Quest for the Elusive Diagnosis

By Lauren Gerstmann, MPH

"One of the most widespread diseases is diagnosis."—Karl Kraus in Beim Wort genommen (1955)

IVIG, or intravenous immune globulin, is a very versatile drug. It has been explored as therapy for such diverse conditions as autoimmune disease, immune deficiencies, cancer, neurological conditions and entrenched infectious diseases. IVIG seems to regulate the immune system and to suppress harmful inflammation.

But, in some ways, its versatility can create challenges for the patients and doctors who use it. Since IVIG has so many uses, and because it treats conditions that may also be treated with other drugs, doctors may have trouble deciding when to use it, and insurance companies may be reluctant to approve it. This article will set out some of the most common diagnoses that are treated with IVIG, and it will briefly tell the stories of people who have struggled with these conditions.

The patients' stories illustrate the potential benefits of IVIG and the barriers to having IVIG prescribed and covered by public and private insurers. However, it is important to note that each patient's situation is unique, and IVIG is one of several therapeutic options that can be considered for immunological conditions. Ultimately, treatment choices should be made with the patient's physician.

The Many Uses of IVIG

IVIG can be used to treat both autoimmune disorders and immune deficiencies. Your immune system can malfunction if it becomes overactive and begins attacking your own tissues or nerves (an autoimmune disorder) or it can be lacking a key component to protect you from disease (an immune deficiency). More than 80 autoimmune disorders have been identified.[1] Diagnosis can be time-consuming and difficult, as many of these disorders have overlapping features. But, a correct diagnosis is critical in order to be sure that you receive appropriate treatment. Similar problems with diagnosis affect people suffering from primary immune deficiencies. According to the Immune Deficiency Foundation, ➢

How Are Immunity and Autoimmunity Related?[2, 3]

- One possibility is that immune deficiency makes it harder for the body to rid itself of dead cells, and perhaps those dead cells can contribute to development of an autoimmune response.
- Another possibility is that healthy immature B cells learn to tolerate their own antigens by being exposed to those antigens. If an immune-deficient person does not produce those antigens, and the B cells do not become tolerant, an autoimmune reaction can develop.
- A third possibility involves patients who have low numbers of lymphocytes circulating in their bloodstream (lymphopenia). Lymphopenia may allow T cells to proliferate in an abnormal way, predisposing patients to an autoimmune disease.

[1] US Department of Health and Human Services: National Institute of Health: Autoimmune diseases coordinating committee, NIH Publication 03-5140, December 2002. http://www.niaid.nih.gov/dait/pdf/ADCC_Report.pdf.
[2] Looney, RJ and Uzel, G, *Immunodeficiency Disorders and Autoimmunity* Presentation at the AAAAI Annual Meeting on February 25, 2007.
[3] Uzel, G, *Immunodeficiency Disorders and Autoimmunity* Presentation at the AAAAI Annual Meeting on February 25, 2007.

it can take up to nine years after you start having symptoms for you to get a correct diagnosis of a primary immune deficiency.[4]

One complication is that many people have multiple diagnoses. The relationship between immune deficiencies and autoimmune disorders is still unclear, and there does not appear to be a unifying theory to explain the entire relationship. The bottom line is that if you have an immunological disorder, be it an autoimmune disease or an immune deficiency, you should educate yourself about IVIG and talk with your doctors about it.

The Most Common Condition Treated With IVIG

Primary immune deficiency disease (PIDD)

Ian's Story:

Primary immune deficiency diseases are disorders in which part of the body's immune system is missing or does not function properly. The World Health Organization currently recognizes more than 100 primary immune deficiencies. They are caused by an inherent or genetic defect in the immune system and are not a result of injury, infection or drug use.[5] By far, the most common PIDD is common variable immune deficiency (CVID).[6]

