



Immune Deficiency and A COMPLICATED RELATIONSHIP

THE CAUSES AND EFFECTS OF IMMUNE DEFICIENCY AND AUTOIMMUNE DISEASE MAY HAVE A LOT IN COMMON, AND RESEARCHERS ARE DISCOVERING A LOT OF SIMILAR GROUND FOR STUDY.

By Lauren Gerstmann, MPH

Trying to untangle the relationship between immune deficiency and autoimmune disease is a bit like playing which came first, the chicken or the egg. About 20 percent of people with common variable immune deficiency (or CVID—the most prevalent immune deficiency) have autoimmune complications. And, although it is difficult to get exact statistics, susceptibility to infection is a big part of the burden of autoimmune disease.

At first glance, primary immune deficiencies and autoimmune conditions might seem like opposite sides of a coin. And yet, so many people with ineffective immune systems have autoimmune diseases like rheumatoid arthritis and idiopathic thrombocytopenic purpura (ITP). Conversely, autoimmune patients are frequently sick. Evidence is well-established that autoimmune conditions (and their treatments) are clearly linked to a few very specific infections. And, clinically, doctors and patients report that a major complication for lupus, scleroderma and other patients with autoimmune disease is a generalized increase

in the frequency and severity of all types of infections.

By definition, an immune deficiency is a decreased ability of the immune system to fight infection, whereas autoimmunity is an increased (and abnormal) response of the immune system to tissues or organs in a person's own body. Given that one is a decrease in immune response and the other is a hyperactive immune response, the two would seem like opposite conditions. But, the common theme is that both represent immune system dysfunction. As such, they may be much more closely related than their opposite definitions would imply.

To examine this relationship, let's look at how the body responds to infection. The immune system is a network of cells, tissues and organs that work together to protect the body from infection—generally caused by bacteria, viruses, parasites or fungi. A healthy immune system can recognize and remember millions of different pathogens, and it can produce secretions and cells to match up to and fight each one of them.

HOW THE IMMUNE SYSTEM WORKS

All blood cells, including the white blood cells destined to become immune cells, originate in the bone marrow and then grow into specific immune cell types, such as T cells and B cells (the main types of lymphocytes), and phagocytes. The immune system stockpiles a huge arsenal of cells. Some immune cells (like T cells) take on all comers, while others (like B cells) are trained on highly specific targets.

to the redness, warmth, swelling, pain and loss of function that characterize an inflammatory response.

To work effectively, most immune cells need the cooperation of their comrades. The immune system stores just a few of each kind of the different cells needed to recognize millions of possible enemies. When an antigen appears, those few matching cells multiply into a full-scale army. After their job is done, they fade away, leaving sentries behind to watch for future attacks.¹

Autoimmune Disease

T cells contribute to immune defenses in two major ways: Some (helper T cells) direct and regulate immune responses; others (killer and natural killer—NK—T cells) directly attack infected or cancerous cells and “kill” them by releasing toxic chemicals.

Each B cell is programmed to make one specific antibody that targets an invader cell for destruction. For example, one B cell will make an antibody that blocks a virus that causes the common cold, while another produces an antibody that attacks bacteria that cause pneumonia.

Antibodies are types of immunoglobulins. Different types play different roles in the immune defense strategy:

- Immunoglobulin G, or IgG, works to coat microbes, speeding their uptake by other cells in the immune system. There are four subclasses of IgG.²
- IgM is the first antibody to be made in response to an infection, and it causes other immune cells to destroy foreign substances.³
- IgA concentrates in body fluids—tears, saliva, the secretions of the respiratory tract and the digestive tract guarding the entrances to the body.
- IgE, whose natural job probably is to protect against parasitic infections, is also responsible for the symptoms of allergy.
- IgD remains attached to B cells, and plays a key role in initiating early B-cell response.

Roughly 25 “complement” proteins aid antibodies in destroying bacteria. Complement proteins, which cause blood vessels to become dilated and then leaky, contribute

Clearly, the immune system is a very complex system with many interdependent parts. Because of this complexity, it is easy for part of the system to break down or misfire—causing anything from a simple isolated illness, to a chronic allergy, to a significant immune deficiency that impairs quality of life. For example, more than 50 percent of primary immune deficiency cases involve some sort of failure in antibody production, resulting from a complete absence of B cells (and a resulting complete absence of immunoglobulins) or by a defect anywhere along the line of production that might simply result in an IgG subclass deficiency. The severity of the immune deficiency depends on how much of the immune system remains intact.⁴ One of the most severe presentations is SCID, or severe combined immune deficiency, which involves a major defect in T cell production and function, with contributing defects in B-lymphocytes, and in some genetic types, in NK cell production as well.⁵ Unlike some less comprehensive immune deficiencies, which can be treated with antibiotic therapy or with IVIG, SCID can be treated only by a bone marrow transplant, which is effectively an immune system transplant.

