

Primary immunodeficiency or not? Making the correct diagnosis

Rebecca H. Buckley, MD *Durham, NC*

Making a correct diagnosis of a primary immunodeficiency disease is crucial for the selection of proper therapy. Although many cases go undiagnosed, there are also many instances of incorrect diagnosis that result in years of inappropriate treatment and failure to implement beneficial treatment. This article summarizes 2 actual cases in which incorrect diagnoses led to recommendations of unwarranted high-risk or costly treatments. Had the physicians chosen tests of immune function rather than relying on immunoglobulin levels or cell counts, they would have arrived at the true diagnoses. (J Allergy Clin Immunol 2006;117:756-8.)

Key words: Severe combined immunodeficiency, intestinal lymphangiectasia, T-cell function, common variable immunodeficiency, specific antibody titers, skin prick tests, bacteriophage phi X174

As allergists and immunologists, we see many infants, children, and adults with recurring respiratory or other symptoms suggestive of an underlying problem in host defense. We often order tests of the immune system to exclude those problems. However, it is important to remember which tests are more likely to identify the fundamental problem. In this article I discuss 2 instructive patients who presented to me for a second opinion after receiving diagnoses elsewhere of a primary immunodeficiency disorder but in whom key diagnostic studies of immune function had not been performed.

The first case involved a 6-month-old male infant who was brought in to see me by his parents for a second opinion after he had been given a diagnosis elsewhere of severe combined immunodeficiency (SCID) and his parents had been advised that he would need a chemoablated matched unrelated donor bone marrow transplant. He had a history of recurrent respiratory tract infections beginning at 3 weeks of age, which had been treated with multiple courses of antibiotics. He also began having loose, foul-smelling stools at 2 weeks of age. A 5-week bout of severe

Abbreviations used

IVIG: Intravenous immunoglobulin

SCID: Severe combined immunodeficiency

diarrhea followed a live rotavirus vaccine immunization at age 4 months. Rotavirus was isolated from a stool culture 10 days after vaccine administration. Because of this history, serum immunoglobulin concentrations were obtained, with the following results: IgG, less than 33 mg/dL; IgA, less than 7 mg/dL; and IgM, 12 mg/dL. A complete blood count and manual differential revealed him to be lymphopenic, with an absolute lymphocyte count of 998/mm³. Flow cytometry revealed that he had 17% T cells, 72% B cells, and 4% natural killer cells. No functional immune data were available from the previous evaluation. Physical examination on his first visit to me revealed him to be a well-grown, normal-appearing 6-month-old infant. I obtained a chest radiograph and saw a normal thymic shadow (Fig 1). I also tested his T-cell function, and it was normal (Table I). A repeat IgG measurement after several infusions of intravenous immunoglobulin (IVIG) at the previous hospital was still low at 140 mg/dL. However, we also found that his serum albumin level was low at 1.4 g/dL and that his stool α_1 -antitrypsin level was increased at 370 mg/dL. We subsequently diagnosed intestinal lymphangiectasia by means of endoscopy and biopsy and started him on medium chain triglyceride oil. Six weeks after his last dose of IVIG, his IgG level had normalized at 641 mg/dL, and his absolute lymphocyte count was also normal at 3741 mm³. The teaching point in this patient is that immune function studies are far more important than measuring milligrams of protein or counting cells. In the case of the T-cell functional studies, this is true even if there is no lymphopenia, as in Omenn syndrome, but a clinical picture suggestive of a cellular immunodeficiency. Although lymphopenia and low immunoglobulin levels are certainly concerning for a serious underlying primary immunodeficiency disease, such as SCID,¹ these measurements provide no information about the patient's ability to produce functioning T cells or specific antibodies. The presence of a normal thymic shadow on his initial visit also essentially ruled out SCID. It should be noted that protein-losing enteropathies in older children and adults typically present with a low albumin level and a low IgG level, whereas in young infants with immature gastrointestinal tracts, other

From the Duke University School of Medicine.

Disclosure of potential conflict of interest: The author has declared she has no conflict of interest.

Received for publication November 27, 2005; revised January 9, 2006; accepted for publication January 11, 2006.