Ian[7] was diagnosed with CVID in November of 2004, after a series of illnesses. As an infant, he was hospitalized for a week with a rotavirus, and his mom, Valerie, thought that they might lose him. She knew something was wrong because Ian was always sick. He would go on antibiotics for an ear infection in his right ear, and without notice his left eardrum would rupture. Between the time Ian was 1 and 3 years old, he had eight sets of tubes surgically placed in his ears to drain the infections. He saw an allergist/immunologist in Washington, who couldn't figure out what was wrong and referred the family to Children's Hospital in Washington. The specialists there concentrated on ruling out cancers (such as leukemia) and cystic fibrosis. Relieved to dodge these bullets, the family moved to California, where Ian did very well—for about nine months. Suddenly, they were back to square one when Ian ended up in the hospital for a week and a half with symptoms similar to viral meningitis. Once again, Valerie thought "we were going to lose him." Three months later, the scenario repeated. The doctors in California repeated all of the same tests that had been run in Washington with no new findings. Eventually, Ian's pediatrician began her own investigations. She decided to run immunological studies, to consult with other specialists, even to get in touch with the Centers for Disease Control. Once she began to close in on the answer, Ian's pediatrician referred him to experts at UCLA.

It took a long time, and several false starts, for Ian to get the correct diagnosis. But, now that he has overcome these barriers, Ian receives IVIG therapy every three weeks. He is a very active kid and a skilled hockey player! Ian told me that since he has been diagnosed and treated, he feels "way better, and can do all kinds of stuff."

Note: See the companion article, "Cracking the PIDD Diagnosis Code" on Page 8.

Diagnosing PIDD

http://www.emedicine.com/med/topic1161.htm

Physical Examination
- Unexplained frequent and severe illnesses of infectious origin

Lab Studies
- Blood work, including immunoglobulin levels, IgG subclasses and measurements of specific antibodies

Imaging Studies
- X-rays and/or CT scans may be useful to monitor lung involvement

Examples of Some Autoimmune Conditions Treated With IVIG

Myositis

Kristin's story:

Myositis is swelling and loss of muscle. A small amount of myositis can be a normal result of exercise. But, in its extreme form, myositis becomes an inflammatory myopathy, an autoimmune disease where the immune system attacks the body's own normal, healthy tissue through inflammation or swelling. All of the diseases that fall under the general term myositis, including dermatomyositis (DM), polymyositis (PM), inclusion-body myositis (IBM), and juvenile forms of myositis (JM or JPM), can cause muscle weakness,

[4] Immune Deficiency Foundation Releases National Statistics on the Treatment of Primary Immune Deficiency Diseases: Results Show Average Time From Onset of Symptoms to Diagnosis a Staggering Nine Years http://www.primaryimmune.org/news/survey_release.pdf.
[5] Immune Deficiency Foundation: *What Is a Primary Immune Deficiency Disease?* http://www.primaryimmune.org/pid/whatis_pid.htm.
[6] Park, CL, *Common Variable Immunodeficiency,* eMedicine—last updated 8/10/2006 http://www.emedicine.com/ped/topic444.htm.
[7] Ian and his mother, Valerie, were interviewed by the author on 2/16/2007.

but each type is different[8], and therapy varies depending on the cause of the myositis, i.e., IVIG is likely not effective for all types of myositis.

Kristin's[9] symptoms began slowly, and then suddenly. When she was 25 years old, she began to feel worn out. Tiredness was easily explained by her busy workload, and she started canceling plans with her friends so she could sleep through the weekend. She felt as though someone was constantly pushing her down. Her doctor listened to her concerns. He ran basic blood work and checked her thyroid, but found nothing wrong. Then her feet began to swell. Again, there was no explanation. Kristin was able to function through the fatigue and discomfort, so she stopped questioning her symptoms. By the time she turned 27, Kristin could no longer keep up with her 60-year-old co-workers when they went for lunchtime walks. One day when Kristin was out shopping, she realized she could no longer walk at all. Convinced she had the flu, she went home to recuperate. But, the next weekend, she could hardly "walk, open my mouth or even use my right arm too much. …My [calf] muscles, jaw muscles and right forearm muscle [were] so tight that I [could] hardly move them. So, as you can imagine, walking, talking, eating, standing, writing… all the everyday stuff [was] extremely painful." She went to the emergency room, but all the doctors could tell Kristin was that she "had a lot of inflammation." They gave her anti-inflammatories and sent her home. When she followed up with her regular doctor, and he realized how inflamed she was, he began to suspect myositis. He checked her creatine kinase levels (a lab test that measures muscle damage), ordered a muscle biopsy, and sent her to a rheumatologist.

