Highlights from the IG Living Teleconference, June 27, 2017

Topic: Primary Immunodeficiencies and Comorbidities

[This is an edited version of a live teleconference presentation.]

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Patients with immune deficiencies often ask why they also present with autoimmune disorders. A misconception that we've had for some time is that immune deficiency means low immunity and autoimmunity means high immunity. They were considered opposite of each other. It turns out that's not the case. Immunodeficiency and autoimmunity are not opposites.

We now know there are numerous genes with mutations that have been identified in the activation and regulation of immunity. When the normal immune system acts up, there are many genes involved that play a role in activation and regulation. When we get an infection, we want our immune system to rev up and get rid of the infection. After the infection is over, we want the immune system to calm down and go back to its homeostatic state. But, the immune system is set up with a number of checkpoints to try to prevent it from becoming activated because activation can cause a lot of inflammation and damage. As such, multiple events have to come into play so the immune system can activate.

The underlying cause of immunodeficiency is the immune system failing to activate. But when it does activate, it channels other parts of the immune system to misbehave and generate autoimmunity. So immune deficiency and autoimmunity may be a result of these various activation pathways and regulation pathways if there are mutations present to alter the way they should be occurring.

We now know that there are more than 350 mutations of specific genes that result in immune abnormalities that can be present in various types of immunodeficiencies. The majority of these result in common variable immune deficiency (CVID). For example, there's one mutation called the BAFF receptor, another called the CTLA4 and another called LVR gene that result in CVID. People who have BAFF receptor deficiency may first show up in the hematology clinic because they're having problems with anemia, thrombocytopenia or their white blood cell count has gone up. They may not be having lots of infections yet and may be diagnosed with having some type of a hematological disorder, but their true underlying disease process is CVID for which they need IG to help take care of the problem. People with a mutation in CTLA4 may present with what appears to be lymphoproliferation, or they might be initially diagnosed with leukemia because white cells are overabundant and are growing too rapidly. But, again, the underlying problem is a CVID-like illness for which they need IG replacement. And, in some of these cases, the individual may also need to be given specific agents that may suppress components of the immune system. Their entire immune system is not being suppressed; only those components that are overactive. By suppressing the overactive components, the immune system is brought back in line where it should be, and the autoimmune features are eliminated. Those with thee LBR receptor will also present with a CVID-like illness, but the person may present first to the GI clinic because of inflammatory bowel disease (IBD) and will be treated with lots of medications that treat IBD, again not recognizing the underlying problem is CVID. If they had been given IG to treat the CVID, it would have both prevented the infections thought to be due to IBD, as well as the underlying CVID.

So, these things are going hand in hand, meaning that the gene mutation that will result in immune abnormality can also result in an autoimmune disease process. And, whether one presents with CVID or autoimmunity first depends on other environmental factors. If a person were to come down with a certain viral infection earlier such as Epstein Barr virus, that might trigger more of an immune deficiency-type situation to be present and apparent earlier so the appropriate therapies would be applied. On the other hand, certain bacterial infections may promote the appearance of IBD, and that would be the primary reason for seeking care. And, by not going to an immunologist first, the immune deficiency is diagnosed until much later.

What we now recognize is that immune deficiency and autoimmunity are not extremes. Immune deficiency doesn't mean low immunity, and autoimmune disease doesn't mean high immunity. What we're dealing with is a state of dysregulation, which sometimes results in the immune system not responding appropriately to threats such as infections, but overresponding to self tissues that result in harm.

In summary, there are many genes involved in activation of immunity, and there are multiple steps that are involved in these activation processes. There also are many steps in trying to downregulate the immune system or to counterregulate to keep it in a normal homeostasis. If we have alterations in certain genes or mutations present that then result in genes either overfunctioning or underfunctioning, the downstream effect could be an immune deficiency, as well as an autoimmune disorder. For instance, in the same family, someone might have CVID and someone else might have an autoimmune disorder. So, it's not the simple concept of having low immunity or high immunity. It's all a part of the same immunity that's not being regulated appropriately.