Draft

IIV Working Group: National Children's Study

Proposed Core Hypothesis:

Selective IgA deficiency increases susceptibility to infection, autoimmune disease and atopy

Submitted to Dr. Robert Yolken and Dr. Bill Rodriguez
June 13, 2002

By
Dr. Howard M. Lederman
Division of Pediatric Immunology
Johns Hopkins University School of Medicine
Baltimore, MD 21287-3923

I. Proposed Core Hypotheses

IgA deficiency is a risk factor for the development of chronic/recurrent sinusitis and bronchitis, and may be a modifying factor for limiting the number and severity of gastrointestinal infections.

IgA deficiency is a risk factor for the development of a variety of autoimmune disorders including but not limited to juvenile rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, pernicious anemia and endocrinopathy.

IgA deficiency may increase the penetration of food allergens across the gastrointestinal mucosa, thereby increasing the chances for sensitization and the development of food allergy.

The identification of IgA as a genetic risk factor for the development of chronic/recurrent infections, autoimmunity and/or food allergy may lead to new strategies for the prevention and/or treatment of these disorders.

II. Workgroups

Primary Working Group:
Infection, Immunity and Vaccine Working Group.

Potential Collaborating Working Groups:
Gene-Environmental Interaction
Early Origins of Adult Health
Repository
Immune Deficiency Foundation

III. Contact

Howard M. Lederman
Division of Pediatric Immunology
Johns Hopkins University School of Medicine
Hlederma@jhmi.edu
Phone: 410-955-5883
Fax: 410-955-0229

IV. Public Health Significance

IgA deficiency is the most common primary immune deficiency disease, occurring at a frequency of approximately 1 in 500 individuals. As such, it may be an important genetic modifier for modulating host-environment interactions. However, the importance of IgA to general health remains a controversial issue, largely because there have been no prospective population studies performed to compare the health of IgA deficient individuals with those who have normal levels of IgA.

IgA deficiency has been proposed as a factor in the development of chronic/recurrent sinopulmonary infections, autoimmune diseases such as juvenile rheumatoid arthritis and systemic lupus erythematosus, and food allergies. These are among the most common diseases in the United States leading to significant morbidity and mortality, as well as large health care expenditures.

V. Need for Cohort Study

IgA levels are not performed as a part of general health screening tests, and most patients with this disorder are never identified. Patients with IgA deficiency (defined by the WHO Working Group on Primary Immunodeficiency Diseases as having serum IgA level < 5 mg/dl) have been identified in a variety of ways, leading to divergent views of the importance of IgA to health. Among patients referred to tertiary care clinics for evaluation of chronic/recurrent infections, the prevalence of IgA deficiency is greater than among the general population. Similarly, the prevalence of IgA deficiency is greater among patients with juvenile rheumatoid arthritis (as high as 1 in 20), systemic lupus erythematosus, or inflammatory bowel disease than among the general population. In contrast, a number of population-based studies of blood donors have identified IgA deficient individuals who are entirely asymptomatic. Nobody has performed analyses to compare individuals with low serum IgA (more than 2 s.d. below the mean for age but greater than 5 mg/dl), serum IgA level <5 mg/dl but detectable by low level radial immunodiffusion, and those with no detectable serum IgA. There is only limited information about whether selective IgA deficiency is a congenital defect or is acquired later in life, and whether the IgA deficiency observed in a toddler is a life-long deficiency. Exposure to several drugs, most notably phenytoin, is a known risk factor for the development of selective IgA deficiency, but this association is identified in only a minority of patients. Other risk factors for the development of selective IgA deficiency have not been identified. Data from a prospective population-based cohort is necessary to make progress in this area..

Given that estimated frequency of IgA deficiency (defined as <5 mg/dl) is 1 in 500-600, we expect to identify 167-200 individuals among the cohort of 100,000 live births to be enrolled in this study. If IgA deficiency is defined as serum IgA level more than 2 sd below the mean for age, we expect to identify approximately 5% of the population or 5000 individuals.

