

Common variable immunodeficiency associated with stiff-person syndrome



Common variable immunodeficiency (CVID) is a primary immunodeficiency.^{1,2} The autoimmune diseases associated with CVID commonly affect the hematologic, dermatologic, and gastrointestinal systems.^{3–6} Neurologic autoimmune disorders associated with CVID are seen infrequently.⁷ We describe the first case of CVID associated with stiff-person syndrome (SPS), a neurologic autoimmune disorder. SPS 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.⁸ Stiff-person syndrome manifests itself as rigidity, stiffness, and weakness of the truncal muscles due to autoantibody production against glutamic acid decarboxylase 65-kD isoform (GAD65). Inactivation of GAD65 leads to lack of inhibition by gamma-aminobutyric acid, resulting in hypertonicity, muscle-wasting, and skeletal muscular pain.⁹

The patient we describe was a physically active 50-year-old woman with a 5-year history of right-sided pelvic and low-back pain that was accompanied with gluteal muscle atrophy, beginning in 2012. Initial treatment, at the time of the onset of symptoms, included physical therapy, several prednisone courses, and onabotulinum toxin A injections for cervical dystonia, all of which yielded no improvement. An extensive evaluation was performed, which included normal electromyography, negative antinuclear antibodies, and repeatedly absent anti-GAD65 antibodies. Through the initial evaluation by rheumatology and neurology, all testing proved to be within normal limits, which included: partial thromboplastin time; prothrombin time; international normalized ratio; von Willebrand antigen; erythrocyte sedimentation rate; C-reactive protein; lupus anticoagulant profile (negative); cardiolipin; immunoglobulins M, A, and G; creatine kinase; anti-Sjögren type A and B antibodies; rheumatoid factor; antinuclear antibodies; ceruloplasmin; anti-centromere antibody (negative); muscle-specific receptor for tyrosine kinase antibody; acetylcholine-binding antibody; muscle-modulating antibody; and striational antibodies. Coincidentally, the patient also developed recurrent sinopulmonary infections and skin infections from small skin breaks, requiring monthly courses of antibiotics for over 1 year. Her immune evaluation was consistent with CVID (eTable 1).

The patient had poor antibody responses to polysaccharide antigens after both a pneumococcal vaccine and its conjugated version and was diagnosed with CVID in 2014. She was started on intravenous immunoglobulin at 400 mg/kg monthly. The patient's neurologic symptoms of pain and rigidity remained, albeit improving within the first 6 months of intravenous immunoglobulin (IVIg) treatment. Three years later, in 2017, she was again tested for the anti-GAD65 antibody, which was positive at 41.2 IU/mL (reference

range, <5.0 IU/mL). Anti-GAD antibodies can also be seen in diabetes mellitus. The patient had never been diagnosed with diabetes mellitus (type I or II). During her evaluation course, she had a fasting glucose of 93. Her intravenous immunoglobulin dose was increased to 1 g/kg considering the SPS diagnosis as well as changing to a non-glycine-stabilized IVIg formulation.

Although there is not enough evidence for a direct causal relationship between CVID and SPS, more research into a possible link is necessary, especially in light of associations seen with other autoimmune disorders and primary immunodeficiency.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.janai.2018.01.002>.

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Selective IgM deficiency associated with adult-onset Still disease



Selective immunoglobulin M (IgM) deficiency is a rare immunodeficiency disorder characterized by decreased serum levels of IgM. Those with IgM deficiency may present with recurrent infections and have an increased predisposition to allergic and autoimmune

diseases.¹ Adult-onset Still disease (AOSD) is a rare autoinflammatory disease characterized by high-spiking fevers, evanescent salmon-colored rash, and multiorgan involvement. It is a diagnosis based on clinical criteria and age of onset.² A case of selective IgM deficiency associated with AOSD has not been reported previously. Herein we report the first case of AOSD with known selective IgM deficiency.

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A 53-year-old African-American female with selective IgM deficiency and nonspecific lymphadenopathy was admitted for evaluation for fevers without a source, bilateral arthralgias, and a diffuse pruritic rash. The patient meticulously recorded fevers of 40°C, which revealed a quotidian cycle. Peak temperatures occurred in the evening between 5:00 and 8:00 PM. This pattern was confirmed with inpatient monitoring along with the appearance of a rash during her fevers.

She previously had extensive evaluations spanning 10 years and multiple hospital admissions at various healthcare systems for fevers of unknown origin. With each admission, infectious evaluations, including both blood and urine cultures, were all negative. Investigations into malignancies secondary to her fever of unknown origin in addition to her cervical and thoracic lymphadenopathy were negative on repeated occasions. A right cervical lymph-node excisional biopsy earlier that year was negative for acute infection or malignancy, but it did demonstrate follicular and parafollicular hyperplasia. Histologic sections, immunohistochemical stains, and flow-cytometric studies were performed. Numerous reactive follicles with mild expansion of paracortical area and sinus histiocytosis were found on histologic section analysis. Immunohistochemical staining demonstrated numerous positive B cells with a follicular pattern, numerous positive T cells, and a moderate number of positive CD4 and CD8 cells. Flow cytometry showed no definite evidence of lymphoma. After resolution of the fevers, additional imaging demonstrated a decrease in lymphadenopathy. Human immunodeficiency virus, hepatitis panel, cytomegalovirus, and toxoplasma studies were negative.