Although some types of myositis are treated with IVIG, Kristin uses methotrexate (a drug used in treatment of cancer and autoimmune diseases that works by inhibiting the metabolism of folic acid). Methotrexate, while effective, can—with long-term use—cause damage to the lungs and liver.[10] Three years after she was diagnosed, Kristin began to research IVIG therapy, but the expensive treatment was not covered by her insurance company. Since her muscle deterioration was under control, neither Kristin nor her rheumatologist wanted to take on the challenge of protesting the insurance company's decision. In a difficult situation like this, it might be a good idea to get a second opinion to make sure that you are getting the most effective, but also the safest treatment. Kristin would still like to try IVIG if changes in her insurance policy allow it.

Diagnosing Myositis

http://www.myositis.org/about_myositis/getting_diagnosed.cfm

Physical Examination
- Muscular weakness

Lab Studies
- Aldolase Test
- Antinuclear Antibodies (ANA) Test
- Creatine Phosphokinase Test
- Sed Rate (ESR)

Procedures / Imaging Studies
- Muscle biopsy
- Magnetic resonance imaging (MRI)
- Electromyogram (EMG)

Idiopathic thrombocytopenic purpura (ITP)

Jeff's story:

Idiopathic thrombocytopenic purpura is a rare autoimmune bleeding disorder that is a disease of exclusion. In other words, if you have ITP, your immune system attacks your platelets (a type of blood cell), causing them to be destroyed in your spleen. But, with ITP, you have no known disease process to explain why your immune system is targeting your platelets. ITP can lead to abnormal bruising and anemia.[11]

ITP is difficult to diagnose, because there are many disease processes that could cause you to have thrombocytopenia, or low levels of platelets in your blood. In order to diagnose ITP, you need to rule out all the other potential causes of thrombocytopenia, such as leukemia, myelophthisic marrow infiltration, myelodysplasia, aplastic anemia, pseudothrombocytopenia[12] due to platelet clumping, or adverse drug reactions.

In Jeff's[13] case, his mother, Judy, a new nurse, came home one day to find her 13-year-old son covered in hives "15 inches in diameter. They looked like they were filled with blood, and he was having trouble breathing." ➢

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[8] The Myositis Association: *About Myositis*: http://www.myositis.org/about_myositis/index.cfm.
[9] Interviewed by the author on 2/22/2007. Please also visit her blog, "Muscular Mayhem" at http://www.ktsite.blogspot.com.
[10] RxList: http://www.rxlist.com/cgi/generic/mtx_wcp.htm.
[11] WebMD: Idiopathic Thrombocytic Purpura: http://www.webmd.com/hw/anemia/nord258.asp.
[12] Sandler, GS & Shexneider, K, *Idiopathic Thrombocytic Purpura*, on eMedicine- updated 5/30/2006. http://www.emedicine.com/med/topic1151.htm.
[13] His mother, Judy, interviewed by the author on 2/16/2007.

Jeff had been frequently sick as a child, suffering repeated colds, bronchitis, even pneumonia. But, his doctors had always assured Judy that the illnesses were unrelated. When he developed the hives, Jeff was treated at a local hospital with IV cortisone for a week to open his airways. Eventually, he was transferred to Loyola Medical Center, where he saw several specialists, including a hematologist, who eventually concluded that there was no identifiable cause for his disease, and so defined it as ITP.

