

Clinical assessment and management of abnormal IgA levels

Frederick M. Schaffer, MD

INTRODUCTION

In this fourth article of the mini-series dealing with ambulatory diagnoses of immunodeficiency disorders,¹ we discuss issues encompassing IgA deficiency, clinical associations, and the use of blood products in this patient population.

DETERMINATION OF SERUM IgA CONCENTRATIONS

Nephelometry is an automated method used to measure serum antibody concentrations; however, accuracy at low serum antibody concentrations has been a long-standing issue.² The interpretation of IgA levels depends on comparison with age-matched controls. An immunoglobulin level within 2 SDs of the mean value for age-matched controls is considered normal. Nephelometric determinations for IgA levels less than 10 mg/dL usually are not reliable.² Because normal IgA concentrations greater than 10 mg/dL are not achieved until approximately 6 months of age, nephelometric determinations are not accurate in this age range.^{3,4}

Physicians might consider an initial IgA serum determination using nephelometry at a local institution. If the result is less than 2 SDs below the age-matched mean value and is less than 10 mg/dL, then a second, more sensitive, confirmatory determination may prove to be informative. The Mayo Clinic can accurately determine serum IgA levels less than 2 mg/dL by incorporating additional dilution curves to develop a more accurate calibration curve. The volume of serum required for an IgA determination is 1.0 mL, which should be refrigerated during storage and express mailed on ice. An additional source is IBT Laboratories, where IgA concentrations are accurately quantified down to 7 mg/dL. The results are available within 24 to 48 hours of receipt of the specimen from both laboratories.

It is important to determine whether your local laboratory is using age-matched control values. Not all hospital or

commercial laboratories use age-appropriate values. For example, adult concentrations of serum and secretory IgA are achieved between 6 and 8 years of age.^{2,3} It is not uncommon to receive a laboratory result for a patient younger than 6 years with an IgA concentration less than 2 SDs below the mean value when adult control values are used.

IgA DEFICIENCY

IgA deficiency is the most common primary immunodeficiency disorder, affecting 1 in 700 individuals of European extraction.⁵ IgA deficiency is a genetic disorder with a heterogeneous clinical presentation. This heterogeneity, in part, is reflected in the extent of an arrest in B-cell differentiation and in some cases an associated cellular immune defect. IgA deficiency and common variable immunodeficiency (CVID) have been postulated to be at opposite poles of the same spectrum of humoral immunodeficiencies.⁶ In fact, we previously demonstrated that CVID and IgA deficiency have common putative susceptibility genes.^{7,8} Furthermore, the central immunophenotype in both disorders is a common arrest in B-cell differentiation.⁵ These findings further support the concept of clinically related disorders. With this common genetic basis, physicians can readily identify members of extended pedigrees manifesting CVID or IgA deficiency.⁷ Furthermore, in some cases, individuals identified as having IgA deficiency have progressed with time to CVID.⁸ In addition, the offspring of mothers with IgA deficiency or CVID should be periodically tested to determine whether they might develop either primary immunodeficiency disorder.⁹

Selective IgA deficiency is characterized by an IgA serum concentration less than 5 mg/dL, with normal concentrations of the other immunoglobulin classes.¹⁰ In contrast, partial IgA deficiency is associated with a serum IgA level less than 2 SDs below the normal mean value. Similar to selective IgA deficiency, most cases of partial IgA deficiency are also associated with normal concentrations of the other immunoglobulin classes. Most individuals with selective or partial IgA deficiency are asymptomatic. Approximately 20% of IgA-deficient individuals have a concomitant IgG subclass deficiency. These individuals usually present with recurrent sinopulmonary infections, unlike their counterparts with either selective or partial IgA deficiency.¹¹

Affiliation: Section of Pulmonary, Allergy, and Immunology, Department of Pediatrics, Medical University of South Carolina, and National Allergy, Asthma, and Urticaria Centers of Charleston PA, Charleston, South Carolina.

