



CHAPTER

9

DiGeorge Syndrome

DiGeorge Syndrome is a primary immunodeficiency disease which is caused by abnormal migration and development of certain cells and tissues during fetal development. As part of the developmental defect, the thymus gland may be affected and T-lymphocyte production may be impaired, resulting in recurrent infections.

Definition of DiGeorge Syndrome

The DiGeorge Syndrome is a primary immunodeficiency disease which is caused by abnormal migration and development of certain cells and tissues during growth and differentiation of the fetus. Different tissues and organs often arise from a single group of embryonic cells. Although the tissues and organs that ultimately develop from a single group of embryonic cells may appear to be unrelated in the fully formed child, they are related in that they have developed from the same embryonic or fetal tissues. Although many different organs may be involved in the DiGeorge Syndrome, they all evolve from the same embryonic cells.

Most, but not all patients with the DiGeorge Syndrome have a small deletion in a specific part of chromosome number 22 at position 22q11.2. Another name for this syndrome is the chromosome 22q11.2 deletion syndrome. Patients with the DiGeorge Syndrome do not all show the same organ involvement. A given organ may be uninvolved, or so mildly involved that the organ appears to be normal. Thus, patients with the DiGeorge Syndrome may not all have the same organs involved or the same severity. Patients with the DiGeorge Syndrome may have any or all of the following:

Facial Appearance

Affected children may have an underdeveloped chin, eyes with heavy eyelids, ears that are rotated back and defective upper portions of their ear lobes. These facial characteristics vary greatly from child to child and may not be very prominent in many affected children.

Parathyroid Gland Abnormalities

Affected children may have underdeveloped parathyroid glands (hypoparathyroidism). The parathyroids are small glands found in the front of the neck near the thyroid gland (hence the name “parathyroid”). They function to control the normal metabolism and blood levels of calcium. Children with the DiGeorge Syndrome may have trouble maintaining normal levels of calcium, and this may cause them to have seizures (convulsions). In some cases, the parathyroid abnormality is relatively mild or not present at all. The parathyroid defect often becomes less severe with time.

Heart Defects

Affected children may have a variety of heart (or cardiac) defects. For the most part, these anomalies involve the aorta and the part of the heart from which the aorta develops. As with other organs affected in the DiGeorge Syndrome, heart defects vary from child to child. In some children, heart defects may be very mild or absent.

Thymus Gland Abnormalities

Affected infants and children may have abnormalities of their thymus. The thymus gland is normally located in the upper area of the front of the chest. The thymus begins its development high in the neck during the first three months of fetal development. As the thymus matures and gets bigger, it drops down into the chest to its ultimate location under the breastbone and over the heart.

The thymus controls the development and maturation of one kind of lymphocyte, the T-lymphocyte (“T” for “Thymus”) (see chapter titled *The Immune System and Primary Immune Deficiency Diseases*). The size of the thymus affects the number of T-lymphocytes that can develop. Patients with a small thymus produce fewer T-lymphocytes than someone with a normally sized thymus. T-lymphocytes are essential for resistance to certain viral and fungal infections. Some T-lymphocytes, the cytotoxic T-lymphocytes, directly kill viruses. T-lymphocytes also help B-lymphocytes to develop into plasma cells and produce immunoglobulins or antibodies. Patients with the DiGeorge Syndrome may have poor T-cell production compared to their peers, and as a result, they may have an increased susceptibility to viral, fungal and bacterial infections.

As with the other defects in the DiGeorge Syndrome, the T-lymphocyte defect varies from patient to patient. In addition, small or mild deficiencies may disappear with time.

Miscellaneous Clinical Features

In addition to the above features, patients with the DiGeorge Syndrome may occasionally have a variety of other developmental abnormalities including cleft palate, poor function of the palate, delayed acquisition of speech and difficulty in feeding and swallowing. In addition, some patients have learning disabilities, behavioral problems, and hyperactivity.

Diagnosis of DiGeorge Syndrome

The diagnosis of the DiGeorge Syndrome is usually made on the basis of signs and symptoms that are present at birth or develop soon after birth. Some children may have the facial features that are characteristic of the DiGeorge Syndrome. Affected children may also show signs of low blood calcium levels as a result of their hypoparathyroidism. This may show up as low blood calcium on a routine blood test, or the infant may be “jittery” or have seizures (convulsions) as a result of the low calcium. Affected children may also show signs and symptoms of a heart defect. They may have a heart murmur that shows up on a routine physical exam, they may show signs of heart failure, or they may have low oxygen content of their arterial blood and appear “blue” or cyanotic. Finally, affected children may show signs of infection because of the underdevelopment of their thymus gland and low T-lymphocyte levels.

Some children have signs or symptoms at birth or while they are still in the hospital nursery. Others may not show signs or symptoms until they are a few weeks or months older. Some children and adults are diagnosed at a much older age due to speech delay, qualitative speech problems, or feeding problems.