Although the cortisone worked, Jeff would have recovered more rapidly with IVIG therapy. But, he was diagnosed too long ago. Even though IVIG use was first documented in the 19th century, it wasn't part of ITP treatment until 1981.[14] Thirty years after Jeff's bout with ITP, he was also diagnosed with common variable immune deficiency (CVID). He has been living with the chronic illnesses associated with CVID for so long that he may never fully recover. But, at last he is receiving IVIG treatments that are improving his quality of life.

Diagnosing ITP

http://www.emedicine.com/med/topic1151.htm

Physical Examination
- Evidence of unusual bleeding or bruising

Lab Studies
- Bloodwork to characterize blood cells, check for autoimmune markers, and rule out Evans syndrome and HIV

Procedures
- Bone marrow aspiration and biopsy

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Kathy's story:

Chronic inflammatory demyelinating polyneuropathy is a rare neurological disorder that may first manifest as progressive difficulty in walking. CIDP causes swelling of nerve roots and destruction of the fatty protective covering (myelin sheath) over the nerves. It is a progressive disorder that causes weakness, paralysis and/or decreased motor function. It can also cause other nerve damage resulting in numbness and tingling. After onset, the progress may be rapid or sporadic, and the end disease-state may vary in severity. Usually CIDP affects people in the same way on both sides of their body. CIDP differs from other similar neurological disorders in that the patient has not necessarily had a viral infection within the three months before the symptoms present. In most cases, there is no family history of other similar disorders or other nerve diseases (such as polyneuropathy).[15]

Like Kristin, Kathy[16] had trouble getting the appropriate diagnosis and getting her insurance to pay for her IVIG. Kathy had been experiencing pain for years that she and her doctor attributed to her weight and her arthritis. In 2000, while she was moving into her new two-story home in Houston, she started having a lot of trouble with the stairs. She kept losing her balance, was weak, and she had a lot of numbness and pain in her foot. She went to see a pain doctor who diagnosed her with a peripheral neuropathy. But none of the medication the pain doctor prescribed worked. So Kathy saw a neurologist who recognized the signs of CIDP. Kathy underwent a biopsy and nerve testing. IVIG, neurontin and lyrica (drugs that treat neuropathic pain), and methadone (a synthetic opiate) were the only things that helped Kathy. Her doctor would not allow her to use steroids because she was borderline diabetic, and it would have upset her glucose balance. When she switched her insurance to Medicare, she could no longer go to her clinic for IVIG treatments. Kathy was directed to the local hospital, but they did not have sufficient IVIG to treat her, and she was told to simply stop her treatments. At that time, she moved to Washington, where she is able to continue her IVIG. Because Kathy was willing to move in order to get her treatments, her condition is stabilized today.

Diagnosing CIDP

http://www.emedicine.com/neuro/topic467.htm &
http://www.gbsfi.com/aboutcidp.htm

Physical Examination
- Difficulty walking
- Abnormal reflexes/sensations

Lab Studies
- Spinal tap
- Blood work to look for markers of infection and autoimmune antibodies
- Urine test
- Genetic testing

Procedures/Imaging Studies
- MRI
- Electromyegram (nerve testing)
- Nerve biopsy

[14] Scheinfeld N & Godwin J, *Intravenous Immunoglobulin*, on eMedicine- last updated 10/11/2006: http://www.emedicine.com/med/topic3546.htm.
[15] Chronic Inflammatory Demyelinating Neuropathy on WebMD: http://www.webmd.com/hw/brain_nervous_system/nord903.asp.
[16] Interviewed by author on 2/22/2007.

