Convergence spasm with horizontal nystagmus in anti-GAD65 antibody syndrome

Anti-glutamic acid decarboxylase (anti-GAD) autoantibody syndrome produces symptoms and signs related to loss of the inhibitory neurotransmitter gamma aminobutyric acid. Patients with GAD antibody may present with hyperexcitability disorders, including stiff-person syndrome, limbic encephalitis, and nystagmus. There has been only one previous report of convergence spasm in a patient with GAD antibody. Here we present a case of convergence spasm and, to our knowledge, the first case in the English-language ophthalmic literature to have concomitant horizontal nystagmus, in a patient with anti-GAD65 antibody syndrome.

A 40-year-old Hispanic woman presented with end-gaze nystagmus and convergence spasm. She was previously healthy with no medical or psychiatric history until age 30 years. Since then, she had a 10-year history of progressive neurocognitive decline, seizures and pseudoseizures, depression and anxiety, limbic encephalitis, and cerebellar ataxia. Her medical history was significant for hypothyroidism. Family history was negative for epilepsy and psychiatric conditions. She did not have stiff-person syndrome or latent autoimmune diabetes of adults (LADA). Her surgical history was noncontributory. Her medications were lamotrigine, dicyclomine, pantoprazole, melatonin, and vitamin supplementation.

Neuro-ophthalmic examination demonstrated visual acuity of 20/30 in the right eye (OD) and 20/40 in the left eye (OS). Pupils were equal and reactive without a relative afferent pupillary defect. Ishihara color plates were 14/14 OU. Motility testing showed end gaze horizontal nystagmus with episodes of convergence-spasm-related intermittent esotropia and pupillary miosis (see Video 1 included in supplementary materials, available online). Slit-lamp, intraocular pressure, and external examinations and dilated fundus examination were all normal. Humphrey visual field testing was normal in both eyes (OU). Serial neuroimaging studies with magnetic resonance imaging (MRI) of the head were normal. Cerebrospinal fluid composition was normal. Laboratory testing for syphilis, human immunodeficiency virus, sarcoidosis, tuberculosis, hypercoagulable state, toxin screen, and paraneoplastic antibody panel were all negative. Anti-GAD antibodies were positive at 457 nmol/L and was repeated and persistently elevated. The patient was treated with corticosteroids, intravenous immunoglobulin, and plasma exchange with some variable improvement over the next several years. Search for underlying neoplasm, including whole-body imaging, was negative.

Antibody against the GAD enzyme inhibits the formation of inhibitory neurotransmitter gamma aminobutyric acid, resulting in an excitatory or hyperexcitable state. The most common GAD antibody is GAD65, the type present in this patient. The neurological findings in patients with anti-GAD are variable and include stiff-person syndrome, cerebellar ataxia, limbic encephalitis, epilepsy, nystagmus, and Miller Fisher syndrome variant.[1]

The neuro-ophthalmic presentations include various forms of nystagmus, most commonly downbeat nystagmus. Interestingly, there is one prior reported case of convergence spasm.[2] Convergence spasm is characterized as intermittent episodes of convergence, miosis, and accommodation. Convergence spasm can be nonorganic, but one must exclude organic pathology such as encephalitis, aromatic L-amino acid decarboxylase deficiency, tabes dorsalis, thyroid disease, or multiple sclerosis.[3] Nonorganic causes include conversion disorder, pseudoseizures, and other neuropsychiatric conditions.

Tilikete et al. reported cases of 2 patients with anti-GAD65 antibody syndrome both of whom had cerebellar ataxia with nystagmus.[4] One patient presented with periodic alternating nystagmus and another with downbeat nystagmus. Chen et al. reported another case of a 59-year-old woman with LADA and a 4-week history of oscillopsia. Downbeat nystagmus in the primary position was noted that worsened on right and left gaze.[5] MRI showed enhancement and signal abnormality in the right temporal lobe without evidence of a cervicomedullary junction lesion, and anti-GAD65 antibody titres were elevated. Both the nystagmus and vertigo were attributed to the anti-GAD65 antibody syndrome. Similarly, in our patient, the patient had no lesion on MRI to explain the nystagmus and has consistently high titres of anti-GAD65 antibody.

