Fatigue is a common symptom of primary immunodeficiency, and while it is better understood today, its cause and treatment vary from patient to patient.

By Terry O. Harville, MD, PhD
IN THESE MODERN times, it’s common for people to complain about “fatigue.” Bright lights at night, television, computers, social media, telephones and other handheld devices, etc., all contribute to keeping us awake and have disrupted the normal diurnal rhythms of our bodies, particularly melatonin secretion in our brains. Yet, people with acute or chronic illnesses such as primary immunodeficiency disease (PI) complain about fatigue that is beyond the disruption of normal sleep — even when appropriate treatment has begun. What is the basis of this fatigue in patients with PI, and are there possible therapeutic interventions?

What Is Fatigue
The older definition of fatigue is “extreme tiredness, typically resulting from physical exertion.” This is distinguished from “malaise,” which is a medical term defined as a “feeling of weakness, overall discomfort, illness or simply not feeling well.” Thus, when most patients with chronic disease lament about fatigue, they are not exhausted due to physical exertion, but are suffering from the medical definition of malaise. However, since the newer definition of fatigue includes “mental exhaustion and tiredness due to illness,” fatigue and malaise may be used somewhat interchangeably.

Feeling fatigue while ill has always been an issue. When someone becomes ill, it is often recommended to “let the patient rest.” But, it is important to determine what is actually causing fatigue. For instance, many years ago, I helped to manage an athlete who competes in Ironman triathlons and runs 10 miles every day at noon in the Florida heat. She called me to complain about feeling fatigued, and I suggested she may be overtraining, causing her to become physically fatigued. But, she felt it was different than physical exhaustion, so I examined her and found signs of sinusitis. Two days after starting antibiotics, she called to tell me the fatigue she had experienced was gone. This and many other examples demonstrate that fatigue usually occurs when an infection is present. As such, those with arthritis conditions, autoimmune disorders or any state of immune system activation can experience fatigue.

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What Causes Fatigue?
The basis of fatigue in patients with illness was in large part discerned when HIV became an issue. Before effective therapy was available, most patients infected with HIV, and particularly those who developed AIDS, exhibited fatigue and frequently lost interest in eating. Sometimes, this was severe enough that
patients would waste away, and a condition known as “chronic wasting syndrome” was named. When animal studies were conducted, a protein found in the serum could result in “normal” animals becoming lethargic, seeking a warm, dark and quiet place, and not wanting to eat. If the serum was continually injected, the animals would not move about, would lose weight and eventually die from starvation. The serum factor was termed “cachexin,” since the general clinical features were those of cachexia (lack of activity with extreme weight loss). Eventually, cachexin was found to be tumor necrosis factor-alpha (TNF). When an infection occurs and the immune system becomes activated, TNF is one of the factors released early in the process. Thus, TNF can make a person feel tired and cold, have photophobia (light bothering the eyes), be bothered by noises and cause anorexia. This is highly relevant from an evolutionary perspective: If one can rest and heal from an illness, then one is more likely to survive, rather than wander about looking for food, thereby becoming a target for a larger predator.

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Besides TNF, other immune system activators (cytokines) such as gamma-interferon, IL-1 and IL-6 can also contribute to a person’s discomfort, including fevers, muscle soreness and generalized aches and pains. It can be inferred through the immune system development process over many eons of evolution that it was important for an infected creature to feel so bad that it would remain hidden away in a dark, warm and quiet place until healing could complete. But, for modern humans, feeling lousy when ill is more than an inconvenience because people feel the need to get on with their daily lives. This is greatly amplified in those with medical conditions in which the immune system is not performing correctly.

Normally, once an infection has been cleared and the immune system dampens down the activated state, the factors and cytokines such as TNF that are promoting fatigue wane, and the fatigue resolves. Unfortunately, for those with states of chronic activation of the immune system such as in autoimmune disorders and immunodeficiencies, fatigue does not wane.

**Fatigue in PI Patients**

Today, more than 300 genes with mutations have been identified as having roles in causing immunodeficiencies. What is unexpected is most of the same gene mutations can also result in autoimmune disorders! Previously, it was thought that “overactivation” of immunity was the driving force behind autoimmune disorders, whereas “underactivation” of immunity led to immunodeficiencies. This implied that either different genes were involved or, if the same gene was involved, there were different mutations with opposite effects. Demonstrating that the same mutation in a gene can result in autoimmunity in some patients and immunodeficiency in others has obviously changed the paradigm. This helps to explain issues such as fatigue that are shared by those with autoimmunity and immunodeficiency; in both cases, the immune system is likely inappropriately overactivated.

