

Respiratory Infections, Antibody Deficiency, and Gene Mutations

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AN ARTICLE BY CARUTHERS AND KNUTSEN¹ in this issue of *Pediatric Allergy, Immunology, and Pulmonology* describes a patient with an unusual antibody deficiency phenotype and a genotype affecting a gene whose mutations, when present, are usually associated with common variable immunodeficiency (CVID).

The immunologic phenotype of CVID is characterized by an IgG decrease below 2 *SD* plus a decrease in immunoglobulin A (IgA) and sometimes also in IgM concentrations accompanied by abnormally specific antibody production.² The patient described here had normal IgG and IgA concentrations with persistently low IgM levels. He also had abnormally low specific antibodies against pneumococcal polysaccharides.

Clinically this patient presented with recurrent respiratory infections and a history of intermittent thrombocytopenia. Further investigations, including whole genome sequencing, identified a gene mutation not previously associated with an IgM deficiency.

This interesting patient description deserves several comments presented below.

Respiratory Infections: When Should a Primary Immunodeficiency Be Considered?

In this patient, the diagnosis of an antibody deficiency was established at 5 years of age. He had a history of recurrent respiratory infections, including otitis media, sinusitis, and bronchitis since infancy. Information about the exact frequency and severity of these infections was not available. This would be required to apply criteria based on the Jeffrey Modell and other published warning signs for primary immunodeficiency diseases (PID). These suggested warning signs are arbitrary and, if strictly applied, miss many patients with an immunodeficiency. The patient described here should have been evaluated for PID in the first or second year of life based on the description that he was different from normal infants and that his recurrent infections caused a significant problem for him and his parents' quality of life.

What Type of Immunodeficiency Is Most Likely?

There are many PID that manifest themselves early in life. A practical consideration is that the vast majority of these immunodeficiencies either are or have an antibody deficiency as part of their immunologic combined pheno-

type (combined immunodeficiencies).³ Recurrent upper and lower respiratory infections caused by common viral and bacterial pathogens that do usually have a transient response to antibiotic treatment are typical for all forms of antibody deficiencies.

The presence of less frequent pathogens such as *Pneumocystis carinii*, atypical mycobacteria, or fungal infections suggests that a combined immunodeficiency or deficiencies of cellular immunity, phagocytosis, complement, or innate immunity might be present.

The recurrent thrombocytopenia suggested a form of Wiskott–Aldrich syndrome (WAS). This is one of many primary immunodeficiencies in which an antibody or immunoglobulin deficiency is associated with T-cell or other immune function deficiencies. In WAS and several other PID, associated, non-immune abnormalities such as non-immune thrombocytopenia are also present.

The family history of this patient was not provided in this case. Family history is important to orient to specific defects or PID. When evaluating a family history, it needs to be considered that the clinical phenotype for the same genetic defect may be quite different in different family members.

When there is a positive family history for any form of immunodeficiency, an evaluation is indicated even in asymptomatic family members that are at risk but do not become symptomatic. Most gene abnormalities do not cause clinical symptoms until infections and other complications occur. Presymptomatic diagnosis based on family history should always be performed, since most complications can be avoided with proper treatment.

If the history is “negative” for PID in a patient with one or more siblings, the negative history needs to be qualified. If the patient described here would have been the only one of two or more siblings suffering recurrent infections, his history is actually positive, since it rules out environmental or social factors as a cause for the recurrent infections.

How Do We Evaluate a Suspected Primary?

Because of the frequency of predominant antibody deficiencies or combined immunodeficiencies that also have an antibody deficiency, evaluation of antibody-mediated immunity is the most appropriate screening test for the majority of patients in whom a PID is suspected.

In the patient discussed here, the infection phenotype was clearly suggestive of a predominant antibody deficiency.³ These deficiencies include immunoglobulin deficiencies, IgG subclass deficiencies that may have normal total IgG concentrations, and specific antibody deficiencies that have normal IgM, IgG, and IgA concentrations.

For most immunologists, the basic evaluation of antibody-mediated immunity consists of measuring IgM, IgG, and IgA and specific antibodies to polysaccharide antigens, as was done in this patient. These simple tests allow one to diagnose most immunoglobulin deficiencies and also most specific antibody deficiencies with normal immunoglobulins. The evaluation of specific antibodies allows one to define further the immunologic phenotype of immunoglobulin deficiencies by determining the patient's ability to develop relevant specific antibodies. IgG subclass determination can be used as a secondary test when the evaluation of immunoglobulins and specific antibodies does not identify an abnormality.

