities, which suggests the absence of any malignancy.

A treatment cycle of three days of intravenous immunoglobulins was then instituted. Within two weeks from their administration, his coordination and gait improved significantly; he showed the ability to walk unassisted without a tendency to fall, and the Romberg test became negative.

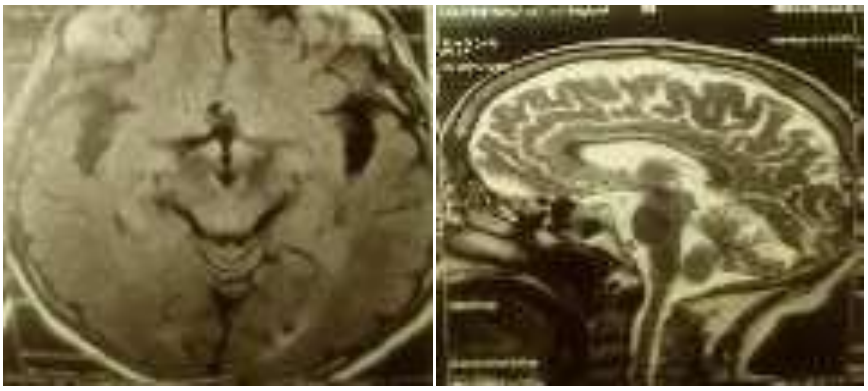

Figure 1.
MRI of the brain with contrast showing marked cerebellar atrophy

III. Discussion

Cerebellar ataxia can be potentially treatable, and a complete understanding of the etiology must be achieved in order to establish an effective management plan. This is especially important because it is usually a disabling condition, and treating it can substantially improve the quality of life of a patient when possible. The search for a potentially treatable cause should include a broad spectrum of different disorders, and genetic evaluation should be considered only when other etiologies can be ruled out. Disorders commonly encountered in clinical practice, such as vitamin B12 deficiency and hypothyroidism, can occasionally cause ataxia and, in rare cases be present with it [5,6]. Adverse reactions to drugs (especially certain antiepileptic and chemotherapeutic agents), systemic autoimmune diseases (such as sarcoidosis, systemic lupus erythematous, and Sjogren syndrome) [7–9], deficiencies of vitamin E and B1 (thiamine), as well as mineral deficiencies (such as copper or zinc), have all been occasionally linked with neurological symptoms, including ataxia [10–12]. Antibody-mediated ataxia is another potentially treatable etiology that should be considered. Multiple autoantibodies have been associated with cerebellar ataxia [13], and it has been demonstrated that anti-VGCC and anti-GAD antibodies can directly cause ataxia in experimental models *in vivo* [14].

Anti-GAD antibody-associated cerebellar ataxia was diagnosed based on neuro clinical manifestations, elevated serum anti-GAD antibody level, MRI findings, exclusion of other diseases, and clinical response. and the patient to immunomodulation. Steroid treatment for 6 months showed improvement in dysmetria, ataxia, and dysarthria. The anti-GAD spectrum includes limbic encephalitis, opsoclonus-myoclonus-ataxia syndrome, palatal myoclonus, epilepsy, stiff man syndrome, encephalomyelitis with rigidity, Guillain-Barré syndrome, myasthenic syndrome, and cerebellar ataxia with or without nystagmus. It is considered part of the group of polyglandular autoimmune diseases, which includes diabetes mellitus, myasthenia gravis, thyroiditis, and pernicious anemia.

Cerebrospinal fluid analysis may be normal or show oligoclonal bands, mild pleocytosis, and intrathecal synthesis of anti-GAD antibodies in some cases. Cerebellar ataxia associated with anti-GAD antibodies is rare, particularly when accompanied by nystagmus [15].

Furthermore, the cerebellar zinc finger (ZIC) protein family includes five transcription factors involved in cerebellar development and maturation [16] and encoded by one of the five ZIC genes. Abnormal expression of ZIC genes during embryogenesis can lead to Dandy-Walker malformation (Zic1 and Zic4), neural tube defects (Zic2), holoprosencephaly (Zic2), and heterotaxy syndrome (Zic5) [16]. In adults, alterations of the ZIC protein family manifest primarily as cerebellar dysfunction.

Zic4 antibodies are considered onconeuronal antibodies whose target antigen is the zinc finger domain of the intracellular transcription factor Zic4 [17]. Several reports have indicated that antibodies against zinc finger protein 4 (Zic4) are associated with paraneoplastic cerebellar degeneration (PCD) in patients with small cell lung carcinoma. Paraneoplastic syndromes linked to isolated Zic4 antibodies are rare and generally present with a benign clinical course. Our patient was explored for probable paraneoplastic syndrome by a PET Scan, which returned no abnormalities. However, regular monitoring is recommended for him.

IV. Conclusion

Anti-GAD antibody-associated cerebellar ataxia is part of a growing spectrum of neurological disorders associated with the GAD enzyme required to convert the excitatory amino acid glutamate to gamma-aminobutyricacid, an inhibitory neurotransmitter.

GAD enzyme-associated cerebellar ataxia can be diagnosed on the basis of neuroclinical manifestations and elevation of anti-GAD antibodies, supported by the patient's response to immunomodulation. Cerebellar ataxia associated with anti-GAD is a syndrome potentially treatable by immunomodulation.

Anti-GAD antibodies should be sought not only in patients with polymorphic, persistent, or refractory neurological syndromes but also in cases of associated cancer and polyglandular autoimmune diseases.

The prevalence and importance of anti-Zic4 antibodies may be underestimated due to their co-occurrence with more common antibodies, such as anti-Hu antibodies.

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