Reprint requests: Rebecca H. Buckley, MD, Box 2898 or 363 Jones Building, Duke University Medical Center, Durham, NC 27710. E-mail: buckL003@mc.duke.edu.

0091-6749/\$32.00

© 2006 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2006.01.008

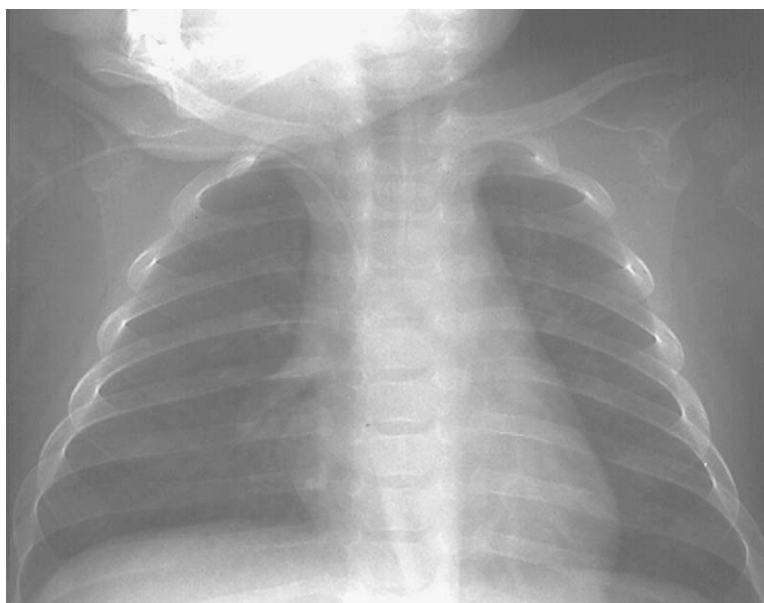


FIG 1. Case 1: chest radiograph showing normal lung fields and a normal thymic shadow.

immunoglobulin isotype levels can also be low, and there can be loss of lymphocytes as well.

By performing the above studies, we saved the infant from a chemoablated matched unrelated donor bone marrow transplantation and all of its associated risks of infection, veno-occlusive disease, graft-versus-host disease, and sterility. Moreover, that treatment would not have helped his underlying disease,^{2,3} whereas the treatment given did.

The second case involved a 17-year-old boy who presented with the chief complaint, "I want gene therapy to cure my common variable immunodeficiency." His mother, a nurse, gave a history that he had been well until 1 year of age, when a urinary tract infection developed. Over the next 6 months, he had recurrent otitis, sinusitis, pneumonia, and impetigo. A diagnosis of common variable immunodeficiency was reportedly made on the basis of IgG subclass measurement, but the actual values were not available. He was started on monthly IVIG at age 18 months and was continued on this treatment throughout the next 16 years. His subsequent infection history was primarily that of central-line infections. He had had 3 or 4 central lines placed over his lifetime for the purpose of receiving IVIG. On his first visit, I asked what his main symptoms were currently, and he noted severe upper airway congestion. On pointed questioning, I learned that he had nasal pruritis and sneezing. I then recommended allergy skin testing. He had 4+ positive skin prick tests to a large number of allergens. I informed him that that was the "good news, bad news" result. It meant that his respiratory symptoms were likely caused by allergy to a wide variety of environmental allergens, but it also meant that his B cells could isotype switch and that he could make specific IgE antibodies to a wide variety of antigens,

TABLE I. Case 1: lymphocyte responses* to mitogens

Stimulant	Patient	Healthy control subject
PHA	123,246	251,560
ConA	59,166	235,090
PWM	66,993	168,170
Medium	2,170	1,382

ConA, Concanavalin A; PWM, pokeweed mitogen.

