



# Diagnosing PIDD in

By Melvin Berger, MD

There are many forms of PIDD, most of which can be diagnosed early and correctly by recognizing the signs and using a variety of testing methodologies.

**P**rimary immune deficiency diseases (PIDDs) are caused by genetic abnormalities that increase patients' susceptibility to infection. Since the immune system cannot readily be seen when we look at a baby or child, most forms of PIDD are diagnosed only after the patient has suffered unusual, severe or recurrent infections. Recognizing those patterns of infection that suggest PIDD

requires awareness and astute observation by primary care physicians. The National Institutes of Health, the Immune Deficiency Foundation (IDF) and the Jeffrey Modell Foundation (JMF) devote considerable effort to raising the awareness of PIDD among physicians and the general public, and they have developed guidelines for the recognition, diagnosis and management of these diseases.<sup>1,2,3</sup>



# Infants

## Diagnosing SCID

The most serious form of PIDD is called severe combined immune deficiency (SCID). The incidence of SCID is about one in 50,000 to one in 100,000 live births.<sup>4</sup> In the 1970s, a patient with SCID whose story has been widely recounted was kept free from infection only by having him live inside a sterile plastic chamber to completely isolate him from all infectious agents. This led to the adoption of the term “bubble boy disease” for SCID. Today, many forms of SCID can now be corrected by stem cell transplantation, gene therapy or enzyme therapy.

SCID is caused by mutations in genes that control the development and most basic functions of the immune system, which makes these patients nearly defenseless. Surprisingly, in most cases, there is no outward sign that a newborn baby has SCID. As a consequence, that child may experience devastating infections that result from exposure to germs that are everywhere in the environment — germs that are harmless to people with normal immune systems. Once a serious or life-threatening infection sets in, expensive and complicated intensive care may be needed, and damage to organs such as the lungs or liver may make subsequent definitive corrective therapy difficult.

There are some conditions that can mimic SCID, but they are not nearly as serious.<sup>5</sup> Therefore, a correct and early diagnosis is extremely important. Fortunately, there are now tests for SCID that can be performed on the dried blood spots obtained from all babies in the U.S., allowing physicians to detect SCID before infection occurs.<sup>6</sup> Essentially all forms of SCID result in very low levels of T cells,<sup>4</sup> and SCID babies have extremely low levels of a unique kind of DNA fragment called T cell receptor excision circles (TRECs), which are formed when T lymphocytes are made. Tests for TRECs performed on the dried blood spots have been adopted in several states to screen newborns for SCID. Once diagnosed with SCID, these babies can receive stem cell transplants that provide them with a new immune system. When stem cell transplants are performed in the first few months of life, the long-term survival rate is greater than 95 percent, and many of these babies can be considered cured.<sup>7</sup>

Unfortunately, only a few states offer newborn screening for SCID. Where screening is not available, awareness by the primary care physician and/or principal caregiver is key. The family history can provide important clues, particularly if male relatives on the mother’s side died or had serious infections in infancy.

## Diagnosing Other Serious PIDDs

Several of the most common PIDDs, including an important form of antibody deficiency known as Bruton’s type of agammaglobulinemia (antibody deficiency), as well as Wiskott-Aldrich syndrome, are called “X-linked” because the mutation that causes the disease is carried on the X-chromosome. Females have two X chromosomes, so even if one has a PIDD-causing mutation, they are usually healthy carriers. On the other hand, males have only one X chromosome, so if that has a mutation, the male will have the disease.

Some serious immune deficiencies such as DiGeorge's syndrome, Wiskott-Aldrich syndrome, hyper-IgE syndrome and others are associated with other abnormalities that may be more readily apparent. Unusual cases of pneumonia, severe or prolonged diarrhea with failure to thrive, and certain skin rashes all can be indicative of serious immune deficiencies.

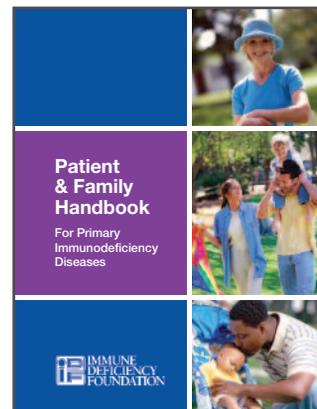
Evaluation of suspected immune deficiencies in infants should include a careful physical exam with documentation of the presence or absence of tonsils and lymph nodes, as well as a search for other abnormalities that might suggest immune deficiency. Laboratory evaluation by the primary care physician should include a chest X-ray for assessment of the presence or absence of the thymus and a complete blood count with differential. The latter test may reveal low numbers of lymphocytes, suggesting a deficiency of T cells or of neutrophils, which are needed for engulfing and killing bacteria and other invaders. It is important to

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compare blood count results against age-adjusted normal values, since babies should have higher numbers of lymphocytes than older children and adults. If these tests suggest a serious PIDD, consultation by an experienced immunologist should be sought without delay.