VI. Scientific Merit

The mucosal immune system provides protection against the wide variety of microorganisms and antigens that are in constant contact with the respiratory and gastrointestinal mucosa. This host defense system primarily depends upon IgA antibody that is synthesized locally. Secretory IgA comprises approximately 85% of the total immunoglobulin in mucosal secretions such as saliva and milk. Its functions are to neutralize viruses and toxins, inhibit binding of bacterial pathogens, and exclude environmental antigens from penetrating the mucosal surface. Mucosal IgA is only one part of a complex host defense system. In the absence of a prospective study of a well-defined cohort of individuals with selective IgA deficiency, it has been impossible to clearly delineate the importance of IgA to overall health

IgA was defined by the WHO Working Group for Primary Immunodeficiency Diseases as a disorder with serum IgA level < 5 mg/dl (the limits of detection by standard commercial techniques of radial immunodiffusion and rate nephelometry) and no other abnormalities of immune function. The latter definition has evolved as our knowledge of the immune system has increased, but currently requires the exclusion of individuals with abnormalities of serum IgG, IgM or IgG subclasses, and individuals with lymphopenia or clinical abnormalities of cell-mediated immunity. This definition is arbitrary and ignores the issue of individuals with low but detectable serum IgA.

The current understanding of selective IgA deficiency is likely to be skewed by ascertainment biases, since the majority of such individuals have been identified because of a pre-existing clinical abnormality (e.g., recurrent infection, arthritis, failure to thrive). The characteristics of selective IgA deficiency defined in this way include:

- Increased susceptibility to infection
  - Chronic/recurrent sinopulmonary infections
  - Giardiasis
- Increased susceptibility to autoimmune diseases
  - Juvenile rheumatoid arthritis
  - Inflammatory bowel disease
  - Pernicious anemia
  - Systemic lupus erythematosus
  - Endocrinopathy, especially involving the thyroid and adrenal glands
- Increased susceptibility to atopic disease
  - Allergic rhinitis
  - Asthma
  - Food allergy
- Increased susceptibility to cancer

There is no other population–based cohort that will be large enough to define the clinical characteristics of selective IgA deficiency.

VI. Potential for Innovative Research

The samples collected in the Repository will allow future analyses of other mutations and polymorphisms that affect immune function and might help to identify those individuals with selective IgA deficiency at highest risk for specific complications (e.g., development of chronic sinopulmonary disease). If such individuals can be identified before they develop symptoms, a number of therapeutic approaches (e.g. additional immunizations to boost other parts of the immune system, or more aggressive therapy of acute infections) could be tested to prevent that complication. It is also expected that as we learn more about immune function, cytokine therapies may become available to increase the levels of IgA in deficient patients. Such intervention strategies could be justified if this study discloses significant health risks for an identifiable subgroup of individuals with selective IgA deficiency.

VII. Feasibility

The prevalence of selective IgA deficiency is estimated to be at least 1 in 600 in the U.S. population. Thus, we expect to identify 150-200 such individuals among this large cohort. The test can be done on a 5-10 ul serum sample, stored either as a dried blot or a frozen aliquot. The most useful specimens for diagnosis will be those obtained at 5 years of age. [To answer questions about age at onset and persistence of IgA deficiency, specimens obtained at (i) age 1-2 years for every subject and (ii) additional longitudinal specimens for those identified as IgA deficient at age 5 years will be useful.] Epidemiologic data, stored serum and DNA will be available for every participant, and no additional specimens or tests are anticipated.

IX. References

Ammann AJ, Hong R. Selective IgA deficiency: presentation of 30 cases and a review of the literature. Medicine 1971; 60:223-236.

Brandtzaeg P. The role of humoral mucosal immunity in the induction and maintenance of chronic airway infections. Am J Respir Crit Care Med 1995; 151:2081-87.

Burgio GR, Duse M, Monafo V, Ascione A, Nespol L. Selective IgA deficiency: clinical and immunologic evaluation of 50 pediatric patients. J Pediatr 1980; 133:101-106.

Cassidy JT, Nord by GL. Human serum immunoglobulin concentrations: prevalence of immunoglobulins deficiencies. J Allergy Clin Immunol 1975; 55:35-48.

Cunningham-Rundles C. Physiology of IgA and IgA deficiency. J Clin Immunol 2001; 21:303-309.

Hammarstrom L, Vorechovsky I, Webster D. Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). Clin Exp Immunol 2000; 120:225-31.

Itescu S. Adult immunodeficiency and rheumatic disease. Rheum Dis Clin North Am. 1996; 22:53-73.

Koistinen J. Selective IgA deficiency in blood donors. Vox Sang 1975; 29:192-202.

Ruff ME, Pincus LG, Sampson HA. Phenytoin-induced IgA depression. Am J Dis Child 1987; 141:858-859.