*Data are presented as counts per minute of tritiated thymidine incorporation into DNA.

suggesting that he might not need IVIG. He also had normal levels of IgA and IgM on his first visit (proteins not present in IVIG). I then immunized him with bacteriophage phi X174, and he had quantitatively normal primary and secondary antibody responses and demonstrated normal isotype switching from all IgM antibodies after the primary immunization to dominantly IgG antibodies after the secondary immunization. I then discontinued his IVIG and started him on a daily antihistamine and intranasal steroids, and he has done well since. After stopping IVIG, we immunized him with standard vaccines and found that he responded to both protein and polysaccharide antigens with normal antibody titers. The teaching point here is that positive allergy skin test responses mean that B cells can produce specific antibodies and that they can isotype switch from IgM to IgE. The presence of normal IgA and IgM levels in his serum was also circumstantial evidence against a diagnosis of an antibody deficiency syndrome. However, the definitive evidence came from the functional antibody studies, that is, the skin prick test results, the bacteriophage immunization results, and, later, the postimmunization antibody titers to standard vaccines. We did not cure him with gene therapy, but

we did correct his diagnosis and started him on the proper treatment.

Unfortunately, too often patients are started on IVIG for a clinical trial before functional antibody studies are performed. Frequently, the initial diagnosis is based on low IgG or IgG subclass levels and not on an inability to produce specific antibodies. When the patient is subsequently seen by other physicians, there is a tendency to continue the treatment. This is in large part due to the fact that one cannot assess the ability to produce antibodies to standard vaccine antigens while the patient is receiving monthly infusions of antibodies from a minimum of 60,000 healthy donors. Because the half-life of IgG is 19 to 21 days, it takes several months after IVIG is discontinued to know whether the antibodies detected in functional antibody tests are actually from the patient or whether they are from the IVIG administered. Thus it is of crucial importance to obtain these test results before IVIG is started. If the patient is receiving monthly IVIG, the only available vaccine that can provide useful information is bacteriophage phi X174, but this vaccine is only obtainable at centers that have applied for an investigational new drug application to the US Food and Drug Administration.⁴ However, as allergists, we have another way to detect endogenous antibody production and isotype switching: skin prick testing to allergens. If the results of the latter are positive, that means that the patient is producing specific antibodies because there is little if any IgE in most IVIG preparations. With positive skin prick test responses, the physician can then feel comfortable in discontinuing IVIG for 3 to 4 months, administering standard vaccine boosters, and then comparing preimmunization

and postimmunization antibody titers to these antigens. The patient could be started on prophylactic antibiotics during this period if the clinical history is unclear. The costs of performing the skin prick tests, giving the booster immunizations, and obtaining the antibody titers are trivial compared with the cost of administering IVIG each month. It should also be remembered that IVIG is a blood product and that although great progress has been made in ensuring the safety of these preparations, there is always the potential of transmitting blood-borne pathogens with them.⁵ Finally, administration of passive antibodies to antigens that the patient has not previously encountered can suppress his or her endogenous capacity to produce antibodies, as clearly shown by the administration of anti-Rh D antibodies to Rh-negative women who carry Rh D-positive fetuses.

REFERENCES

1. Buckley RH. Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. *Annu Rev Immunol* 2004;22:625-55.
2. Waldmann TA. Protein losing enteropathy. *Gastroenterology* 1966;50:422-43.
3. Fuss IJ, Strober W, Cuccherini BA, Pearlstein GR, Bossuyt X, Brown M, et al. Intestinal lymphangiectasia, a disease characterized by selective loss of naive CD45RA+ lymphocytes into the gastrointestinal tract. *Eur J Immunol* 1998;28:4275-85.
4. Ochs HD, Davis SD, Wedgwood RJ. Immunologic responses to bacteriophage phi-X 174 in immunodeficiency diseases. *J Clin Invest* 1971;50:2559-68.
5. Durandy A, Wahn V, Petteway S, Gelfand EW. Immunoglobulin replacement therapy in primary antibody deficiency diseases—maximizing success. *Int Arch Allergy Immunol* 2005;136:217-29.

ON THE MOVE?

Send us your new address at least six weeks ahead

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.

JOURNAL TITLE:

Fill in the title of the journal here. _____

OLD ADDRESS:

Affix the address label from a recent issue of the journal here.

NEW ADDRESS:

Clearly print your new address here.

Name _____

Address _____

City/State/ZIP _____

COPY AND MAIL THIS FORM TO:

Elsevier Periodicals Customer Service
6277 Sea Harbor Dr
Orlando, FL 32887-4800

OR FAX TO:

800-225-6030
Outside the U.S.:
407-363-9661

OR PHONE:

800-654-2452
Outside the U.S.:
407-345-4000

OR E-MAIL:

elspcs@elsevier.com