Another aspect of fatigue is “mental fatigue” or “mental fog,” even when a patient may not be experiencing physical fatigue. Patients describe mental fatigue as being unable to think clearly, having difficulty with decision-making and having faulty memory. It is now known that immune system-activating factors and cytokines such as TNF, as well as inflammatory byproducts produced in the brain, can contribute to this phenomenon. Thus, delirium during a fever is incited by the inflammatory cytokines. Reduction in inflammation can go a long way toward resolving delirium and body fatigue. Again, from an evolutionary standpoint, this cause and effect was likely to keep the mind from being active to promote rest until the illness resolved.

While things such as muscle strength can be measured in patients with weakness, fatigue is difficult to quantify because it is considered subjective. Fortunately, there are quality-of-life (QoL) questionnaires that can quantify the extent of fatigue in patients, as well as monitor changes over time. Unfortunately, these are not commonly used in the routine clinical setting; they are more typically used when conducting studies (for example, testing a new immune globulin [IG] replacement product). Therefore, while these questionnaires are helpful for indicating...
that fatigue is a major limiting factor for PI patients, practical use in the day-to-day management of PI patients is lacking for several reasons: 1) patients may not feel well enough to complete the questionnaire appropriately at each visit; 2) there may be staffing limitations in the clinic to administer and interpret the results; and 3) slight variations in successive visits may not be very meaningful, especially if visits are far apart. However, simplified versions of QoL questionnaires with fewer questions and use of a visual analog scale of perception of the disease state can be useful in successive visits, and many clinics do use these to help monitor patients’ levels of fatigue. These measurements can be especially useful when altering patients’ therapies to try to improve the level of fatigue.

Treat Fatigue

In patients with arthritis, anti-TNF medications have not only greatly alleviated symptoms and features of the disease, but have also greatly reduced fatigue in most. And, while this supports the role of TNF in fatigue in such conditions, there is a downside. Some of the medications may allow reactivation of latent tuberculosis or fungal infections. And, there is concern they may allow some cancers to develop. Therefore, the routine use of these types of medications solely for helping to reduce fatigue in PI patients who do not have a specific arthritis condition has not occurred because the risks may outweigh potential benefit.

At this point, there is no single successful therapy for alleviating fatigue in PI patients. For many patients, especially younger ones, merely introducing the correct treatment can improve fatigue levels. There could be a couple of reasons for this. One is that young patients have not acquired chronic indolent infections such as chronic sinusitis. Another is that they have not accumulated as many autoimmune-provoking components in their immune system as older patients have over time. Thus, the great burden of fatigue tends to be in adult PI patients, especially in those with mixed autoimmunity and immunodeficiency and/or chronic infections such as chronic sinusitis.

Treatment of the underlying components of disease is the first step to help ameliorate fatigue in PI patients. In some cases, this means giving higher doses of intravenous or subcutaneous IG than the minimal starting doses. Or, it may mean prolonged usage of antibiotics until chronic lung, sinus or gastrointestinal infections are cleared (or even continuing antibiotics indefinitely). A patient’s nutritional status should also be assessed. Improvements in dietary intake, especially supplementing nutrients that may be deficient, can be very helpful. Undertaking mindfulness exercises, participating in stress reduction, performing yoga, etc., can also be very helpful, even though fatigue may not be fully relieved. In some cases, antidepressant medications may be required. Interestingly, especially for patients with mental fog, medications such as Ritalin and Adderall that are commonly used to treat attention deficit hyperactivity disorder in children may be useful. Lastly, vitamin supplementation, including vitamin B12 injections and especially vitamin D, has received more attention as being beneficial in helping relieve symptoms of fatigue. This remains controversial, however, since there are no good widespread studies that indicate overall benefit.

When fatigue is not improved despite treatment, investigating additional issues may help identify treatable conditions that are causing fatigue. For example, has the patient developed diabetes mellitus or hypothyroidism? Does the patient have allergic disease or asthma that is not being fully addressed? Is the patient anemic? Are the liver and kidneys functioning normally? Has the patient’s uric acid level gone up (mild gout)?

Common, But Not Unsolvable

Unfortunately, fatigue is a common problem in PI patients and in patients in whom activation of immunity may be present. Many things can contribute to fatigue, including emotional distress from having a chronic disease. Therapeutic intervention must be individualized for each patient, with his or her physician willing to continue to investigate for potential causes that can be treated or otherwise ruled out as contributing to fatigue. Regrettably, despite the best efforts, patients may remain fatigued. This should not be taken as a sign to give up, but as an indication to delve further into the potential causes until optimal therapeutic intervention has been achieved.

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