CLINICAL VIGNETTE

Selective Serum IgA Deficiency (sIgAD)

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Introduction

Selective serum IgA deficiency (sIgAD) is the most common immunodeficiency in humans. It is a primary humoral immune deficiency and is defined as an isolated sIgAD in a person over the age of four years old in the setting of normal IgM and IgG levels and no other cause of hypogammaglobulinemia. Patients are usually asymptomatic and are often incidentally diagnosed. However, patients can also present with recurrent infections, specifically sinopulmonary and gastrointestinal, autoimmune disorders, allergic disorders, and anaphylactic transfusion reactions. Treatment varies, including monitoring immunoglobulin levels, treating the underlying etiology of the immunologic defect with immunoglobulin, or other medications for autoimmune disorders, prophylactic antibiotics, screening for anti-IgA antibodies prior to blood transfusions, and receiving recommended vaccinations for primary prevention.[1] We present an account of a patient incidentally diagnosed with selective serum IgA deficiency during the work up of chronic fatigue.

Case Report

The patient is a 29-year-old underweight female with history of irritable bowel syndrome with constipation (IBS-C), abnormal uterine bleeding-heavy menstrual bleeding (AUB-HMB), and anxiety who presented to establish care. Her primary concern was chronic generalized anxiety disorder. However at the end of the visit, she mentioned chronic fatigue for over ten years, which she thought was related to insomnia due to chronic generalized anxiety disorder. She has chronic cold intolerance and always had borderline AUB-HMB but denied a history of anemia. She has always been underweight with no recent weight changes. She has had IBS-C for years that was previously well-controlled on Linaclotide but was discontinued due to undesirable side effects and the desire for natural treatments. It is now moderately controlled with peppermint oil and a gluten-free diet (though never tested for celiac disease). She denied depression; emotional, physical, or sexual abuse; tobacco, drug, or alcohol abuse; unintentional weight loss; fevers; night sweats; lymphadenopathy; hemoptysis; exposure to tuberculosis or infectious mononucleosis; muscle pain or weakness; risk factors for hepatitis C or HIV; recent travel; history of cardiac, pulmonary, or thyroid disease; or history of diabetes. She had no known drug allergies, did not take medications, and had no pertinent family history except for her father who was diagnosed with Diabetes Type II at age 40. Her full physical exam was within normal limits. Based on the patient's history, a CBC with differential, TSH, and Hemoglobin A1C were all were within normal limits. She requested B12, folate, and Vitamin D levels with normal B12 and folate levels, and Vitamin D insufficiency,[21] for which she was started on vitamin D supplementation.

At her follow-up 2 months later, additional history was taken, and additional evaluation for fatigue was completed, including normal comprehensive metabolic panel and HIV test. Given her history of IBS-C with symptomatic improvement on a gluten-free diet and no prior celiac disease testing, a transglutaminase (TTG) IgA level and serum IgA level were ordered. If the IgA level was low, the TTG IgA may be false negative, and other celiac disease testing would have to be pursued. The patient's IgA level was <8, making the TTG IgA level irrelevant. Because she had already been on a gluten-free diet for over 2 years, the antibody tests could result in false negatives. Thus celiac genetic testing via HLA DQ2 and DQ8 was suggested, but declined due to costs and Gastroenterology (GI) was consulted. GI advised obtaining TTG IgG and DGP IgG (demaidated gliadin peptide), which returned negative and continued gluten-free diet as her symptoms were well controlled. The patient may have a possible diagnosis of celiac's disease without further work up. GI also agreed that although celiac's disease is one possible cause of sIgAD, other causes should be excluded.

Further questioning about other causes of sIgAD, included at least one sinus infection per year and frequent episodes of bronchitis as a child. Her 34-year-old female first cousin was being evaluated for Lupus. She denied a personal history of autoimmune disorders, food allergies, asthma, prior blood transfusions, joint pain, rashes, hematochezia, and as previously mentioned, denied unintentional weight loss, fevers, night sweats, or medication use. She denied a family history of sIgAD or combined variable immunodeficiency (CVID).

The patient agreed to further testing including repeat serum IgA to ensure it was not a false positive, serum IgG level, serum IgM level, serum total IgE level, ESR, CRP, and iron studies. Labs were within normal limits except for persistently low serum IgA <8, borderline low serum IgM level and iron deficiency likely secondary to menorrhea, for which she was started on iron supplementation. Patient was referred back to GI for iron deficiency without anemia, further treatment of IBS-C and possible celiac disease. Patient was also referred to Immunology for further evaluation and possible treatment of sIgAD and to determine cause of why the serum IgM level, although normal, was not adequately compensating for the

sIgAD. Unfortunately, the patient was lost to follow-up. Thus the final etiology and whether or not she required any treatment remains unknown.