Disclosures: Author has nothing to disclose.

Funding sources: Funded by an unrestricted educational grant from Talecris Biotherapeutics.

Received for publication July 26, 2007; Received in revised form August 9, 2007; Accepted for publication August 9, 2007.

SECONDARY CAUSES OF LOW IgA CONCENTRATIONS

Environmental factors can induce an arrest in B-cell differentiation, which results in IgA deficiency and, less often, CVID. Intrauterine infections, such as rubella, cytomegalovirus, and toxoplasmosis, have been associated with the development of IgA deficiency.^{12,13} Often, the induced IgA deficiency is transient, with full normalization occurring after effective treatment. Some older individuals (without X-linked lymphoproliferative disorder) have acquired transient IgA deficiency after an Epstein-Barr virus infection.

Medications used for the treatment of seizure disorders, rheumatologic disease, and inflammatory bowel disease have been associated with the development of IgA deficiency. The most compelling example is the IgA deficiency induced in 20% to 40% of patients treated with phenytoin for a seizure disorder.^{14,15} Of note, persistence of the IgA deficiency depends on continued use of the medication. Furthermore, some researchers have suggested a genetic predisposition in drug-induced antibody-deficiency disorders. These genes may be the same or may interact with the putative genes associated with IgA deficiency.⁵

TREATMENT OF IgA DEFICIENCY

Theoretic IgA antibody replacement therapy is not generally recommended, and, in fact, it can prove to be life threatening. The infusion of IgA-containing blood products is not favored owing to the short half-life of serum IgA (<6 days). In addition, theoretic serum IgA replacement tends not to be an effective source for generating secretory IgA. In most cases, patients with IgA deficiency are clinically asymptomatic. Thus, in general, antibody replacement therapy is not indicated. However, there is a select group of IgA-deficient patients with functional antibody deficiencies and recurrent sinopulmonary infections who merit treatment. This patient population tends to be individuals with a concomitant IgG subclass deficiency. In this patient population, some do well with a course of prophylactic antibiotics; however, some require antibody replacement therapy (ie, intravenous gammaglobulin [IVGG]).

IgA DEFICIENCY TREATMENT AND THE DEVELOPMENT OF ANTI-IgA ANTIBODIES

The infusion of IgA-containing blood products, such as IVGG or packed red blood cell (PRBC) transfusions, may lead to anaphylactic reactions as a consequence of the development of anti-IgA antibodies.¹⁶ This most often occurs in the IgA-deficient population with a concomitant IgG subclass deficiency. These anti-IgA antibodies are usually of the IgG or IgE isotype.¹⁷ Determinations of pretreatment anti-IgA antibody titers may help discern the risk of subsequent anaphylactic reactions.¹⁴ Specifically, the American Red Cross has provided services to determine the presence and titers of anti-IgA antibodies of the IgG isotype. However, there currently are no commercially available laboratories that will determine anti-IgA antibodies of the IgE isotype.

For patients who either fail treatment with prophylactic antibiotics or are deemed to necessitate treatment with IVGG, it is important to use an IVGG preparation that contains the lowest levels of IgA (eg, Gammaguard and Polygam; Baxter Health Care Corp, Deerfield, Illinois). Both products are reported to contain less than 2.2 $\mu\text{g/mL}$ of IgA in a 5% solution. Note that although these products have low IgA concentrations, there is variability. Thus, it is recommended to select and reserve a stock of IVGG with the lowest IgA concentration available. In this manner, the physician will be providing an IVGG product with the least potential for generating anti-IgA antibodies. Periodic evaluation for the development of anti-IgA antibodies is recommended to anticipate a greater propensity to develop an anaphylactic reaction during subsequent infusions. In addition, all patients with IgA deficiency should be advised to wear medic alert bracelets describing their disorder.