The patient had no history of autoimmune diseases and there was no known family history of either autoimmune or immunologic diseases. However, upon further lab work, she had a low-level antinuclear antibody positivity with titers of 1:40 and anti-Sjögren's-syndrome-related antigen A (SSA) of 2.8 without clinical symptoms of Sjögren or connective tissue disease. Liver function panel revealed an elevated aspartate aminotransferase of 177 U/L and alanine aminotransferase 177 U/L, with total bilirubin 1.7 mg/dL and alkaline phosphatase 146 U/L. Her ferritin was also elevated at 349 g/L.

During the workup of her fevers of unknown origin, serum immunoglobulins were performed, which demonstrated normal levels of IgG and IgA, with undetectable to decreased IgM of less than 10 mg/dL (reference range, 40–230 mg/dL), consistent with selective IgM deficiency. T-cell function was examined and considered to be within normal limits. Antibody titer responses to the pneumococcal polysaccharide and tetanus antigens showed adequate specific antibody response, suggesting adequate humoral memory to these antigens (Table 1).

Overall, the patient fulfilled the Yamaguchi criteria for AOSD with 3 major criteria of evanescent rash; intermittent fevers in a quotidian pattern; and bilateral arthralgias of the hips, knees, and ankles. She also met 2 minor criteria: liver abnormalities and lymphadenopathy.²

The exact etiology of AOSD is not known, but it is hypothesized that there are multiple factors playing a role, such as genetic, environmental, infectious, neuropsychogenic, and immunologic.² Adult-onset Still disease is a diagnosis of exclusion, which requires the absence of infectious, neoplastic, and other forms of autoimmune disorders. It is not associated with elevated rheumatoid factor or antinuclear antibodies. Common nonspecific laboratory findings include liver abnormalities and elevated inflammatory markers erythrocyte sedimentation rate, C-reactive protein, and ferritin. In addition, leukocytosis with a predominant neutrophil count can be present.² AOSD has been reported in natural killer T-cell deficiency³ and in secondary immunodeficiencies such as human immunodeficiency virus.⁴

Selective IgM deficiency is characterized by a decreased serum IgM level of 2 standard deviations below the mean value, with

Table 1

Immunologic and Infectious Evaluation of the Study Patient

Laboratory test	Result	Normal reference range
Immunoglobulin (mg/dL)		
IgG	1,120	700–1,600
IgA	165	70–400
IgM	<10	40–230
Cell surface markers (% of lymphocytes)		
CD4	31.9	
CD8	31.6	
NK	15.5	
CD19	16.5	
<i>Streptococcus pneumoniae</i> IgG antibody (μg/mL)		
Serotype 1	<0.3	>1.3
Serotype 3	2.4	
Serotype 4	<0.3	
Serotype 5	13.2	
Serotype 8	0.7	
Serotype 9N	1.9	
Serotype 12F	<0.3	
Serotype 14	28.2	
Serotype 19F	11.5	
Serotype 23F	<0.3	
Serotype 6B[26]	<0.3	
Serotype 7F[51]	2.0	
Serotype 18C[56]	0.6	
Serotype 9V[68]	1.3	
EBV panel		
VCA IgG antibody	Positive	Negative
EBV EA-D IgG antibody	Positive	
EBV NA-1 IgG antibody	Positive	
VCA IgM antibody	Negative	
HIV antigen/antibody	Nonreactive	Nonreactive
Tetanus antibody	0.22 IU/mL	<0.10 IU/mL

Abbreviations: EA-D, early antigen D; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; IgA/G/M, immunoglobulin A, G, and M, respectively; NA-1, nuclear antigen-1; NK, natural killer; VCA, viral capsid antigen.

normal levels of IgG and IgA in addition to normal cellular components. Approximately 80% of patients with selective IgM deficiency present with recurrent infections due to impaired humoral immune response. Subsequently, there is a decrease in the number and functionality of lymphocytes, although the innate immune response is not affected.¹ Selective IgM has been shown to be associated with multiple autoimmune disorders, such as systemic lupus erythematosus, Hashimoto disease, and glomerulonephritis.^{5–9}

Selective IgM deficiency is an uncommon immunodeficiency disorder associated with increased risk for autoimmune disorders. Recognition of co-morbid autoimmune illnesses in an immunodeficient patient is often complicated by the paucity of examples in the literature and potential confounding of laboratory serology analysis. Proper diagnosis is important to direct therapy and avoid unnecessary procedures and testing. Herein we have reported the first case of a patient with selective IgM deficiency and AOSD.