In this patient, a rare persistent IgM deficiency was identified.⁴ As is the case in most immunoglobulin deficiencies with recurrent infections, specific antibodies to pneumococcal polysaccharides were also abnormal. While IgM deficiency is an accepted diagnosis of an immunoglobulin deficiency, further testing of lymphocyte subsets, including T lymphocytes, B lymphocytes, and memory B cells, helps to define the spectrum of immune abnormalities present in a patient. In particular, low memory B cells (with normal mature B lymphocytes) are associated with clinical severity in CVID and other immunoglobulin deficiencies. In specific antibody deficiencies, very low memory B cells usually are associated with a persistent abnormality in antibody function.⁵

Once the basic evaluation of antibody-mediated immunity identified an immunoglobulin deficiency, testing of other components of the immune system of complement, phagocytosis, and cellular immunity are usually not indicated.

This patient was a male with recurrent thrombocytopenia. While platelets were not smaller than normal and the nature of the thrombocytopenia was not defined, it was reasonable to rule out the presence of a variant of X-linked WAS. Since the clinical and immunologic presentation of WAS is variable, in this case, the WAS protein (WASP) gene sequencing and WASP expression by flow cytometry was appropriate. If a WASP gene mutation and very low WASP expression would have been identified, the prognosis of this patient would have been guarded and stem cell transplantation should have been considered.

What Are the Treatment and Monitoring Options?

The persistent IgM deficiency with specific antibody deficiency and recurrent infections in this patient should be sufficient to indicate either chronic antibiotic treatment or, most likely, a form of IgG replacement therapy. This therapy provides specific IgG antibodies that are helpful even though gammaglobulin preparations have only minimal amounts of IgM and do not restore circulating IgM concentrations.

Monitoring of the effectiveness of IgG replacement therapy in this patient is done clinically. Monitoring of IgM deficiency itself can be done by measuring his immunoglobulin concentrations at 6-month or yearly intervals.

Spontaneous correction of the IgM deficiency is rare; evolution toward a more generalized deficiency including IgG and IgA deficiency suggesting one of the many forms of CVID are possible but occur rarely.

This patient also has a specific antibody deficiency of antipolysaccharide antibodies. This could be the explanation for his recurrent infections and also his positive response to IgG replacement. However, it is important to emphasize that one could have expected the same positive response to IgG replacement if the patient had only IgM deficiency but with normal antipneumococcal antibodies. What we measure and diagnose in these patients is a reflection of a larger problem with their antibody-mediated immunity. Many abnormalities that may affect antibody function cannot be fully assessed with the small number of tests that we are able to perform. The clinical status of a patient should always prevail. Insurance companies and immunologists developing diagnosis and treatment guidelines who would like to have some numeric documentation of the need for IgG replacement need to understand this important fact.

When Is a Molecular Diagnosis Recommended?

In patients with antibody deficiencies in which a genetic basis has not been identified, genetic tests aimed at identifying other known or still unknown genetic abnormalities are not usually required.³ Whole exome sequencing (WES) was performed in this patient on an investigational basis and identified a heterozygous mutation of the gene that encodes for transmembrane activator and calcium modulator and cyclophilin ligand interactor (*TACI*). The mutation identified in this patient has been previously identified in some patients with CVID. *TACI* mutations have also been identified in normal individuals, and many CVID patients do not have this mutation. Therefore, in CVID, the search for a genetic abnormality is only performed on an investigational basis. The unusual immunologic phenotype of this patient clearly justified further investigation.

The identification of a *TACI* mutation using whole genome sequencing in this patient is a suggestion that research of unusual antibody deficiencies should include gene testing. If further IgM-deficient patients have a similar mutation or mutations in the same gene, it may eventually expand our knowledge of the spectrum of antibody abnormalities associated with *TACI* gene mutations.

Conclusions

Patients of any age with recurrent or unusually severe upper and/or lower respiratory infections in the absence of known genetic or anatomic abnormalities predisposing to infections do require an immunologic evaluation. When lower respiratory infections are part of the infectious phenotype, an evaluation should be mandatory to avoid the development of bronchiectasis that adds a further risk factor for recurrent infections.

The most frequent primary immunodeficiencies are predominant antibody deficiencies, including immunoglobulin, IgG subclass, or specific antibody deficiencies with normal immunoglobulins. Most other PID are combined and include some form of antibody deficiency. Therefore, almost all evaluations for immunodeficiency start with an evaluation of antibody presence and function.

Under special circumstances such as very early onset, unusual infections, and/or associated abnormalities, evaluation of cell-mediated immunity, phagocytosis, complement, or innate immunity should be performed.

Increasingly, testing for genetic abnormalities including gene mutations, deletions, duplications, and other complex abnormalities can be performed. These tests should be done or supervised by specialists familiar with the complexities of the interpretation of results obtained with tests such as WES or whole genome sequencing. These tests are an important investigational tool to define further the many phenotypes and genotypes of PIDD, but their inclusion into routine evaluation of immunity at this point is premature.

Author Disclosure Statement

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