



Diagnosing PIDD: Problems and Solutions

The words *defiant* and *truant* often are used to describe children, but they very easily can be used to describe difficult-to-diagnose diseases, especially primary immunodeficiency disease (PIDD).

By Kris McFalls

Primary immunodeficiency disease (PIDD) is a very broad term for more than 140 diseases, all of which occur when an individual's immune system fails to function properly. A specific and early diagnosis of a PIDD is the key to getting proper treatment and minimizing permanent tissue damage. However, since the discovery of PIDD, diagnosis has proved difficult and lengthy. A study commissioned in 2007 by the Immune Deficiency Foundation (IDF) showed that, on average, it takes 12.4 years from the onset of symptoms for a patient to be diagnosed with PIDD. But, there may be hope for the

future. The same study showed that diagnoses since the year 2000 have been occurring at a faster rate: an average of 5.5 years since the onset of symptoms.

How long a diagnosis takes depends upon the specific PIDD disease state. Those with more severe PIDDs, such as severe combined immune deficiency (SCID), are more likely to be diagnosed more quickly. For example, the study reports that it takes, on average, 3.1 years to diagnose SCID. That being said, the more severe the disease state, the more serious a late diagnosis will be. For each month after birth an SCID baby goes undiagnosed, the chances of survival decrease dramatically. Going undiagnosed for a year is almost always fatal.

Why is it so hard to diagnose PIDD? Unlike a broken limb, PIDD is not well understood and cannot be diagnosed from something as simple and as routine as an X-ray. And, most PIDDs cannot be diagnosed with a routine blood test. In fact, a PIDD diagnosis is so complicated that it often can be made only by specialty physicians who have the expertise and knowledge not commonly found in the skill-set of primary care physicians (PCPs) and/or pediatricians who are on the front lines of patient care. Many other obstacles also make for a difficult diagnosis, such as poor communication, lack of collaboration between PCPs and specialists, and the current economic environment.

Obstacles to Diagnosing PIDD

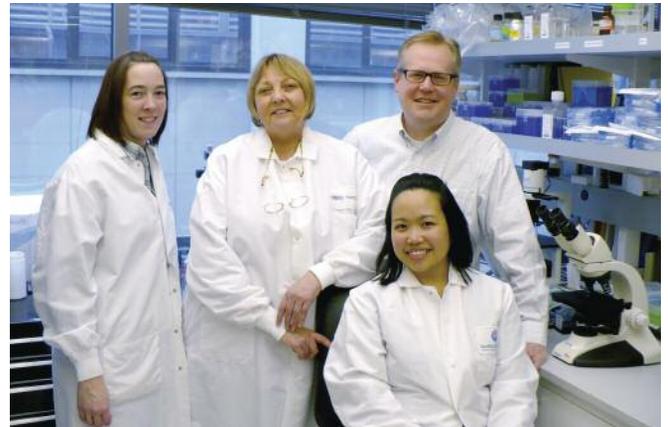
According to Dr. Troy Torgerson, co-director of the Immunology Diagnostic Laboratory Center for Immunity and Immunotherapies at Seattle Children's Research Institute, "Immunology is not well-taught in most medical schools, if it is taught at all." He explains that some medical schools don't even have an immunology department, making teaching medical students about immunology even more difficult. And, because PIDD is a bit esoteric, diagnosing patients without any immunology training is difficult at best.

For the majority of PIDD patients, there is no one cardinal sign or symptom that would lead doctors to automatically suspect PIDD. While doctors are trained in medical school to consider family history when investigating a patient's complaints and symptoms, few PIDD patients report a family history of PIDD. In the 2007 IDF survey, only 17 percent of patients reported having a family history of PIDD prior to their diagnosis.

Therefore, doctors understandably turn to the tools they know best, such as routine blood work, to help guide them in one direction or another. Routine blood work, such as a complete blood count (CBC), can and should immediately set off alarm bells for a small number of severe forms of

PIDD. For instance, babies born with SCID typically have a severely low lymphocyte count, or lymphopenia. However, SCID and other diseases that have obvious hallmark signs make up a very small portion of PIDDs. Therefore, routine blood work may be the start of a workup for the majority of PIDDs, but not much in the routine blood work will lead directly to a PIDD diagnosis.