Guillain-Barré syndrome (GBS)

Aidan and Matt's stories:

Guillain-Barré syndrome (GBS) is sometimes considered to be an acute form of CIDP. The body's immune system begins attacking the nerve system, and progression can be alarmingly rapid. Often, the muscles become nearly useless, and patients may need the assistance of a respirator to breathe. Given its rapid and dramatic course, GBS can be one of the easier autoimmune diseases to diagnose. Fortunately, with treatment, almost all patients experience a total, or near total, recovery (taking anywhere from a few weeks to a few years).[17]

Aidan[18] was perfectly healthy until he was 10 months old. One day, after he recovered from what appeared to be a normal childhood stomach virus, his mother, Amy, found him lying listless and yellow on the bottom of his crib. After a full work-up, doctors assured Amy that this was an isolated incident of autoimmune hemolytic anemia (AHA). Instead, by the time he was 15 months old, Aidan's platelet count had dropped to nearly nothing. Given that he now had AHA and ITP, Aidan was diagnosed with Evan's syndrome (an autoimmune disease where the immune system attacks both red blood cells and platelets). By the age of 2, Aidan's health had stabilized to the point where his family was able to plan a fishing trip in remote Wisconsin. While there, Aidan became unsteady on his feet. His parents took him to an urgent care clinic, where he was diagnosed as having complications of a previous viral illness. The family left the facility, but later that day Aidan could no longer coordinate his muscles to grab a cup. The family rushed back to the clinic, and Aidan was airlifted to the pediatric intensive care unit at St. Mary's Hospital in Duluth, Minn. An alert neurologist at St. Mary's recognized the classic symptoms of GBS. Sure enough, when Aidan's lab work came back, his proteins were elevated. Immediately, Aidan began the IVIG treatments that put him on the road to recovery.

But, GBS is not always straightforward. When Matt[19] woke up feeling "drunk" and "not right," doctors evaluated him for everything from stroke to brain tumors. Typically, GBS starts with weakening in the legs and symptoms progress vertically up the body. Since Matt was initially affected in the eyes and cranial nerves, no one evaluated him for GBS. With no diagnosis in sight, Matt's wife and friends combed the Internet until they discovered Miller Fisher syndrome, a rare variant of GBS. Miller Fisher matched Matt's symptoms; it became a working diagnosis and a reason to begin IVIG therapy. Almost one year later, Matt has made nearly a full recovery.[20] Both Matt and Aidan illustrate that persistent attention to your symptoms is critical to speed your diagnosis, so that you can get treatment and prevent complications.

Diagnosing Guillain-Barré Syndrome (GBS)

http://www.emedicine.com/neuro/topic598.htm

Physical Examination
- Progressive weakness; typically beginning in the legs and progressing up the body

Lab Studies
- Spinal tap
- Blood work to look for elevated proteins without other markers of infection

Procedures/Imaging Studies
- Spine MRI
- Temperature, blood pressure, heart rate, respiratory capacity, blood gases, and urine output of the patient should be monitored
- Electrodiagnostic studies

Example of a Disease of Unknown Origin That Is Treated With IVIG

Kawasaki disease

Carissa's story:

Kawasaki disease causes high fever and inflammation of the blood vessels (vasculitis) in early childhood. Children develop fever, characteristic rashes, eye complications and can suffer a heart attack or aneurysm even after they have recovered from the acute portion of the disease.[21] Researchers are not sure what causes Kawasaki disease; it may be caused by infection, or it may be an unusual autoimmune response to an infection or toxin.

Kawasaki disease is difficult to diagnose because there is no definitive test for it. Also, it is so rare in the ➢

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17 National Institute of Neurological Disorders and Stroke: NINDS Guillain Barre information page—last updated 2/13/2007: http://www.ninds.nih.gov/disorders/gbs/gbs.htm.

18 Amy, Aidan's mom, interviewed by author on 2/19/2007.

19 Interviewed by Jessica Schulman, PhD, MPH, RD, on 2/1/2007.

20 For more information on Matt's amazing journey, please see "Searching for Miller Fisher" on Page 6.

21 Scheinfeld N & Silverberg N, *Kawasaki Disease*, on eMedicine—last updated 12/12/2006 http://www.emedicine.com/ped/topic1236.htm.

Diagnosing Kawasaki Disease

http://www.emedicine.com/ped/topic1236.htm

Physical Examination

- Fever that doesn't respond to medication or antibiotics
- Rash
- Changes in the conjunctiva of the eyes
- Lip changes/swollen, bright red tongue
- Swollen limbs

Lab Work

- Blood work to rule out other sources of infection

Note: Up to 10-45% of published cases have incomplete or atypical clinical presentations.

