Humoral Deficiency Associated with Stiff-Person Syndrome: Case Series

University Hospitals Cleveland Medical Center

David P McGarry, DO[1]; Jason Schend, DO[2]; John Johnson, DO[1]; Robert Hostoffer DO[1,3]

University Hospitals-Cleveland Medical Center, Cleveland, OH; 2. Mercy Health Muskegon, Muskegon, MI; 3. Allergy/Immunology Associates, Mayfield Heights, OH

ABSTRACT

Background:

Humoral deficiencies are common primary immunodeficiencies. Autoimmune diseases are often seen in patients with humoral deficiencies. Neurologic autoimmune disorders are rarely seen in patients with humoral deficiencies.

Methods:

Humoral deficiencies are diagnosed by immunological evaluation of serum immunoglobulin levels and response to polysaccharide and conjugate immunizations. Stiff-person Syndrome is diagnosed by elevated Anti-GAD 65 antibodies in the setting of clinical symptoms in the absence of diabetes mellitus.

Results:

We describe two patients with humoral deficiencies who also developed Stiff-Person Syndrome (SPS). Each patient had humoral deficiencies with elevated anti-GAD 65 levels of 41.2 and 57.1, respectively.

Conclusions:

Humoral deficiencies are the are primary immunodeficiencies. We present the first two reported cases of Stiff-Person Syndrome in patients with humoral deficiencies. In caring for patient's with humoral deficiencies, clinicians should consider SPS as a possible diagnosis in those presenting with concerning symptoms.

INTRODUCTION

Humoral immunodeficiencies are considered primary immunodeficiencies. The autoimmune diseases associated with humoral deficiencies commonly effect the hematologic, dermatological, and gastrointestinal systems. Neurologic autoimmune disorders associated with humoral immunodeficiencies are infrequently seen. Stiff-Person Syndrome is an extremely rare autoimmune neuromuscular disorder with a prevalence of 1-2 per million and an incidence of 1 case per million per year. We describe the first two cases of patients with humoral deficiency associated with Stiff-person Syndrome (SPS), a neurologic autoimmune disorder..

CASE 1

A physically active 50-year old woman with a five-year history of right-sided pelvic and low back pain that was accompanied by gluteal muscle atrophy, beginning in 2012. Treatment at the onset of symptoms, included physical therapy, several prednisone courses, and Botox injections for cervical dystonia, all of which yielded no improvement.

Evaluation included normal electromyography, negative ANA and normal values of PTT; PT; INR; Von Willebrand Ag; ESR; CRP; Lupus Anti-Coagulant profile (negative); Cardiolipin IgM, IgA, IgG; Creatine Kinase (CK); Anti-SSB, Anti-SSA, Rheumatoid Factor; Ceruloplasmin; Anti-Centromere Antibody: negative, MUSK (Muscle-Specific Receptor for Tyrosine Kinase) Antibody; Acetylcholine-binding antibody (MG); Muscle-Modulating Antibody; and Striational Antibodies. During the evaluation for the musculoskeletal issues she developed recurrent sinopulmonary infections requiring monthly courses of antibiotics for over a year.

The immune evaluation demonstrated hypogammaglobulinemia and absent response to polysaccharide and conjugate vaccination (Table 1). The patient had normal flow cytometry results (Table 2). With the patient's diagnosis, she started on IVIG at 400 mg/kg monthly. Patient's neurological symptoms of pain and rigidity remained, albeit improving within the first six months of IVIG.

The patient was tested for the anti-GAD65 antibody, which was positive at 41.2 IU/mL (Table 3). Anti-GAD antibodies can also be seen in diabetes mellitus. The patient has never been diagnosed with diabetes mellitus (type I or II). During her evaluation course, she had a fasting glucose of 93. Her IVIG dose was increased to 1 g/kg considering the SPS diagnosis as well as changing to a non-glycine-stabilized IVIG formulation.

CASE 2

The patient is a 21-year-old female who was diagnosed with a humoral deficiency at age 8. Up to that period, she had a long history of recurrent cases of pneumonia and sinus infections nearly every month. She was found to have normal immunoglobulin levels, absent pneumococcal polysaccharide vaccine response and minimal pneumococcal conjugate vaccination (Table 1). Her flow cytometry was normal (Table 2). Once started on IVIG her infection frequency decreased substantially.

