

Understanding NK Cell Deficiency

Even as more is discovered about the genetics of this group of rare PIs, and the number of NKD diagnoses on the rise, there is still much to learn about how to treat it.

By Jordan S. Orange, MD, PhD

NK CELL DEFICIENCY (NKD) involves a group of primary immunodeficiency diseases (PIs) in which one specific part of the immune system, the natural killer (NK) cells, is defective. Patients with NKD are susceptible to viral infections, most notably infections with two types: papillomaviruses that cause warts and herpes viruses. Common herpes viruses causing problems in patients with NKD are the varicella zoster virus that causes chickenpox, cytomegalovirus (CMV), Epstein Barr virus and herpes simplex virus (HSV). Patients with NKD typically have more of these infections and unusual consequences from them.

Fifty of the more than 350 PIs have some defect in NK cells. For example, in certain types of severe combined immunodeficiency (SCID), NK cells fail to develop. However, it is the absence of T cells rather than NK cells in SCID that represent the greatest challenge to these patients. Whereas in NKD patients, the NK cells are the main defect of immunity. And, while patients and causes of NKD are increasingly being recognized, it is believed NKD is quite rare.

What Are NK Cells?

NK cells are a type of lymphocyte that specializes in the destruction of diseased cells in the body by directly killing them — a process called cytotoxicity (Figure 1). They are especially effective in killing cells that have become infected with a virus or have lost growth control and are in danger of forming a cancer.

NK cells are one of two types of lymphocytes that mediate cytotoxicity; the other is the cytotoxic T cells (CTLs). The main difference between NK cells and CTLs is NK cells are part of the innate immune system, whereas CTLs are part of the adaptive immune system. This means NK cells are ready to function without additional training, but CTLs require education to become active and effective. Thus, NK cells are part of the early defense against viral infection and cells that have lost growth control, while CTLs are called into action to provide more durable defense.

As a result of this duality in cytotoxicity, lacking NK cells leaves a very specific hole in the immune defense, creating

susceptibility to a small number of viruses. The reason for these particular infectious susceptibilities is that the viruses causing difficulty in NKD patients utilize very specific mechanisms to evade and escape CTL responses. Thus, NK cells are somewhat indispensable in these infections.

NK cells also serve other functions besides cytotoxicity, including producing inflammation to help organize other immune defenses and to help control immunity to prevent immune responses from getting out of control. NK cells are found circulating in the blood and also reside in many of the body's organs. And, while people can survive for periods of time without them, they become susceptible to life-threatening viral infections.

Interestingly, NK cells are currently being investigated as a treatment for certain types of cancer, where they are grown in the laboratory and infused back into patients. While experimental at this point, they hold therapeutic promise for the future.

Genes Causing NKD

Since NK cells were first discovered in the 1970s, a number of cases of NKD have been reported in the medical literature. Several notable descriptions of patients with NKD were made in the 1980s, some of which have subsequently been connected with a genetic explanation. The first gene associated with an NKD was found in the 1990s. Today, there are seven gene defects known to cause NKD, and there will undoubtedly be others reported in coming years as this particular diagnostic category is expected to grow.

Genes that are known to cause NKD at present are (in alphabetical order) FCGR3A, GATA2, IRF8, MCM4, MCM10, GINS1 and RTEL1. Some of these genes, when defective, can also cause other conditions, but either particular variants in these genes or particular presentations of the defects can result in NKD. Although the specific details of each of these genes, their impact upon NK cells and how they cause NKD is beyond the scope of this overview, other articles can be accessed for additional information.^{1,2} The clinical sequence analysis of many of these genes can be found on currently available PI diagnostic gene panels, and can also be obtained through whole exome sequencing.

Diagnosing NKD

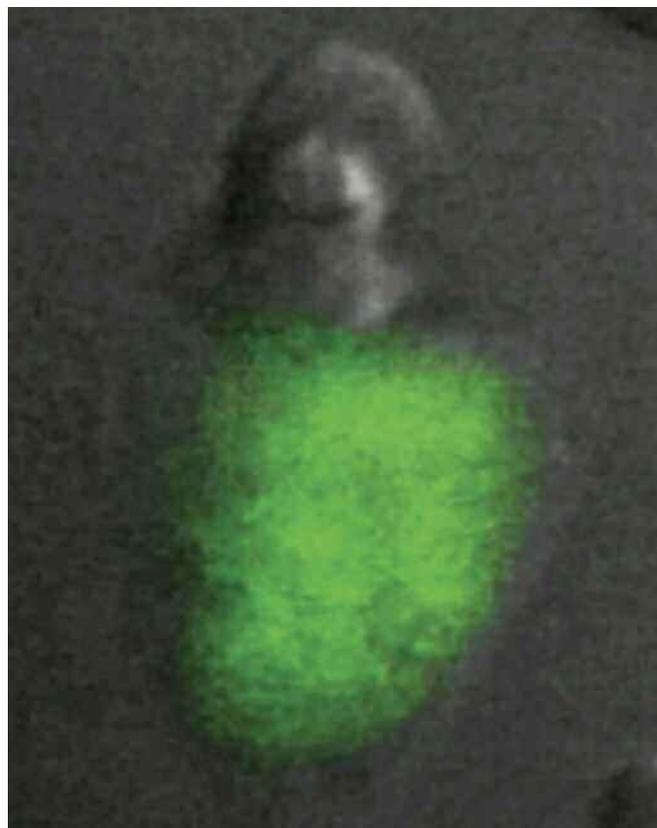
Diagnosing NKD requires patients have a deficiency of NK cell number and function, or just function, as well as a clinical history suggesting NKD.³ Because there are many reasons someone can have slightly low NK cell numbers and function, it is important for laboratory test results to be repeated, significant

and in context of a clinical history suggestive of NKD (i.e., with herpes viral or papillomavirus infections).