United States that many physicians here are not familiar with it. There are characteristic symptoms that physicians can use to diagnose the disease; however, some children may have suggestive heart complications without ever exhibiting all of the characteristic symptoms. Another diagnostic difficulty is that Kawasaki disease mimics other acute infectious diseases in young children and must be distinguished from a more clearly identified bacterial or viral infection.[22]

One evening, Laurisa was alone with her 5-year-old daughter, Carissa, while her husband was out of the country. In the middle of the night, Carissa woke up screaming, and her lymph nodes had swollen to the size of golf balls. She was in tremendous pain. By the next day, Laurisa could not touch her daughter without causing her to scream. Carissa ran a high fever that was not affected by medicine. Initially, her doctor thought it was strep throat. Laurisa demanded a throat culture, even though the doctor felt it was unnecessary. Carissa began antibiotics. But, the next day, she developed a "weird" red and blotchy rash. She became listless, lethargic, and had not eaten or taken in any fluid in two days. Laurisa took her to an urgent care center where a doctor diagnosed her with scarlet fever, treated her with IV fluids and discharged her despite the fact that there was no improvement. By day seven, Carissa's tongue had turned cherry red and swelled to twice its normal size; even the whites of her eyes were red. In tears, Laurisa brought her daughter back to urgent care. The third doctor to examine Carissa was the first to do a complete examination. He took blood work and conducted a full physical. Then, he disappeared. Later, Laurisa learned that he spent three hours conducting research to discover the cause of the mysterious symptoms. When the doctor returned, it was with two other specialists who examined and photographed Carissa. Then they announced that Carissa had Kawasaki disease. Carissa was lucky. By day seven, most Kawasaki patients begin to suffer major organ complications, but, although her diagnosis was difficult and challenging, she began IVIG immediately, and is a healthy teenager today.

In Conclusion

We have looked at a sample of the diagnoses that merit treatment with IVIG. While these diseases may seem wildly different on the surface, each illustrates a different set of circumstances that can happen when your immune system malfunctions. In looking over the diagnostic criteria, there do appear to be some red flags—such as history of unexplained symptoms, unusual infections, unusual weakness and unusual pain. These red flags alone are just that; they are certainly not in themselves diagnostic. And, because they are so nonspecific, getting an accurate diagnosis can be difficult, especially when there is overlap between these diseases. To add to the confusion, certain defects in the immune system are linked with autoimmune disorders, and the reasons why aren't entirely clear. I saw this repeatedly with the people I interviewed. And, I was not interviewing unusual people. Twenty percent to 25 percent of people with the immune deficiency CVID develop symptoms of an abnormal autoimmune response, most frequently immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AHA).[23]

In interviewing Amy, Kathy, Kristin, Judy, Laurisa, Matt and Valerie, I saw one clear theme: You need to push for the thorough examination that will lead to a speedy diagnosis. IVIG may not be the best treatment for every immunological disorder. In any individual case, there may be valid reason for a physician or an insurance company to choose another route. What these stories illustrate is how many different factors can prevent you from getting IVIG even when it is the best way to manage your condition. Early diagnosis is the key to prevent complications, but diagnosis alone is not enough. Once diagnosed, you need to educate yourself about your condition, your therapy options and your insurance policy to make sure that you get the safest and most effective treatment. ■

[22] Burns, JC, The Riddle of Kawasaki Disease, NEJM, Volume 356:659-661 February 15, 2007, Number 7.

[23] Carbonne J, et al, *Partial Response to Anti-CD20 Monoclonal Antibody Treatment of Severe Immune Thrombocytopenic Purpura in a Patient With Common Variable Immunodeficiency.* Annals of the New York Academy of Sciences 1051 (1), 666–671. doi:10.1196/annals.1361.111, 2005.