There is a great deal of variation in the DiGeorge Syndrome from child to child. In some children, all of the different organs and tissues are affected. These children have the characteristic facial characteristics, low blood calcium from hypoparathyroidism, heart defects and a deficiency in their T-lymphocyte number and function. In other children, all of the different organs and tissues may not be affected, and the organs and tissues that are affected may be affected to different degrees.

Not only do children with the DiGeorge Syndrome differ in the organs and tissues that are affected, but they also differ in terms of how severely a given organ or tissue is affected.

In the past, the diagnosis of the DiGeorge Syndrome was usually made when at least three of the characteristic findings described above were present. Unfortunately, this caused many mild cases to be missed. In recent years, the genetic test has been more widely used. Over 90% of patients with the clinical diagnosis of DiGeorge Syndrome have a small deletion of a specific portion of chromosome number 22 at position 22q11.2. This can be identified in a number of ways, but the most common way is a FISH analysis (for Fluorescent In Situ Hybridization). Use of a FISH analysis test has made the diagnosis of DiGeorge Syndrome more precise and more common. Approximately 1 in 4000 babies have DiGeorge Syndrome or chromosome 22q11.2 deletion syndrome. For patients who do not have the deletion, the diagnosis continues to rely on the characteristic combination of clinical features.

Therapy for DiGeorge Syndrome

Therapy for DiGeorge syndrome is aimed at correcting the defects in the organs or tissues that are affected. Therefore, therapy depends on the nature of the different defects and their severity.

Treatment of the low calcium and hypoparathyroidism may involve calcium supplementation and replacement of the missing parathyroid hormone. A heart (or cardiac) defect may require medications or corrective surgery to improve the function of the heart. If surgery is required, the exact nature of the surgery depends on the nature of the heart defect. Surgery can be performed before any immune defects are corrected. It is important that all the precautions that are usually taken with children with T-cell immunodeficiencies be observed, such as irradiating all blood products to prevent graft-vs.-host disease and ensuring the blood products are free of potentially harmful viruses (see chapter titled *Specific Medical Therapy*).

As mentioned above, the immunologic defect in T-lymphocyte function varies from child to child. Therefore, the need for therapy of the T-lymphocyte defect also varies. Many children with the DiGeorge Syndrome have perfectly normal T-lymphocyte functions and require no therapy for immunodeficiency. Other children initially have mild defects in T-lymphocyte function which improve as they grow older. In most cases of the DiGeorge Syndrome, the small amount of thymus that is present provides adequate T-lymphocyte function.

Rarely, the thymus is so small that adequate numbers of T-cells do not develop. In these cases, a special form of bone marrow transplantation or a thymus transplant may be performed.

In some children with the DiGeorge Syndrome, the T-lymphocyte defect is significant enough to cause the B-lymphocytes to fail to make sufficient antibodies. This occurs because antibodies are

produced by B-lymphocytes under the direction of a specific subset of T-lymphocytes (see chapter titled *The Immune System and Primary Immunodeficiency*). When the B-cells are affected, this most often results in a delay in the production of antibodies. Rarely, children may require immunoglobulin replacement therapy.

As described in the preceding paragraphs, not all children with DiGeorge Syndrome require therapy for their immunodeficiency. Approximately 80% of the patients with the chromosome 22q11.2 deletion have diminished T-cell numbers. However, less than 0.2% have an immunodeficiency that requires a bone marrow transplant or a thymus transplant. The majority of children with an immunodeficiency have a mild to moderate deficit in the number of T-cells. These patients usually do not require transplantation; however, strategies aimed at prevention of the bacterial infections can often be quite helpful. This may include antibiotic prophylaxis and adequate treatment of any allergies. Allergies appear to be increased in patients with the DiGeorge Syndrome. They may contribute to the infections and are treated with the same medications used in other patients with allergies.

Approximately 10% of patients with the chromosome 22q11.2 deletion, and an unknown number of patients with the DiGeorge Syndrome without the deletion, have an autoimmune disease. This occurs when the immune system makes a mistake and tries to fight its own body. It is not known why this happens in people with T-lymphocyte problems. The most common autoimmune diseases in the DiGeorge Syndrome are idiopathic thrombocytopenia purpura (antibodies against platelets), autoimmune hemolytic anemia (antibodies against red blood cells), juvenile/adult arthritis and autoimmune disease of the thyroid gland.

Expectations for the DiGeorge Syndrome Patient

The outlook for a child with DiGeorge Syndrome depends on the degree to which the child is affected in all organ systems. The severity of heart disease is usually the most important determining factor. As mentioned above, most children have a mild to moderate deficit in T-cell production

that often improves with age. Overall, the outlook for the infection pattern is optimistic as most patients do not suffer from recurrent infections in adulthood. Nevertheless, approximately one third of adults have minor recurrent infections.