Discussion

Selective Serum IgA deficiency (sIgAD) is the most common human immunodeficiency seen, most commonly in Caucasian, Black, and Middle Eastern populations (1 in 100 to 1 in 1000), and less commonly in Asian populations (1 in 1615 to 1 in 19,000), based on data from healthy bloody donors. The criteria for diagnosis include: ≥ four-years-old to account for transient physiologic sIgAD during development, decreased serum IgA levels, normal IgM and IgG levels, and exclusion of other causes of hypogammaglobulinemia. sIgAD is defined as serum IgA levels of <7 mg/dL (0.07g/L) as that is the lower limit of normal of most labs. Partial IgA deficiency is defined as >7 but two standard deviations below normal for age.[1,2]

The role of IgA is not well-understood, but its main function is to rid of pathogens and maintain intestinal homeostasis. It is the most common antibody isotype, and exists in two forms: subclass IgA1 monomeric form in the blood and subclass IgA2 dimeric form in mucosal secretions. Despite this important task, almost ninety percent are asymptomatic as the body can compensate for IgA deficiency in various ways.

Given the purpose of IgA is not entirely clear, the pathogenesis of sIgAD is not either. The following are possible mechanisms: most commonly, a defect in B cell maturation that normally produces IgA; low levels of T regulatory cells, mutations in transmembrane activator and calcium modulator and cyclophilin ligand interactor gene (TACI); gene variations for interferon-induced helicase C domain-containing protein (*1IFIH1*) and the C-type lectin domain family 16 gene (*CLEC16A*); chromosomal abnormalities; and increase in susceptibility if certain major histocompatibility complex haplotypes are present.[1,3]

Although the genetic basis of sIgAD is unclear, it may be autosomal dominant or recessive, and the major risk factor is a first degree relative with sIgAD or CVID with maternal transmission being more common.[4,5]

The majority of people with sIgAD are asymptomatic, most likely because other immunoglobulins, specifically IgM, which has a very similar structure and function to IgA, increases to compensate for this deficiency. However, some individuals do not have this compensatory increase and still remain asymptomatic. If symptomatic, sIgAD usually manifests as recurrent sinopulmonary infections, gastrointestinal infections and disorders, allergies, autoimmune conditions, and malignancies. Recurrent sinopulmonary infections in sIgAD include: sinusitis (≥4 episodes per year), bacterial pneumonia (≥2 episodes per year), otitis media (≥4 episodes per year) in children, viral URIs, laryngitis, and bronchiectasis from recurrent pulmonary infections. This is in comparison to gastrointestinal infections, and this discrepancy is secondary to the fact that IgM, which often increases to compensate for IgA deficiency, is more prominent in the gut.[1] Giardia is the only gastrointestinal infection. However, other gastrointestinal disorders may be present, including malabsorption, lactose intolerance, ulcerative colitis, nodular lymphoid hyperplasia (benign disorder in the small intestine), and celiac's disease. Celiac's disease is diagnosed in 8% of patients with sIgAD and 1-2% of those with celiac's disease have sIgAD. The theory is it is due to a weakened mucosal barrier resulting in impaired protein clearance and possible IgG antibody production versus antigens and foods.[1,3] The association between sIgAD and various allergies or allergic syndromes, found most commonly in the younger population, including asthma, atopic dermatitis, allergic rhinitis or conjunctivitis, urticaria, and drug and food allergies, varies per study. Thus, the true prevalence is unclear. However, approximately 25% of sIgAD is discovered during allergy testing.[1] There are several different theories regarding the relationship between sIgAD and autoimmune disorders: decreased clearance of self-reactive antibodies, independent genetic risk factors, and decreased mucosal barrier causing accumulation of certain antigens, resulting in auto reactive antibodies and autoimmune disease. Approximately 20-30% of IgA deficient patients develop autoimmune disorders, most commonly systemic lupus erythematosus (SLE), Diabetes Mellitus Type I, Grave's disease, juvenile or adult-onset rheumatoid arthritis, immune thrombocytopenic purpura, hemolytic anemia, and possibly myasthenia gravis. Regardless of symptoms, IgA deficient patients have an increased prevalence of autoantibodies. These can cause false positive pregnancy tests secondary to heterophile antibody production. sIgAD is also associated with several other immune deficiencies: CVID, IgG2 subclass deficiency, selective polysaccharide nonresponse, ataxia-telangiectasia, and DiGeorge syndrome. Those with sIgAD may also present with an anaphylactic reaction to blood transfusions. This is because some with undetectable IgA levels produce anti-IgA antibodies to IgA found in blood products, including whole blood, red blood cells, platelets, fresh frozen plasma, cryoprecipitate, granulocytes, and IgA-containing IVIG products.[1,3,6,7] Malignancies, most commonly lymphoid and gastrointestinal, occur sporadically, usually in the older population. However, there is not enough evidence to support a significantly increased risk of malignancy in these patients.[1,8,9]