### **Diagnosing More Common PIDDs**

Full-term infants are born with the same levels of IgG as normal adults, even though they cannot make much antibody



*The Immune Deficiency Foundation offers several publications, including Diagnostic and Clinical Care Guidelines for PIDD and the Patient and Family Handbook for Primary Immunodeficiency.*

on their own, and they have very low levels of IgA and IgM. This is because IgG is transferred from the mother across the placenta during the last three months of pregnancy. This IgG gives some protection to the newborn, so PIDDs that mainly affect antibody production (more than half of all known types of PIDD) are often not detected in early infancy. However, by the time the baby is 4 to 6 months old, the IgG from the mother is metabolized (used up), and babies with antibody deficiencies or PIDDs other than SCID usually will start to have an increased severity and/or frequency of infections after that age. The frequency and severity of infections, though, are highly variable because of differences in exposure to infectious agents. For example, a first-born baby living at home with his or her mother is much less likely to be exposed to germs that cause ear infections and pneumonia than a baby who starts in daycare or preschool at an early age, or a baby who has multiple school-aged siblings. School-aged children (and adults with a high degree of exposure to children and/or each other) are much more likely to be ill with frequent viral and bacterial infections.

As with older children and adults, awareness by the primary care physician is the most important element in appropriate diagnosis and management of these PIDDs. Unfortunately, the diagnosis is often delayed — by as much as 10 years in many cases. The JMF publishes a poster titled the “10 Warning Signs of Primary Immunodeficiency”. These warning signs have been formulated and periodically updated by expert immunologists. The poster is available in both text and cartoon formats, in versions applicable to adults and children, and in many languages.

If multiple and/or particularly severe infections occur in babies and children who also have histories of diarrhea,

poor weight gain and/or failure to thrive, or in adults who are losing weight and/or having unexplained fevers or cough and other lung symptoms, a careful physical exam may reveal additional signs of PIDD, such as the absence of tonsils and lymph nodes (in Bruton's disease), enlargement of the spleen and/or liver, atypical rashes, and/or chronic changes due to infection. Parents or patients themselves who are concerned about the possibility of PIDD may find helpful information on the websites listed in the Sources section of *IG Living*, and may be interested in downloading or requesting a free hard copy of the *Patient and Family Handbook for Primary Immunodeficiency Diseases* from the IDF. That publication is now in its fourth English edition, and it is also available in Spanish and French versions. The JMF also publishes a poster explaining the four stages in the diagnostic evaluation of patients suspected of having PIDD.

As noted above, the initial screening steps such as a complete blood count with differential, a chest X-ray and a test for immunoglobulin levels can be obtained in virtually any practice or community hospital in the U.S. These tests alone usually can distinguish between those patients who can be reassured that they are unlikely to have a PIDD and that their infections are within the range expected for their degree of exposure, those who should be watched more closely, and those who should be referred to an immunologist. Caution must be used, however, to be sure the results are compared with age-adjusted normal values, since the absolute lymphocyte count (obtained from the CBC and differential) and immunoglobulin (IgA, IgG and IgM) levels vary during a child's development into adulthood.

If any physician does not know to whom to refer a suspected PIDD patient, the IDF, the Clinical Immunology Society and the JMF maintain directories of immunologists with expertise in PIDD. The IDF also publishes a booklet titled *Diagnostic and Clinical Guidelines for PIDD*, which is very useful and represents a consensus among experts in PIDD.

The second stage of the diagnostic evaluation includes tests for specific antibodies to immunizations patients should have received as part of the regular childhood immunization schedule.<sup>8</sup> These tests may also involve looking at the specific antibody response before and after certain vaccines like Pneumovax. Blood samples for these tests are frequently sent to large national reference laboratories, but they can be ordered by any doctor. These tests help to distinguish between patients who have low or borderline IgG levels but whose antibody production is really normal, and those who have PIDDs such as common

variable immune deficiency (CVID) and other defects in antibody production.

The third tier of testing involves determination of the numbers of each different type or "subset" of lymphocytes in the blood using a technology called "flow cytometry." This test is usually performed at regional referral centers and often leads directly to a definitive diagnosis of the specific type of PIDD the patient has. This level of testing also includes tests of the lymphocytes' ability to respond to stimulation in the laboratory and/or of the ability of certain white blood cells to generate active oxygen molecules that kill bacteria.