A misfire in the system can cause the immune system to wreak havoc in the form of cancer or autoimmune disease. In autoimmunity, B cells develop antibodies to your own organs and/or tissues, misidentifying parts of the body as foreign invaders. Autoimmune conditions are surprisingly common, as conditions like diabetes or thyroid disease may have autoimmune causes.⁶ Lupus, a systemic autoimmune disease affecting more than 1.5 million to 2 million ➤

Americans, causes inflammation and other damage in one or more organs or organ systems and can distress everything from the skin and joints to the lungs, kidneys, blood, brain or other organs and tissues. Untreated, lupus can have fatal consequences for the kidney, heart and brain.⁷

WHAT IS THE CONNECTION BETWEEN IMMUNE DEFICIENCY AND AUTOIMMUNE DISEASE?

According to Dr. Josiah Wedgwood, chief of the division of Allergy Immunology and Transplantation at the National Institute of Allergy and Infectious Diseases (part of the National Institutes of Health), “there appears to be [quite a bit] of dysregulation of the immune system in people with autoimmune disease,” and clinicians who treat patients with autoimmune disease and immunodeficiency are beginning to notice a similarity in symptoms. In other words, “people with autoimmune diseases have the same problems that people with immunodeficiencies have.” Researchers are beginning to realize that there are a few key genes that are significant in both immunodeficiency and autoimmunity. According to Wedgwood, “Peter [Gregersen]⁸ and others have been investigating the genes that are involved in autoimmune disease. Well, guess what? The genes that they are identifying are the same genes that the people in the primary immunodeficiency field are identifying as the source of primary immunodeficiency!”

Given that many medications used to treat autoimmunity broadly suppress the immune system, it is very difficult to determine whether patients are getting infections because of the disease or because of the cure.

Sometimes, the relationship between the immunodeficiency and autoimmunity is very subtle. Researchers are learning that even though many aspects of the immune system appear to have duplicate functions, in reality, they have a protective effect that is difficult to tease out. As Wedgwood puts it, “If your T cells are working well, and your antibody response isn’t so good, you’re probably OK” —or at least you seem to be OK when you are fighting a routine infection. “But, under the same circumstances, it may be that because your antibody response isn’t so good, if you are exposed to a similar thing, you may develop an

antibody that you really don’t want to have: autoimmune disease. You survived the infection, but you get an autoimmune disease.” One of the main culprits here may well be Epstein-Barr virus, the same virus that can cause mononucleosis. In susceptible individuals, it may play a role in the development of many different autoimmune diseases, including rheumatoid arthritis and lupus.⁹

Immune deficiencies offer researchers a unique opportunity to study the function of the immune system. We know that there are a handful of immunodeficiencies (polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), Omenn syndrome, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), autoimmune lymphoproliferative syndrome (ALPS) and C1q deficiency) that are very tightly linked with very specific autoimmune conditions.¹⁰ The reason that this is helpful is due to a concept called “penetrance.” Penetrance is another way of explaining your risk of getting a condition if you have the genes that are responsible for that condition. The immune deficiencies listed above have a very high penetrance; individuals are almost 100 percent sure to have one of these conditions if they have the genetic defect responsible. But most autoimmune deficiencies have a much lower penetrance, which can make it really difficult for researchers to find the genes responsible for them. In these specific immunodeficiencies, we already know quite a bit about the responsible genes. And, because we know a great deal about the genetic defects responsible for these conditions (and their autoimmune consequences), they can give us a lot of insight into what is causing other kinds of autoimmune conditions.

WHY DO PEOPLE WITH IMMUNE DEFICIENCY OFTEN HAVE AUTOIMMUNE COMPLICATIONS?

A working immune system is filled with redundancies; often multiple players have the same or similar function. For that reason, many members of the general population might have, for example, an IgA deficiency with no clinical symptoms. The immune system is also filled with a series of checkpoints (checks and balances, if you will) to make sure that the immune cells being produced are healthy and functional. It turns out that something like three-quarters of newly formed B cells are autoreactive,¹¹ which is just a way of saying that a majority of brand-new B cells are destined to attack the organs of the body rather than infectious invaders. But, at various points in their development, these autoreactive cells are destroyed. Failure at any of these checkpoints can cause autoimmunity. One reason people with immune deficiencies might have more

autoimmune issues may be that, in addition to generalized B cell dysfunction, they may also have defective elimination of autoimmune B cells.¹²

Interestingly, IgA deficiency, one of the more common immune deficiencies, is associated with a variety of autoimmune conditions, including rheumatoid arthritis, systemic lupus erythematosus, pernicious anemia and ITP. Even when they don't have symptoms, blood samples from patients with IgA deficiency often reveal autoantibodies.¹³ However, we don't yet know if IgA deficiency in fact causes the autoimmunity, or if it is something that simply commonly coexists with autoimmunity. The association might be explained by the fact that when individuals with IgA deficiency get certain infections, they are later more likely to develop autoimmune consequences. But, research has not yet demonstrated this conclusively.

WHAT IS THE RELATIONSHIP BETWEEN AUTOIMMUNE DISEASE AND INFECTION?