In addition to blood work, PIDD patients have few tell-tale physical signs that would lead a doctor inexperienced



Stacey Rylaarsdam, Mary Hackett, Dr. Troy Torgerson and Stephanie Anover-Sombke (pictured left to right) at the Seattle Children's Immunology Diagnostic Laboratory Center for Immunity and Immunotherapies play an important role in the Jeffrey Modell Centers Network, which contains more than 100 diagnostic, research and referral centers throughout the world.

in immunology to consider PIDD. Only some of the more severe PIDDs have hallmark signs that should raise a red flag for PCPs. For instance, patients with X-linked agammaglobulinemia (XLA) have no tonsils. Seeing a patient with no tonsil tissue should raise a red flag and prompt further evaluation. And, about 20 percent of common variable immune deficiency (CVID) patients have an enlarged spleen, which also should prompt further evaluation.

Symptoms typically thought of as classic signs of infection, such as a fever, also can be misleading. A fever is often an indicator of infection, but an infection also can be present without a fever, and that infection may be wrongly discounted by PCPs when no fever accompanies it. In fact, many PIDD patients feel the lack of running a fever, despite long-term infections, is a red flag for PIDD that many PCPs miss or poorly understand. Indeed, patients often hear from these physicians that they couldn't be that sick or they would be running a fever.

Dr. Terry Harville, consultant and medical director of the Special Immunology Laboratory at the University of Arkansas, further explains that the lack of ability to mount a fever is not really an indicator of immune disease or even

infection for that matter. Immune deficiency is the result of a dysfunction of adaptive immunity (T and B cells). The ability to run a fever is a function of innate immunity, which includes white blood cells. Therefore, a person with a low white blood cell count or an impaired ability to produce white blood cells also may have trouble mounting a fever, but that does not mean they have a PIDD. Consequently, Dr. Harville states, "We tend not to rely on the febrile response as the main indicator that an infection is present."

Further complicating the picture are the kinds of infections PIDD patients most often get. Probably the most common complaint among PIDD patients is sinusitis brought on by sinus infections. But, sinusitis does not always mean there is a bacterial-caused sinus infection present. Sinusitis is a very common complaint among the normal population, which means PCPs see people with sinusitis every day and consider the cause allergies or a virus. And, because sinusitis is treated as an acute care problem, the patient and doctor are allotted very little time together. Consequently, undiagnosed PIDD patients with chronic sinusitis brought on by bacterial infection as their chief complaint tend to linger in primary care much longer than they should.

The bigger problem for PIDD patients occurs when they present with recurrent infections, but their PCP still does not connect the dots that paint the bigger picture. The PCP may see one hard-to-treat infection, when instead that infection might actually be a series of infections being undertreated. Again, this underscores the importance for doctors and patients to have enough time to spend together to understand the patient's health history.

In addition to a lack of immunology training, the current economic climate adds undue pressure on all healthcare providers. PCPs in particular are under increasing pressure by employers and payers to cut costs, increase efficiency and take more responsibility for chronic care patients who

often have complicated disease states. As a result, patients are given less time with their doctors, and doctors often feel forced to treat all patients with a "treat them and street them" mentality historically used by emergency room personnel.

The results of all of these factors is that PIDD patients go undiagnosed and suffer much longer than necessary, which ultimately leads to decreased health outcomes.

Where Do We Go From Here?

It is hoped that the evolution of electronic medical records (EMRs) will help with many of the problems caused by our current healthcare system. Having access to all of a patient's healthcare records should help all doctors involved with that patient to see the bigger picture. Dr. Torgerson feels that programs such as Microsoft's Health Vault are a step in the right direction, but he cautions that all EMRs need to be accessible to both patients and doctors. In the meantime, he highly recommends patients come prepared with either a

health binder or flash drive containing their medical history, current medications and a health log that details their symptoms and responses to treatment regimens.

Even with the advent of improved recordkeeping, raising awareness and funds for research is still the main key to early PIDD diagnosis and treatment. Nonprofit organizations, such as the Jeffrey Modell Foundation (JMF) and IDF, have committed a lot of resources toward public awareness, campaigns, research and advocacy.

JMF has been the driving force behind the establishment of immunology centers of excellence around the world. Seattle Children's Immunology Diagnostic Laboratory Center for Immunity and Immunotherapies is an important part of the Jeffrey Modell Centers Network (JMCN), which contains several Jeffrey Modell (JM) diagnostic and research centers and JM referral centers throughout the world. Currently, there are more than 100 centers in the JMCN. The next center is planned at Johns Hopkins Medical Center in Baltimore, Md.