NK cell number is assessed by flow cytometry of the lymphocytes in peripheral blood. NK cell function is determined by a cytotoxicity assay that measures the ability of NK cells to kill a tumor cell in a culture dish in the laboratory. People with low NK cell numbers can have a defect in their NK cells' ability to normally develop, which can be a clue to NKD. And, normal development of NK cells must be assessed in context of NK cell function to ensure they are actually abnormal.

Importantly, the normal range for low NK cell numbers from commercial laboratories is one in 20 people (5th percentile). This does not mean having a low number of NK cells equates to an NKD. For some people, having a slightly low number is just their own personal set point (we get especially concerned, however, when someone has less than 1 percent). Therefore, it is again

Figure 1.



The image shows a human NK cell taken directly from a normal person's blood attacking a CMV-infected cell (shown in green). The NK cells will go on to kill and destroy the CMV-infected cell representing one of their major roles in keeping us healthy. (Image taken by Dr. Stacy Smith while in the laboratory of the author.)

important to be sure these low numbers of NK cells are indeed also dysfunctional to determine whether the patient has an NKD. To ensure valid results, tests must be performed by a reputable laboratory and during a time when someone is generally well, because illness can suppress the test result. And, it is essential these abnormalities in the test results be found repeatedly, with a recommendation that there be consistent abnormalities on three separate occasions scheduled at one-month intervals.

Looking to the future, as we gain a greater understanding of the genes underlying NKD, we should be able to increasingly rely upon genetic results for diagnosis.

Presently, there is
preciously little known about
treatment for NKD.

What Is Not NKD

Unfortunately, the diagnosis of NKD is frequently misapplied. NK cell numbers are low in many people as defined by normal threshold ranges found in laboratories. The percentages and function of NK cells are affected by stress, depression and illness, and can be low because the body is in the midst of fighting a challenge. Thus, individual values in tests do not define NKD. People with NKD have abnormal values repeatedly and in the context of a convincing clinical history. Borderline low results are also a problem. Many patients with NKD have very clear absent or near-absent test values.

For clinical history, there are certain things typically not found in association with NKD. One example is patients who get sick frequently from cold (and related) viruses. While there are likely many reasons for that, we have not found NKD as an explanation. Another is patients who get frequent cold sores or focused outbreaks of HSV. While there are likely reasons people get frequent cold sores, NKD is typically not one of them. Patients with NKD do have problems with HSV, but these typically occur in many places on the body (not just on the lips) or when it is especially severe. Finally, postherpetic neuralgia is a real problem that occurs when there is excess pain after an HSV outbreak, but this is typically not a main feature of patients with NKD.

Treating NKD

Presently, there is preciously little known about treatment for NKD.⁴ It is hoped more will be learned as further experience is gained and more patients are diagnosed.

There has never been an interventional trial or drug study in patients with NKD, so we really cannot say that particular treatments are proven to work. However, we do know certain medications are effective against the viruses that cause problems in NKD patients, and we prescribe those to help. In particular, continual prophylaxis with the synthetic nucleoside analogs such as Acyclovir can help fill in some of the void left by defective NK cells. Some patients have benefited from immune stimulatory treatments to try to boost NK cell function (like interleukin-2 or interferon), or prophylaxis with intravenous immune globulin to try to provide additional defense against some of the susceptible viruses. While bone marrow transplantation is not a treatment the author has experience with, there have been reports in the literature of its success for NKD in patients with particularly severe consequences.

Virus-specific T cells are one treatment of interest for the future. With this, CTLs directed against a particular virus can be infused into a patient to help control a viral infection.⁵ Although only experimental at this point, it could represent a new path for PI and NKD patients who have defective immunity and challenges fighting viruses.

A Hopeful Future

NKD is a rare but emerging PI in which an abnormality in NK cells is the main immune defect. Patients have susceptibility to herpes viruses and papillomaviruses, and anecdotal experience has provided some hope for treatment. Understanding NKD from an immunologic, clinical and scientific standpoint is leading to advances and new identifiable causes. We are optimistic that future and ongoing research will bring new answers and, hopefully, new treatments for patients suffering from deficiencies in NK cell defenses. ■

JORDAN S. ORANGE, MD, PhD, is chief of the Section of Immunology, Allergy and Rheumatology at Texas Children's Hospital, and professor of pediatrics-rheumatology at Baylor College of Medicine in Houston, Texas.

References

1. Orange, JS. Natural Killer Cell Deficiency. *Journal of Allergy and Clinical Immunology*, 2013; 132:515-25.
2. Mace, EM, and Orange, JS. Genetic Causes of Human NK Cell Deficiency and Their Effect on NK Cell Subsets. *Frontiers in Immunology*, 2016. DOI: 10.3389/fimmu.2016.00545.
3. Orange, JS. Natural Killer Cell Deficiency Syndromes: Clinical Manifestations and Diagnosis. In: Rose, BD (Ed.), *UpToDate*, Wellesley, MA.
4. Orange, JS. Natural Killer Cell Deficiency Syndromes: Treatment. In: Rose, BD (Ed.), *UpToDate*, Wellesley, MA.
5. Naik, S, Nicholas, SK, Martinez, CA, et al. Adoptive Immunotherapy for Primary Immunodeficiency Disorders with Virus-Specific T-Lymphocytes. *Journal of Allergy and Clinical Immunology*, PMID:26920464.