Common Variable Immunodeficiency Presenting as Anti-GAD Cerebellar Ataxia

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INTRODUCTION

Anti-glutamic acid decarboxylase (anti-GAD) autoantibodies are associated with several neurological syndromes, including cerebellar ataxia, limbic encephalitis, and stiff-person syndrome.[1] Although some evidence supports the pathogenic link between anti-GAD autoantibodies and neurological syndromes, the immunopathogenic trigger remains unclear.[1] Common variable immunodeficiency (CVID) is associated with numerous autoimmune neurological disorders, of which there is only one reported case with anti-GAD autoantibodies.[2] To our knowledge, this is the first report of anti-GAD cerebellar ataxia as the presenting symptom of CVID.

CASE REPORT

A 19-year-old man with a history of recurrent childhood ear infections and recent admission for pneumonia, presented with cough, fever, weight loss, and vomiting. Family history was unremarkable and he had no history of alcohol, tobacco, or substance use. On hospital day 6, he acutely developed nystagmus, dysmetria, dysarthria, and severe gait ataxia. CT of head, and MRI, MRA, and MRV of brain showed no abnormalities. He was empirically treated for meningitis as cerebrospinal fluid (CSF) studies showed polymorphonuclear pleocytosis and elevated protein (**Table**). Extensive work-up for infectious, neoplastic, toxic, and metabolic etiologies were negative (**Table**). Shortly thereafter, he was found to have hypogammaglobulinemia and CD4+ T-cell deficiency and was subsequently diagnosed with CVID. He became more lethargic and developed new onset refractory status epilepticus. Treatment with IVIG and steroids resulted in significant symptom improvement. Serum anti-Yo, anti-Hu, and anti-Ri antibodies were negative. Further testing revealed serum anti-GAD antibodies 83 IU/mL (< 5 IU/mL).

Table. Overview of Evaluation

Cerebrospinal Fluid Analysis	
Glucose	50 (38–85 mg/dL)
Protein	117 (15–45 mg/dL)
Red blood cells	3 (0–5/mm³)
Nucleated cells	148 (0–5/mm³)
Polymorphonuclear cells	23 (0–2%)
Lymphocytes	76 (63–99%)
Monocytes	1 (3–37%)
Blast	0 (0%)
Cerebrospinal Fluid PCR	
Escherichia Coli K, Haemophilus Influenzae, Listeria Monocytogenes, Neisseria Meningitidis, Streptococcus Agalactiae, Streptococcus Pneumoniae, CMV, Enterovirus, HSV 1, HSV 2, HHV 6, Human Parechovirus, VZV, Cryptococcus Neoformans/Gattii, Lyme, West Nile IgM/IgG	Negative
Serum Antibodies	
Anti-GAD	83 (< 5 IU/mL)
Anti-Hu, Anti-Yo, and Anti-Ri	Negative

Abbreviations: CMV = Cytomegalovirus, HSV = herpes simplex virus; Human Herpesvirus = HHV; VZV = varicella zoster virus; GAD = glutamic acid decarboxylase

DISCUSSION

We present the first case of CVID manifesting as acute cerebellar ataxia. Cerebellar ataxia is often associated with paraneoplastic and immune-mediated autoantibodies, most notably anti-GAD autoantibodies.[1,3] Controversy exists regarding the evidence of the direct pathogenic role of anti-GAD antibodies and there are no established diagnostic criteria for anti-GAD mediated neurological syndromes.[1] The recommended diagnostic criteria for anti-GAD cerebellar ataxia includes serum anti-GAD, CSF anti-GAD, and subacute cerebellar symptoms[1]. Although serum anti-GAD was elevated in our patient, CSF anti-GAD was not available. Serum titers of anti-GAD autoantibodies in cerebellar ataxia are generally >1800 IU/mL and remain elevated for up to two years.[1,4] However, there are reports of anti-GAD cerebellar ataxia with anti-GAD serum titer of <100 U/mL, which is consistent with the low titer in our case report.[5] Improvement of his neurologic symptoms after steroids supports an autoimmune-mediated pathogenesis of his cerebellar dysfunction and seizures.[6]

Common variable immunodeficiency (CVID) is a heterogenous group of disorders characterized by hypogammaglobulinemia and abnormalities of B and T cells.[6] It is a primary immunodeficiency classically associated with recurrent

infections, but can also present paradoxically with features of autoimmunity.[6] Autoimmune mediated cytopenias (AICs) have been examined in CVID patients to better characterize the pathogenesis of autoimmunity.[7] AICs include autoimmune hemolytic anemia, immune thrombocytopenia, or both (Evans syndrome). Patients with CVID who develop AICs have naive B cells that express immunoglobulin variable heavy chain 4-34 (VH4-34) which encodes for autoreactive antibodies that recognize motifs on commensal bacteria. These same autoreactive antibodies recognize conserved I/i carbohydrate self-antigen found on hematopoietic cells, possibly providing an immunologic trigger for AICs in patients with CVID.[7] We propose that our patient may have also developed autoreactive antibodies to motif shared by commensal bacteria and GAD, thereby triggering the production of anti-GAD antibodies.

CONCLUSION

This case underlines the importance of considering immunodeficiency disorders in patients with new neurological symptoms. CVID can present with many different neurological syndromes including anti-GAD cerebellar ataxia. The immunopathogenesis of anti-GAD cerebellar ataxia remains to be elucidated.

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