Finally, specific tests and mutation analyses performed in specialized research laboratories can identify the exact molecular defect responsible for many, but not yet all, specific types of PIDD. This information is very useful for genetic testing and for developing a specific treatment plan for each type of PIDD. When developing a treatment plan, the IDF *Patient and Family Handbook for Primary Immunodeficiency* can be an invaluable aid to understanding what the doctors are talking about when they slip into their medical jargon, as well as a guide to knowing what treatment options are available. In addition, the IDF makes

**10 Warning Signs**  
of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. **If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.**

- 1** Four or more new ear infections within 1 year.
- 2** Two or more serious sinus infections within 1 year.
- 3** Two or more months on antibiotics with little effect.
- 4** Two or more pneumonias within 1 year.
- 5** Failure of an infant to gain weight or grow normally.
- 6** Recurrent, deep skin or organ abscesses.
- 7** Persistent thrush in mouth or fungal infection on skin.
- 8** Need for intravenous antibiotics to clear infections.
- 9** Two or more deep-seated infections including septicemia.
- 10** A family history of PI.

This poster is available from the Jeffrey Modell Foundation in both text and cartoon formats.

available a guide for teachers and other school personnel, which can be helpful in ensuring that appropriate provisions are taken when a child with PIDD is in the classroom.

### **PIDDs and Childhood Vaccinations**

Although most of the early childhood vaccines can be given safely to babies with SCID and other PIDDs, a few of these vaccines contain live viruses and should be avoided. The only live vaccines currently recommended for routine childhood immunization<sup>8</sup> in the U.S. are those against rotavirus, measles, mumps and rubella (MMR), chicken pox (varicella/zoster) and the nasal influenza vaccine. Routine diphtheria, tetanus and pertussis (DTaP), injectable influenza, inactivated (Salk) polio vaccine, hepatitis A and B vaccines, and hemophilus and pneumococcal vaccines may or may not be effective in patients with PIDD, but they do not pose special risks for them. If there is any question about the safety of vaccines for any child, a CBC and differential count to rule out lymphopenia (low lymphocyte counts) should be conducted, and inquiries should be directed to an expert immunologist.

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### **Advances and Education Are Key to Diagnosing PIDD**

With modern diagnostic testing, a definitive diagnosis can be made in most cases of PIDD, and the precise molecular defect often can be identified. None of the sophisticated laboratory tests or special techniques will be of any value, however, if PIDD is not suspected and the patient is not referred. The JMF, the IDF and several other professional organizations devote considerable effort to educating physicians about PIDD. However, awareness by the patient's family and the primary care doctor(s) is the



key first step in appropriate evaluation and diagnosis of PIDD. With advances in replacement of IgG and other important proteins, stem cell transplants, and even gene therapy in some cases, there are now many treatments that can help PIDD patients live happy, productive lives. We must all work to ensure that these treatable diseases are recognized and properly diagnosed so the right therapy can be given to the right patient. ■

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### **References**

1. National Institutes of Health. When the Body's Defenses Are Missing: Primary Immunodeficiency. Accessed at [www.nichd.nih.gov/publications/pubs/primary\\_immuno.cfm](http://www.nichd.nih.gov/publications/pubs/primary_immuno.cfm). See also: [www.niaid.nih.gov/topics/immune\\_deficiency/Understanding/Pages/Default.aspx](http://www.niaid.nih.gov/topics/immune_deficiency/Understanding/Pages/Default.aspx).
2. Immune Deficiency Foundation. Patient and Family Handbook for Primary Immune Deficiency Diseases, 4th edition. Accessed at [primaryimmune.org/publications/patient-family-handbook](http://primaryimmune.org/publications/patient-family-handbook). See also: [primaryimmune.org/about-primary-immunodeficiency-diseases](http://primaryimmune.org/about-primary-immunodeficiency-diseases).
3. Jeffrey Modell Foundation. Primary Immunodeficiency Resource Center and 10 Warning Signs of Primary Immunodeficiency. Accessed at [www.info4pi.org](http://www.info4pi.org).
4. Lindegren, ML, Kobrynski, L, Rasmussen, SA, et al. Applying Public Health Strategies to Primary Immunodeficiency Diseases: A Potential Approach to Genetic Disorders. *MMWR Recommendation Report*. 2004 Jan 16; 53(RR-1):1-29. Accessed at [www.ncbi.nlm.nih.gov/pubmed/14724556](http://www.ncbi.nlm.nih.gov/pubmed/14724556).
5. Buckley, RH. Primary Immunodeficiency or Not? Making the Correct Diagnosis. *Journal of Allergy and Clinical Immunology*. 2006; 117: 756-8.
6. Puck, JM. Neonatal Screening for Severe Combined Immunodeficiency. *Current Opinion in Pediatrics*. 2011 Dec; 23(6):667-73.
7. Buckley, RH. Transplantation of Hematopoietic Stem Cells in Human Severe Combined Immunodeficiency: Longterm Outcomes. *Immunology Research*. 2011 Apr; 49(1-3):25-43.
8. Advisory Committee on Immunization Practices. Recommended Immunization Schedules for Persons Aged 0 Through 18 Years. Accessed at [www.cdc.gov/vaccines/recs/schedules/default.htm](http://www.cdc.gov/vaccines/recs/schedules/default.htm).