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LETTER TO THE EDITOR

Glutamic acid decarboxylase antibody-spectrum disorders: An evolving concept

Özlem Kayım Yıldız, Gülsüm Aslı Tatlı

Department of Neurology, Cumhuriyet University Faculty of Medicine, Sivas, Türkiye

Glutamic acid decarboxylase (GAD), the rate-limiting enzyme for the decarboxylation of glutamate to gamma-aminobutyric acid (GABA), is widely expressed in neurons and pancreatic beta cells.[1] Antibodies against GAD have been associated with type 1 diabetes mellitus as well as autoimmune neurological disorders characterized by neuronal hyperexcitability, including stiff-person syndrome (SPS), temporal lobe epilepsy, cerebellar ataxia (CA), and limbic encephalitis.[2] The neurological disorders resulting from abnormal GABAergic synaptic transmission, now comprise the GAD antibody-spectrum disorders (GAD-SD), and they have both overlapping and distinctive symptomatology.[2] A rare disease, progressive encephalomyelitis with rigidity and myoclonus (PERM), characterized by brainstem and spinal cord symptoms, long tract signs, and consciousness, autonomic, and respiratory disturbances, has also been associated with anti-GAD antibodies.[3]

A 51-year-old male was admitted with stiffness, leg spasms, and walking disturbance. Neurological examination revealed axial rigidity and limited movements of the legs. Results of the routine laboratory tests, including complete blood count, glucose, blood urea nitrogen, creatinine, electrolytes, liver enzymes, erythrocyte sedimentation rate, C-reactive protein, thyroid function tests, vitamin B12, and folate, were within normal limits. Serologic testing for viral hepatitis, HIV (human immunodeficiency virus), and syphilis was negative. Results of the magnetic resonance images (MRI) of the whole neuraxis and whole-body positron emission tomography (PET) were normal. Electromyography revealed continuous motor unit activity at rest. Serum anti-GAD antibody level was 221 U/mL. A diagnosis of SPS was made, and the patient was treated with clonazepam 2 mg three times a day, baclofen 60 mg/day, and intravenous immunoglobulin (IVIG) 0.4 g/kg/day for five days. After the treatment, the patient's functional status gradually improved, and the patient could walk independently. A written informed consent was obtained from the patient.

A 62-year-old male with arterial hypertension and bronchial asthma was admitted due to slurry speech and unsteadiness lasting for a few years. Neurological examination showed cerebellar dysarthria, dysmetria, dysdiadokinesia, and ataxia. Results of routine laboratory tests and serologic tests described above were either negative or within normal limits. Brain MRI revealed mild cerebellar atrophy. Whole-body PET was normal. Serum anti-GAD antibody level was >2000 U/mL. A diagnosis of CA associated with GAD-SD was made, and the patient was treated with steroids and IVIG (0.4 gr/kg/day for five days) with significant clinical response. A written informed consent was obtained from the patient.

A 33-year-old male was admitted with the complaints of agitation, incomprehensible speech, severe painful muscle spasms, and inability to use his limbs and walk. Neurological examination revealed dysarthria, agitation, axial rigidity, spastic tetraparesis, hyperreflexia on the lower limbs, bilateral extensor plantar reflexes, limited mobility of the limbs due to painful muscle spasms, and

Correspondence: Özlem Kayım Yıldız, MD. Cumhuriyet Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, 58140 Sivas, Türkiye.
E-mail: ozlemkayim@yahoo.com
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allodynia. No myoclonus was observed. Results of routine laboratory tests and serologic tests described above were either negative or within normal limits. Magnetic resonance imaging of the whole neuraxis and the whole-body PET were normal. Electromyography showed continuous motor unit activity at rest. Cerebrospinal fluid analysis revealed elevated protein level (93 mg/dL; normal range: 15 to 45 mg/dL) and lymphocytic pleocytosis. Serum anti-GAD antibody was 137 U/mL. During hospitalization, the patient was transferred to the intensive care unit due to progressive consciousness and respiratory disturbance. Based on the patient's clinical manifestations, including painful muscle spasms, upper motor neuron signs, encephalopathy, and respiratory disturbance, the diagnosis of PERM was made despite the absence of myoclonic jerks, and the patient was treated with clonazepam, baclofen, high dose steroids, IVIG, and plasma exchange. The patient was successfully extubated, and the clinical condition gradually improved. A written informed consent was obtained from the patient.

Stiff-person syndrome, the most common neurological disorder associated with GAD autoimmunity, is characterized by axial stiffness, rigidity, and spasms mainly in proximal and truncal muscles, resulting in lumbar hyperlordosis, gait disturbance, and electromyographic evidence of continuous motor unit activity in muscles.[2] The second most common neurological disorder associated with GAD autoimmunity is CA, which is characterized by older age at disease onset, gait and limb ataxia, ataxic dysarthria, and mild cerebellar atrophy on brain MRI.[4] Initially considered a subtype of SPS, PERM is characterized by rigidity, muscle stiffness, myoclonus, spasms, brainstem and autonomic dysfunction, dyspnea, and consciousness disturbance. Dysarthria and ataxia preceding muscle rigidity and spasms and altered level of consciousness are distinctive features.[4]

Immune-mediated therapies are used to treat GAD-SD, including steroids, plasma exchange, IVIG, cyclophosphamide, and rituximab.[2,5] Patients with classical SPS should first be treated with symptomatic medications enhancing GABAergic transmission, such as benzodiazepines and baclofen. When these drugs are not effective, immune-mediated therapies should be employed. Patients with CA and PERM should be treated with immune-mediated drugs since clinical deterioration occurs without immunotherapy.[2]

This paper shows that GAD autoimmunity is associated with diverse neurological syndromes, including classical SPS, PERM, and CA, emphasizes the evolving clinical manifestations of GAD-SD, outlines the importance of GAD antibody testing in a variety of neurological disorders, and aims to enhance awareness of these syndromes.

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