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Detection of anti–glutamic acid decarboxylase antibodies in immunoglobulin products

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TO THE EDITOR

Anti–glutamic acid decarboxylase (GAD) antibodies are found in approximately 80% of patients with stiff person syndrome (SPS), a relatively rare autoimmune neurological disorder characterized by muscle rigidity, changes in posture, and episodic painful muscular spasms.¹

GAD catalyzes the decarboxylation of L-glutamate to γ -aminobutyric acid, the most common inhibitory neurotransmitter in both neurons and β pancreatic cells. Anti-GAD antibodies are found in 80% of patients with type 1 diabetes,² 5% of patients with other neurological disorders, and 1% of the normal population.¹

During the evaluation of suspected SPS, we report the detection of anti-GAD antibodies in 2 immunodeficient patients receiving immunoglobulin replacement therapy. The first patient is a 54-year-old white female diagnosed with common variable immune deficiency complicated by immune thrombocytopenic purpura and lymphoid hyperplasia, who has required intravenous immunoglobulin (IVIG) replacement therapy for 22 years. Additional medical history is significant for allergic rhinitis, asthma, arthritis, trigeminal neuralgia, hypothyroidism, and Sjogren syndrome. Over the course of past 10 years, she developed joint pains involving her small joints and spine. She also developed stiffness involving her hands, feet, and neck with increased muscle tone and painful spasms. GAD antibodies were detected (Table I), which prompted further evaluation with several neurologists and rheumatologists. Extensive neuroimaging was completed with no significant findings. Electromyographic evidence of continuous motor unit activity in antagonist muscles was noted; otherwise, the study was unremarkable. Despite these findings, and several neurologic consultations, the final impression was not definitive for an SPS diagnosis. For management, the patient was begun on high-dose IVIG (1 g/mo), oral benzodiazepines, and intermittent steroids but with minimal improvement.

The second patient is a 73-year-old white male with a history of recurrent upper respiratory tract infections, pneumonia, bronchiectasis, and hypogammaglobulinemia with impaired

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specific antibody production. Because of recurrent infections, the patient required IVIG and has been on this therapy for 15 years. Additional medical history is significant for fibromyalgia syndrome diagnosed 40 years ago, prediabetes, prostate cancer in remission, and obstructive sleep apnea. Over the past 6 years, he developed diffuse muscle pain, stiffness, and reduced mobility with no history of spasms. Anti-GAD antibodies were detected (Table I), which prompted further neurological and rheumatologic evaluations. Electromyographic findings were not suggestive of SPS. However, with the positive anti-GAD antibody, this patient was given high-dose IVIG (1 g/mo), benzodiazepines, and intermittent steroids with no clinical improvement.

We hypothesized that the detection of anti-GAD antibodies could be secondary to passive transfer from immunoglobulin products. To test this concept, 6 patients with X-linked agammaglobulinemia (XLA) (aged 5–39 years) receiving immunoglobulin replacement were selected and serum anti-GAD antibodies were measured to examine for potential passive transfer. Three of these subjects were treated with IVIG (2 different products), and 3 were treated subcutaneously with 1 product. None of the patients with XLA was ill or had neurological or musculoskeletal complaints. All studies were undertaken with the consent of the Mount Sinai Medical Center Institutional Review Board. Table I includes each patient's sex and age at time of study, indication for immunoglobulin replacement, the brand and dose (mg/kg/mo) at the time of anti-GAD testing, duration of therapy (in years), and quantitation of anti-GAD65 antibodies (IU/mL). On the basis of ranges of the 2 laboratories used, 5 of the 6 patients with XLA had detectable serum anti-GAD65 antibodies and 1 patient, before his scheduled infusion, had a level higher than that found in the serum of the 2 patients suspected of having SPS.

In the United States, immunoglobulin products are prepared from purified plasma collected from a large pool of screened donors, usually between 10,000 and 50,000 individuals.³ Donor plasma contains a broad range of specific antibodies that include multiple autoantibodies.^{4–8} As noted, GAD antibodies are found in a significant proportion of patients with type 1 diabetes, patients diagnosed with other neurological disorders, and 1% of the normal population, all of whom may contribute to the donor pool. Radioimmunoassay detection of GAD65 antibodies in several batches of a commercial immunoglobulin preparation was noted some years ago.⁹ Transient detection of anti-GAD antibodies after treatment with IVIG for presumed opsoclonus-myoclonus-ataxia syndrome has been reported.¹⁰ As demonstrated in the present study, anti-GAD antibody detection was observed in patients with immunoglobulin on immunoglobulin therapy who could not produce these immune globulins, demonstrating that their detection in the serum of other subjects on immune globulin may yield false-positive serological tests, with the potential for misleading interpretation and diagnosis. In classical SPS, higher GAD65 antibody titers are usually detected¹ compared with what we have observed in our study. Therefore, the diagnosis of classical SPS should be approached with caution with the lower levels seen in our patients. However, the levels we observed compare to the levels measured in patients with partial SPS¹¹ and patients with type 1 diabetes.¹² As a result, further confirmatory testing must be pursued in a patient suspected of SPS or its variant while on immunoglobulin replacement therapy.

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Clinical Implications

- Clinicians should be aware that passive transfer of anti-glutamic acid decarboxylase antibody in immunoglobulin products may confound the use of this diagnostic test for stiff person syndrome.

TABLE 1
Immunodeficiency patients on immunoglobulin therapy with detectable anti-GAD antibodies

Patient	Sex	Age (y)	Indication for immunoglobulin replacement	Product	Route	Immunoglobulin dose at time of anti-GAD antibody measurement (mg/kg/mo)	Duration of therapy (y)	GAD antibody (GAD65) detection (IU/mL) (reference range, 0.0–5.0 IU/mL)
1	F	54	COVID	Gammagard 10%*	IV	480	22	160 [†]
2	M	73	Hypogammaglobulinemia: Low IgG and antibody defects	Gammagard 10%*	IV	500	15	103.8 [†]
XLA 1	M	9	XLA	Gamunex 10% [‡]	IV	600	7	3.1 [§]
XLA 2	M	6	XLA	Hizentra 20%	SC	630	5	89.0 [‡]
XLA 3	M	7	XLA	Hizentra 20%	SC	600	6	77.2 [‡]
XLA 4	M	5	XLA	Hizentra 20%	SC	533	4	54.9 [‡]
XLA 5	M	34	XLA	Gamunex 10% [‡]	IV	580	20	93.9 [‡]
XLA 6	M	39	XLA	Gammagard 10%*	IV	642	30	>250.0 [‡]

COVID, Common variable immune deficiency; F, female; M, male; SC, subcutaneous; IV, intravenous.

* Gammagard (human 10% liquid IVIG), Baxter Healthcare Corporation, Westlake Village, Calif.

[‡] ARUP Laboratories, Salt Lake City, Utah.

[§] Gamunex (human 10% liquid IVIG), Talecris Biotherapeutics, Inc, Research Triangle Park, NC.

^{||} Quest Diagnostics Nichols Institute, San Juan Capistrano, Calif.

^{||} Hizentra (human 20% liquid), CSL Behring LLC, Kankakee, Ill.