While it may seem obvious that a missing piece of your immune system weakens your ability to fight infection, the relationship between autoimmune disease and infection is more complicated. There is evidence that some infections may cause or set off an autoimmune disease. There also is evidence that autoimmune disease may make patients vulnerable to infection either because the disease wreaks havoc with the patient's immune system or because drugs taken to treat the disease (like steroids) can weaken the immune system. In addition, there is evidence that autoimmune disease may protect the patient from infection. And, there have even been a few case studies where it seems as though an infection has sent an autoimmune disease into remission!

Given that many medications used to treat autoimmunity broadly suppress the immune system, it is very difficult to determine whether patients are getting infections because of the disease or because of the cure. And, there are some very disturbing reports of specific illnesses that can be directly linked to immunosuppressive drugs. For example, one of the known side effects of certain drugs that target tumor necrosis factor (or anti-TNF drugs) is that in rare cases, patients become susceptible to progressive leukodystrophy (PML), which is fatal. And, now, we are learning that there are other immunosuppressive drugs that might carry this risk. According to Wedgwood, "there are now reports associated with Rituximab in the treatment of a number of autoimmune diseases and again very recently with the use of a drug called Efalizumab in the treatment of psoriasis." As he explains, PML "is the result of the presence of an

unchecked virus that is present in the brain of a large number of us, probably including you and me. With a normal immune system or a relatively normal immune system, you manage to control the virus. But, when you are treated with these agents that blunt your immune system, you lack the ability to control the infection and you get these horrible sequelae. It doesn't happen to most people, [but] it can happen to a few, and obviously it can be devastating."

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In fact, many physicians and researchers believe that it is not merely these treatments that make autoimmune patients more susceptible to infection. And, according to Wedgwood, reports dating back to the 1950s (prior to modern treatment protocols) show that patients with autoimmune conditions were suffering a disproportionate number of infections before they began treatment. With modern treatment protocols, however, we do not find untreated patients in the literature. And so, it becomes very difficult to ascertain the role of autoimmunity itself on susceptibility to infection.

One of the recent breakthroughs in our understanding of autoimmunity comes from a new study by Isnardi,¹⁴ who according to Wedgwood, has discovered that "there is a control point in the development of autoantibodies produced in the cell that is defective in a number of individuals with primary immunodeficiencies, and that probably that defect ... is present in people with autoimmune disease."

WHAT ROLE DOES IVIG PLAY IN IMMUNE SYSTEM DYSFUNCTION?

Immune globulin therapy (IVIG) is used to support the immune systems of people with immune deficiencies, but also to regulate the immune systems of people with certain kinds of blood cancers (like leukemia and lymphoma) and people with autoimmune conditions.¹⁵ In immune deficiency, IVIG can be a replacement for what the body is missing. In autoimmune or inflammatory disease, IVIG serves more of a regulatory function, interacting with various parts of the immune system to help them work more appropriately. Interestingly, the dosing is very different in these conditions.¹⁶ People with primary immune deficiencies need a much ➤

smaller dose of IVIG to manage their symptoms than do people who are using IVIG to manage an inflammatory or autoimmune condition.

Research regarding how this might impact someone who has both an immune deficiency and a significant autoimmune condition is limited to case reports (there aren't any big clinical studies). But, the case reports do indicate that a regular replacement dose of IVIG can help control autoimmune arthritis.¹⁷ A mother whose daughter has both CVID and rheumatoid arthritis, and who receives dosing at the immunodeficiency level, says that level of dosing seems to help manage her daughter's arthritis symptoms. It doesn't get rid of the pain, but it makes it manageable. When her daughter gets sick, her pain intensifies. When IVIG controls her infections, it helps prevent her pain flare-ups. But, even on a day-to-day level, IVIG blunts the pain a bit. When the daughter was on SCIG (subcutaneous immunoglobulin therapy, which kept the amount in her system more constant), her pain was still there, but it was better controlled.

CONCLUSIONS

This overview of the current thinking on the relationship between immune deficiency and autoimmunity, and what that relationship means for vulnerability to infection, is really broad. Research in this area is often condition-specific, even gene-specific. Frequently, the research is sharply separated by field—with immunology researchers being distinct from rheumatology researchers—which can make it hard to synthesize the latest knowledge.

Further complicating the picture is that the terms “immune deficiency” and “autoimmune condition” are extreme

generalizations. The World Health Organization has identified more than 80 kinds of primary immune deficiency diseases,^{18,19} each of which affects the body in different ways. And, there are also more than 80 known autoimmune diseases.²⁰ Many people have autoimmune indicators without having a diagnosed condition; we do not know the implications for the health of their immune system or how this might affect their immune system response. Also, an autoimmune condition that targets a very specific organ (for example, localized scleroderma that causes hardening of a small patch of skin) might have a different impact on immune function from a systemic disease (for example, the diffuse form of scleroderma that may affect the entire skin, as well as the lungs, gastrointestinal tract and many other organs).

But, what we do know is that knowledge in this area is evolving rapidly. And, as it evolves, it is becoming increasingly clear that immune deficiency and autoimmunity are not so distinct after all. They are both caused by immune dysfunction. And, one dysfunctional gene can be responsible for both a deficiency and an autoimmune response. Rather than being opposite sides of the coin, or different ends of the spectrum, immune deficiency and autoimmunity may simply be different expressions of a related dysfunction. ■

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