Is it just an infection?
You should be suspicious if you have an infection that is...

Severe
requires hospitalization or intravenous antibiotics

Persistent
won't completely clear up or clears very slowly

Unusual
caused by an uncommon organism

Recurrent
keeps coming back
or if it

Runs in the Family
others in your family have had a similar susceptibility to infection

If any of these words describe your infection, the Immune Deficiency Foundation (IDF) recommends that you ask your physician to check for the possibility of a primary immunodeficiency disease. These diseases are caused by genetic defects and can affect anyone, regardless of age or sex. People with primary immunodeficiencies are more susceptible to infections and health problems that lead to serious and debilitating diseases. It is critical to get an early diagnosis and proper medical care.

 IMMUNE DEFICIENCY FOUNDATION

Questions? Contact IDF to learn more.
www.primaryimmune.org • 800.296.4433

Reprinted with permission from the Immune Deficiency Foundation: http://www.primaryimmune.org/idfthink_zebra/materials/zebra_is_it_just_an_infection_infocard.pdf

IDF is a major player in bringing PIDD patients and immunologists together at regional and national meetings, including its national conference to be held June 23 through 25 in Phoenix, Ariz. In addition, IDF is a staunch supporter of patient rights, frequently lobbying on the behalf of PIDD patients in Washington, D.C., to ensure they retain access to immune globulin treatment.

IDF, JMF, SCID Angels for Life Foundation and SCID.net have been instrumental in raising awareness of the need for newborn screening for SCID. Newborn screening is the best way to diagnose babies born with SCID, who when treated at birth have a 95 percent survival rate (see the related story on page 9). Additionally, JMF collaborated on and funded the first statewide screening program in 2008 in Wisconsin. Since that time, the United States Department of Health and Human Services has recommended that all states add SCID to the core screening panel for newborns. Now it is up to each state to adopt the recommendations. For updates on state activities, go to <http://idfscidnewbornscreening.org>.

Professional organizations also are doing their part to raise awareness about PIDD in the medical community. The Clinical Immunology Society for several years has conducted a summer immunology school to teach interested doctors more about immunology. When instructing PCPs, Dr. Torgerson tries to help them spot PIDD with three simple things to look for:

1) Too many or difficult-to-treat infections. This would include patients who require too many antibiotics, unusual antibiotics and recurrent antibiotics.

2) Odd infections. Dr. Torgerson terms this the “Huh?” factor. For example, a nail fungal infection in a young child is never normal. When a PCP finds himself thinking, “Huh, that’s strange, why does this patient have that?” the doctor needs to be encouraged to take the next step and refer that child for further testing.

Finding the genes that cause the diseases can make curing the diseases much more likely.

3) Lymphopenia in neonates (children under 1). This is never normal, and counts below 2,500 could indicate SCID. Low lymphocyte counts in a neonate should always be evaluated with no delay.

What Does the Future Hold?

No matter which PIDD patients have, they all want to know two things: Where did the disease come from? And, when is there going to be a cure? We already can identify the genes for several PIDDs carried on the X gene, such as SCID and XLA. And, now, several researchers are focusing on CVID to identify the gene(s) involved.

Finding the genes that cause the diseases can make curing the diseases much more likely. Dr. Torgerson believes we are getting closer. “I would predict in five years, maybe 10 years, we are going to be doing whole genome sequencing. We are not going to identify every gene that causes immune deficiency, but we are going to identify a whole lot more,” he says. “I would predict that we are going to have an answer for at least a handful of the CVID patients.” But, as Dr. Torgerson cautions, the problem with CVID is that it might be multi-factorial, which will make the most common PIDD also the most difficult disease to figure out.

As the field of immunology continues to progress with more doctors specializing in this area, more research being conducted and more organizations advocating for and taking action to find solutions for an easier and faster PIDD diagnosis, the future can only look better for the growing number of PIDD patients. ■

KRIS MCFALLS is IG Living’s full-time patient advocate.

10 Warning Signs of Primary Immunodeficiency

1. Four or more new ear infections within one year
2. Two or more serious sinus infections within one year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within one 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 primary immunodeficiency disease

Reprinted with permission from the Jeffrey Modell Foundation:
<http://www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=warningsigns&TrkId=24&CFID=38869430&CFTOKEN=86906960>