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Food allergy management and anaphylaxis preparedness in a suburban school district varies by school level



Food allergy (FA) affects up to 8% of school-age children,¹ and management of FA in schools has become a major public health issue. Although there are few proven strategies for improving FA safety in schools, consensus guidelines recommend that all students at risk for anaphylaxis due to FA have an individualized emergency action plan (EAP), as well as an epinephrine auto-injector (EAI) available at all times.^{2,3} Few studies have evaluated the percentage of children with FA with an EAP and an EAI available at school and, to our knowledge, none have evaluated for differences between school levels.^{4,5} The objective of our study was to determine the percentage of students with FA who had an EAP and EAI available, according to school level in a suburban school district.

The school district we assessed had a total of 5,738 students, with a mean household income of \$106,134, per United States Census data. The district was comprised of 5 elementary schools (grades K–5), 2 junior high schools (grades 6–8), and 2 high schools (grades 9–12). All 9 schools in the district were staffed with a school nurse, and each school nurse provided data for grades K–12 for the 2015–2016 school year. Data were collected at the start of the school year, and included the types of self-reported FA for each student and whether these students had an EAP and EAI available at school. Students with permission to self-carry an EAI were also required to provide an EAP to the school nurse. All schools had undesignated stock EAI.

Data were available for 5,015 of 5,738 (87.4%) students in the district. Of the students, 2,327 (46.4%) were in grades K–5, 757 (15.1%) in grades 6–8, and 1,931 (38.5%) in grades 9–12. Of the 418 (8.33%) students who self-reported FA, 235 (56.2%) reported a peanut allergy, 196 (46.9%) a tree nut allergy, 58 (13.9%) a cow's milk allergy, 46 (11.0%) an egg allergy, and 45 (10.8%) a shellfish allergy. One hundred eighty students (43.1%) reported an allergy to other foods, including 22 (5.3%) to sesame, 18 (4.3%) to wheat, and 17 (4.1%) to soy. Forty-nine students (11.7%) reported an allergy to various fruits. There was minimal variation in the percentage of students with reported FA per grade (mean, 8.3%; range, 6.3%–10.1%, $P = .82$). There was also minimal variation in type of reported FA per grade (peanut, $P = .11$; tree nuts, $P = .66$; milk, $P = .08$; egg, $P = .12$; and shellfish, $P = .12$).

In grades K–5, the percentage of students with EAPs was 70.5% (136 of 193), as compared with 67.2% (41 of 61) of students in grades

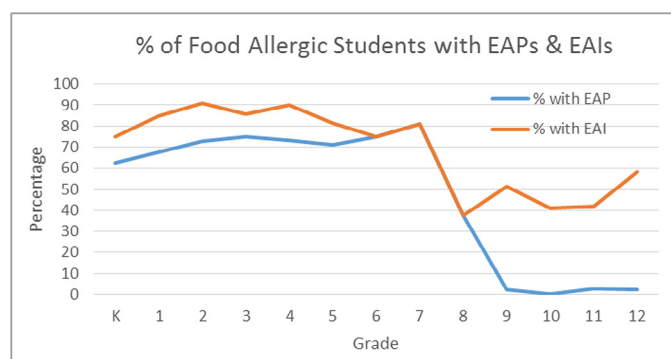


Figure 1. Percentage of food allergic students with an emergency action plan (EAP) and an epinephrine auto-injector (EAI).

6–8 (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.46–1.59) (Fig 1). For grades 9–12, 1.8% (3 of 164) of students had an EAP, significantly lower than for grades K–5 and grades 6–8 (odds ratio, 0.01; 95% CI, 0.00–0.03).

In grades K–5, the percentage of students with an EAI was 85.0% (164 of 193), compared with 67.2% (41 of 61) of students in grades 6–8 (OR, 0.36; 95% CI, 0.19–0.70). For grades 9–12, 48.2% (79 of 164) of students had an EAI. Compared with grades 6–8, the OR of a student in grades 9–12 having an EAI was 0.45 (95% CI, 0.24–0.84). Compared with K–5, the OR of a student in grades 9–12 having an EAI was 0.19 (95% CI, 0.10–0.27). These figures accounted for students with permission to self-carry their EAI.

In this study, there was a significantly lower percentage of students with EAPs in grades 9–12 compared with grades K–5 and 6–8. In addition, students in grades 9–12 were less likely to have an EAI compared with students in grades K–5 and 6–8. Students in grades 6–8 were also less likely to have an EAI compared with students in K–5. Although previous studies have shown suboptimal rates for EAPs and EAI in the school setting, to our knowledge, this is the first study to show a significant difference between high school vs middle school and elementary school students.⁶ The lower percentage of students with individualized EAPs and EAI in grades 9–12 may reflect a decreasing parental vigilance as children grow older and progress through the school system. It may also reflect the consequences of shifting responsibility for FA management in the school setting from parents to adolescents.