At the age of 14, she began to have neck pain, stiffness and decreased range of motion. Physical therapy was initiated and show steady progression with worsening of musculoskeletal symptoms. Pain and stiffness progressively moved to shoulders and back. Eventually, whole body pain developed which was unremitting to any therapy. MRI of neck and back were unremarkable. Acupuncture, dry needling, gabapentin, and amitriptyline provided no relief. Based upon the constellation of symptoms and knowledge of Patient 1, this patient had an Anti-GAD 65 level of 57.1 (Table 3). Diabetes Mellitus was ruled out. Patient has recently had her IVIG increased to immune modulating dosing of 1 mg/kg.

Table 1. Immunological Evaluation

Immunoglobulin Analysis	Patient 1		Patient 2	
	Level	Reference Range	Level	Reference Range
Serum IgA	54	81-463 mg/dL	102	43-208 mg/dL
Serum IgG	551	694-1618 mg/dL	836	546-1170 mg/dL
Serum IgM	113	48-271 mg/dL	137	26-170 mg/dL
Pneumococcal Titers	**Pre-Titers**	**Post-Titers**	**Pre-Titers**	**Post-Titers**
S. pneumo Serotype 1 (1)	1.1	1.2	<1.4	1.5
S. pneumo Serotype 3 (3)	0.9	0.6	<1.4	<1.4
S. pneumo Serotype 4 (4)	0.4	<0.3	<1.4	<1.4
S. pneumo Serotype 5 (5)	10.9	6.1	N/A	N/A
S. pneumo Serotype 6/26 (6A/6B)	N/A	N/A	<1.4	2.1
S. pneumo Serotype 8 (8)	7.4	7.2	<1.4	<1.4
S. pneumo Serotype 9 (9N)	2.2	1.8	<1.4	2.1
S. pneumo Serotype 12 (12F)	0.4	0.4	<1.4	<1.4
S. pneumo Serotype 14 (14)	0.6	0.6	6.3	13.0
S. pneumo Serotype 19 (19F)	2.8	2.6	4.7	>179.7
S. pneumo Serotype 23 (23F)	3.3	3.2	<1.4	2.0
S. pneumo Serotype 26 (6B)	2.1	1.8	N/A	N/A
S. pneumo Serotype 51 (7F)	17.9	11.3	<1.4	<1.4
S. pneumo Serotype 56 (18C)	10.5	5.3	<1.4	2.1
S. pneumo Serotype 68 (9V)	35.7	35.2	N/A	N/A

Table 2. Immunophenotyping

	Patient 1	Patient 2	
	Value	Value	Reference Range
% CD3+	83%	67%	58-86%
% CD 19+	6%	6%	6-24%
% CD16+CD56+	10%	14%	4-28%
% CD4+	49%	39%	32-64%
% CD8+	34%	26%	13-40%
CD3+	1023	1849	550-2202 cells/mcL
CD 19+	72	469	70-409 cells/mcL
CD16+CD56+	120	386	59-513 cells/mcL
CD4+	597	1076	365-1437 cells/mcL
CD8+	415	718	145-846 cells/mcL

Table 3. Anti-GAD 65 Testing

Patient 1	Patient 2	
Level	Level	Reference Range
41.2	57.1	< 5.0 IU/mL

Discussion

Humoral deficiencies include a spectrum of primary immunodeficiencies including Common Variable Immune Deficiency (CVID), Selective Antibody Deficiency and Hypogammaglobulinemia. Patients with humoral deficiencies often have recurrent sinus and lower respiratory tract infections. It often takes patients many years to obtain a diagnosis of their immune deficiency.

Humoral immunodeficiencies are frequently associated with autoimmune diseases. Various organ systems are affected by the autoimmune diseases associated with humoral deficiencies. However, rarely seen are neurologic autoimmune diseases in these patients.

Stiff-Person Syndrome is a neurologic autoimmune disease which manifests as rigidity, stiffness, and weakness of the truncal muscles due to the antibody production against glutamic acid decarboxylase 65 kD isoform (GAD 65). Inactivation of GAD 65 leads to lack of inhibition by GABA, resulting in hyper-tonicity, muscle wasting, and musculoskeletal pain.

Immunoglobulin replacement is often required as treatment for patients with humoral deficiencies. Patients with Stiff-Person Syndrome can benefit from high dose immunoglobulin therapy for its immune modulating effects.

These cases do not definitively demonstrate evidence of a direct causal relationship between humoral deficiency and Stiff-Person Syndrome. Further research could more fully elucidate a causative relationship as there has been demonstrated clear associations with other autoimmune disorders and humoral deficiency.

CONCLUSSION

- Humoral Immunodeficiencies are common primary immunodeficiencies
- Neurologic autoimmune diseases are rarely seen in patients with humoral deficiencies.
- We present the first two cases of patients with humoral deficiency and Stiff-Person Syndrome, a neurologic autoimmune disorder.