Anti-GAD65 antibody syndrome is in the differential diagnosis in a patient with unexplained multiple neurological symptoms without a unifying diagnosis and negative neuroimaging. Anti-GAD65 antibody syndrome can cause nystagmus, especially downbeat. Although convergence spasm is often attributed to nonorganic etiologies, there have been reports of organic etiologies. We believe that anti-GAD65 antibody syndrome should be added to the list of potential etiologies for convergence spasm especially in the setting of organic findings (e.g., nystagmus) or other presentations of GAD65, including ataxia, LADA, or stiff-person syndrome.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2020.06.005.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

Branch retinal vein occlusion associated with fingolimod treatment for multiple sclerosis

Visual manifestations are the presenting symptom in approximately 20% of patients with multiple sclerosis (MS). The management of relapsing-remitting forms of MS relies on disease-modifying drugs to reduce the frequency of recurrent episodes and slow progression.

Fingolimod is an orally administered medication that modulates the immune response by sequestering thymocytes and lymphocytes in lymph nodes through the activation of sphingosine-1-phosphate-1 (S1P) receptors.[1] Reported adverse events include arterial vasospasm, bradycardia, infections, and macular edema (ME). We report here a case of MS treated with fingolimod resulting in a branch retinal vein occlusion (BRVO) that resolved with discontinuation of the medication.

A 31-year-old woman noted a 5-day history of decreased vision in her right eye. She denied pain with eye movement. She had a 16-year history of MS previously treated with interferon beta-1A and glatiramer acetate. Her MS regimen at the time of presentation included only fingolimod 0.5 mg for the previous 10 months. She denied oral contraceptive, tobacco, alcohol, or illicit drug use and reported no personal or family history of a coagulation disorder. Surgical history was significant for a splenectomy performed after abdominal trauma 18 years before the current presentation.

Her best-corrected visual acuity was 20/60-1 and 20/20 in the right and left eyes, respectively. Pupils were normal, with no relative afferent pupillary defect, dyschromatopsia, or brightness desaturation. Visual fields were full to confrontation. Dilated fundus examination of the right eye demonstrated disc and retinal hemorrhages and venous congestion consistent with a limited BRVO; optical coherence tomography (OCT) of the macula revealed ME (Fig. 1). The left eye was unaffected. Subsequent serological evaluation revealed a normal coagulation panel, all peripheral blood counts were within the normal range, and there were no other vasculopathic comorbidities. We suspected a potential association with fingolimod treatment, and the medication was discontinued the same day. No other form of treatment was initiated.

On follow-up examination 3 weeks later, acuity improved to 20/20 in the affected eye with near-complete resolution of the BRVO and intraretinal fluid (Fig. 2). The patient was transitioned to dimethyl fumarate with no reported issues on 1-year follow-up.

To date, there has been one reported case of a BRVO in a patient taking fingolimod. The reported patient was much older (an independent risk factor for BRVO), and a causal relationship between fingolimod and vein occlusion could not be clearly established as the patient received treatment with an intravitreal ranibizumab injection.[2] In our case, fingolimod was discontinued, and relatively rapid spontaneous resolution of the BRVO was observed. The timing of resolution also coincided with fingolimod and fingolimod phosphate pharmacokinetics with an established half-life of 6–9 days.[3] For a typical BRVO, retinal hemorrhages and intraretinal edema usually take many months to resolve.

The mechanism by which fingolimod could induce a vaso-occlusive event is speculative. Fingolimod is converted to fingolimod phosphate and binds to S1P receptor subtypes as an S1P analogue.[1] Lymphopenia is mitigated by initial

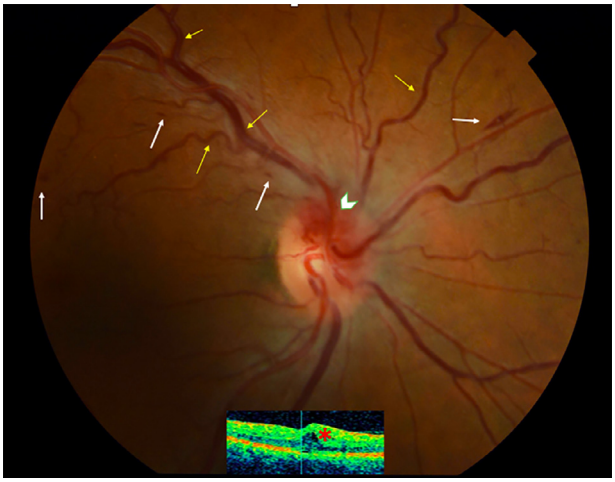

Fig. 1—Fundus photography of the right eye demonstrating tortuous and congested veins (yellow arrows), intraretinal hemorrhages (white arrows), and disc congestion (arrowhead) consistent with a superior branch retinal vein occlusion, with inset optical coherence tomography image (horizontally oriented section through the fovea) showing intraretinal edema just superior to the foveal centre (asterisk).