IgA-deficient patients who require blood product infusions, such as PRBCs, will have a minimal risk of developing an anaphylactic reaction if either double-washed PRBCs or matched blood acquired from a donor with IgA deficiency is administered. These patients could also have their own PRBCs and plasma stored for potential future use.¹⁸ Some IgA deficiency disorders are also associated with defects in cellular immunity (eg, ataxia-telangiectasia). Live viral vaccines should not be administered to these individuals if the T-cell deficiency persists.⁵

DISORDERS ASSOCIATED WITH IgA DEFICIENCY AND ELEVATED SERUM IgA CONCENTRATIONS

The clinical consequences of IgA deficiency are variable. Some individuals with IgA deficiency have recurrent infections, autoimmune disorders, gastrointestinal disorders, atopy, and malignancies. Individuals with IgA deficiency are susceptible to sinopulmonary infections. The recurrence of pneumonia, in some cases, has resulted in bronchiectasis.¹⁹ There have been several cases of systemic infectious disorders reported, such as viral hepatitis, bacteremia, and meningoencephalitis.^{20–22}

The most common autoimmune disorders are rheumatoid arthritis and systemic lupus erythematosus, which may be manifested in as many as 7% of IgA-deficient individuals.^{23,24} Of note, the IgA-deficient status only plays a role in the severity of arthritis in juvenile rheumatoid arthritis.⁵ The treatment of autoimmune disorders in individuals with IgA deficiency, in most cases, follows the same regimen established for patients with normal IgA concentrations.

Gastrointestinal disorders, such as celiac disease, pancreatic insufficiency, disaccharidase deficiency, inflammatory bowel disease, nodular lymphoid hyperplasia, and pernicious anemia, have been associated with IgA deficiency.⁵ Also, IgA deficiency tends to predispose those with allergic disorders to a more severe clinical course.^{5,25} Individuals with IgA deficiency have an increased risk of malignancies. Most commonly identified are gastric and colonic adenocarcinomas. However, other malignancies encountered include leukemia,

melanoma, ovarian carcinoma, hepatoma, and malignant thymoma.⁵

Elevated levels of IgA are consistent with determinations greater than 2 SDs above the mean normal value. Elevated concentrations are not specific to one disease entity. The differential is rather extensive, and some examples include perinatal human immunodeficiency virus type 1 infection, glomerulonephritis with mesangial IgA deposition, hyper-IgD syndrome, diabetic nephropathy, hepatitis, myeloma, plasma cell leukemia, and eosinophilic fasciitis.

ACKNOWLEDGMENT

I thank Dr Chitra Dinakar for her valuable editorial comments.