Diagnosis of sIgAD is often incidental given most are asymptomatic. However, it normally involves a combination of clinical history and laboratory evaluation. The following patients should be tested: children with recurrent otitis media, sinusitis, and pneumonia ≥ 6 months old as maternal immunoglobulins disappear around this age; any adult with recurrent or chronic sinusitis or pneumonia; those of any age with 1 or more of the following: absent or decreased serum IgA levels, celiac disease, Giardia, unexplained and recurrent autoimmune disease, family history of IgA deficiency and/or CVID, or an anaphylactic reaction to a blood transfusion. This disease is defined by isolated low serum IgA levels in patients ≥4 years old, with exclusion of other causes of hypogammaglobulinemia, and is considered a severe, definitive deficiency if serum IgA levels <7 mg/dL (0.07g/L), and a partial, probable deficiency if >7 but two standard

deviations below normal for age.[1,2] Thus, initial laboratory testing includes: a repeat serum IgA level, serum IgM level, and serum IgG level. Other labs that can be ordered according to the patient's symptoms include CBC with differential, antibody tests, ESR, CRP, and total serum IgE. For a patient with recurrent infections, the following should be considered: CBC with differential, total hemolytic component (THC or CH50 assay) to screen for other immunodeficiencies, sinus/chest imaging, and vaccine response (not required for diagnosis but if impaired can treat with immunoglobulin and monitor for CVID).

The differential diagnosis sIgAD includes the aforementioned immunodeficiences, as well as transient hypogammaglobulinemia of infancy prolongation of the physiologic hypogammaglobulinemia, usually manifesting around 3-6 months old. The definition varies from decreased IgG and/or other immunoglobulin deficiencies but can also present as sIgAD. Vaccine response is intact. However due to varying definitions, this diagnosis is often differentiated from sIgAD by using four years as the cut off age. Evolving CVID is defined by a serum IgG deficiency and IgA deficiency or IgM deficiency and impaired vaccine response. These patients also have recurrent infections along with other conditions associated with CVID.[7] There are also multiple drugs that can decrease various immunoglobulin levels but are usually reversible with discontinuation of the medication. These include anticonvulsants, captopril, sulfasalazine, fenofenac, gold, thyroxine, and cyclosporine (can result in permanent sIgAD).[10]

Treatment depends on symptoms, severity, and underlying etiology. In asymptomatic, incidentally diagnosed partial sIgAD, no treatment is required except for education and periodic serum IgA, IgM, and IgG levels. However, those with partial sIgAD with a previous anaphylactic blood transfusion reaction and severe asymptomatic or symptomatic sIgAD, should wear a medical alert bracelet stating the diagnosis and that there is an increased risk for an anaphylactic reaction to blood products and should be checked for anti-IgA antibodies if a blood transfusion is necessary. If blood transfusion is unavoidable, the patient should receive washed red blood cells or be desensitized to the blood products.[1,6,11] In those with symptomatic sIgAD, the underlying disorder should be tested, including prophylactic antibiotics (daily over a six month period or seasonal), and intravenous or subcutaneous immunoglobulin with smallest amount of IgA, if they fail prophylactic antibiotics or have other associated immunodeficiencies. Although it does not replete IgA, it provides pathogen specific IgG.[1,6] Whether or not the patient is symptomatic, all medications that may be causing sIgAD should be discontinued. In terms of preventive health measures, all should receive the pneumococcal vaccine. For asymptomatic partial sIgAD, there are no restrictions to live vaccines. For severe sIgAD the following live vaccines should be avoided: oral polio, BCG, and yellow fever vaccines. All other live vaccines are safe. If immunodeficiency evaluation is pending, avoid all live vaccines until complete given many other live vaccines are contraindicated if other immunodeficiencies exist.[12] Cancer screening should proceed as in healthy patients, as overall, there is no increased risk for malignancy.[9] Prognosis varies, but it does not correlate with severity of sIgAD. Unless severe, it can resolve in children, but is more likely than adults to progress to CVID. There are no well-defined studies involving prognosis of adults. Overall it is good if no significant disease.[1]

Conclusion

Despite selective serum IgA deficiency being the most common immunodeficiency worldwide, the physiology and function of IgA are not clearly understood, and thus the inheritance patterns and pathophysiology are uncertain. Until then, screening should continue per guidelines recommended above, as should treatment of associated infections, diseases, or immunodeficiencies, and periodic follow up.

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