REFERENCES

1. Dinakar C. Practical aspects of ambulatory diagnoses and management of immunodeficiency disorders. *Ann Allergy Asthma Immunol.* 2007;99:201–202.
2. Isaacs D, Altman DG, Tidmarsh CE, Valman HB, Webster AD. Serum immunoglobulin concentrations in preschool children measured by laser nephelometry: reference ranges for IgG, IgA, IgM. *J Clin Pathol.* 1983;36:1193–1196.
3. Stiehm ER, Fudenberg HH. Serum levels of immunoglobulins in health and disease: a survey. *Pediatrics.* 1966;37:715–727.
4. Burgio GR, Lanzavecchia A, Plebani A, Jayakar S, Ugazio AG. Ontogeny of secretory immunity: levels of secretory IgA and natural antibodies in saliva. *Pediatr Res.* 1980;14:1111–1114.
5. Schaffer FM, Monteiro RC, Volanakis JE, Cooper MD. IgA deficiency. *Immunodef Rev.* 1991;3:15–44.
6. Schaffer FM, Palermos J, Zhu ZB, Barger BO, Cooper MD, Volanakis JE. Individuals with IgA deficiency and common variable immunodeficiency share polymorphisms of major histocompatibility complex class III genes. *Proc Natl Acad Sci U S A.* 1989;86:8015–8019.
7. Volanakis JE, Zhu ZB, Schaffer FM, et al. MHC class III genes and susceptibility to IgA deficiency and common variable immunodeficiency. *J Clin Invest.* 1992;89:1914–1922.
8. Ashman RF, Schaffer FM, Kemp JD, Yokoyama WM, Cooper MD, Volanakis JE. Genetic and immunologic analysis of a family containing 5 patients with common variable immunodeficiency or selective IgA deficiency. *J Clin Immunol.* 1992;12:406–414.
9. Schaffer FM, Newton JA. Intravenous gamma globulin administration to common variable immunodeficient women during pregnancy: case report and review of the literature. *J Perinatol.* 1994;14:114–117.
10. Clark JA, Callicot PA, Brenner NA, Bradley CA, Smith DM. Selective IgA deficiency in blood donors. *Am J Clin Pathol.* 1993;80:210–213.
11. Oxelius VA, Laurell LB, Lindquist B, et al. IgG subclasses in selective IgA deficiency: importance of IgG2-IgA deficiency. *N Engl J Med.* 1981;304:1476–1477.
12. Soothill JF, Hayes K, Dudgeon KA. The immunoglobulins in congenital rubella. *Lancet.* 1966;1:1385–1388.
13. Rosen FS. Immune deficiencies: an overview. In: Gelfand EW, Dosch HM, eds. *Biologic Basis of Immunodeficiency.* New York, NY: Raven Press; 1980:1–14.
14. Sorrell TC, Forbes IJ, Burness FR, Rischbieth RHC. Depression of immunological function in patients treated with phenytoin sodium (sodium diphenylhydantoin). *Lancet.* 1971;2:1233–1235.
15. Aarli JA. Drug-induced IgA deficiency in epileptic patients. *Arch Neurol.* 1976;33:296–299.
16. Vyas GN, Perkins HA, Fudenberg HH. Anaphylactoid transfusion reactions associated with anti-IgA. *Lancet.* 1968;2:312–315.
17. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gammaglobulin administration in patients with hypogammaglobulinemia: detection of IgE antibodies to IgA. *N Engl J Med.* 1986;314:560–563.
18. Burks AW Jr, Steele RW. Selective IgA-deficiency. *Ann Allergy.* 1986;57:3–8.
19. South MA, Wollheim FA, Warwick WJ, Cooper MD, Good RA. Local deficiency of immunoglobulin A in the saliva of patients with chronic sinopulmonary disease. *J Pediatr.* 1965;67:940–941.
20. Amman AJ, Hong R. Selective IgA deficiency: presentation of 30 cases and a review of the literature. *Medicine.* 1971;50:223–226.
21. Klemola T. Deficiency of immunoglobulin A. *Ann Clin Res.* 1987;19:248–257.
22. Cursons RTM, Keys EA, Brown TJ, Learmonth J, Campbell C, Metcalf P. IgA and primary amoebic meningoencephalitis. *Lancet.* 1979;1:223–224.
23. Cassidy JT, Burt A, Petty R, Sullivan D. Selective IgA deficiency in connective tissue diseases. *N Engl J Med.* 1969;280:275.
24. Pelkonen P, Avilahti E, Makela A-L. Persistent and transient IgA deficiency in juvenile rheumatoid arthritis. *Scand J Rheumatol.* 1983;12:273–279.
25. Buckley RH. Clinical and immunologic features of selective IgA deficiency. *Birth Defects Orig Artic Ser.* 1975;11:134–142.

Requests for reprints should be addressed to:

Frederick M. Schaffer, MD

Section of Pulmonary, Allergy, and Immunology

Department of Pediatrics

Medical University of South Carolina

135 Rutledge Ave

Charleston, SC 29425

E-mail: schaffer@musc.edu

or

National Allergy, Asthma, and Urticaria Centers of Charleston PA

1879 Savage Rd

Charleston, SC 29407