DiGeorge Syndrome

Chapter 13

DiGeorge Syndrome is a primary immunodeficiency disease 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 low T-lymphocyte numbers and frequent infections.

Definition of DiGeorge Syndrome

DiGeorge Syndrome (DGS) is a primary immunodeficiency, often but not always, characterized by cellular (T-cell) deficiency, characteristic facies, congenital heart disease and hypocalcemia. DGS is caused by abnormal formation of certain tissues during fetal development. During fetal development, various tissues and organs often arise from a single group of embryonic cells. Although the tissues and organs that ultimately develop from this group of embryonic cells may appear to be unrelated in the fully formed child, they do have a similar origin.

Approximately 90% of patients with DGS have a small deletion in chromosome number 22 at position 22q11.2. Thus another name for this syndrome is the 22q11.2 deletion syndrome. Other names include velocardiofacial syndrome and conotruncal anomaly face syndrome.

While the genetic defect is the same in the majority of patients with DGS, they all do not present in the same way. For example, some patients with DGS have severe cardiac anomalies; some have none at all. Some have major learning disabilities; others have none. This is called phenotypic variability. There is wide phenotypic variability in patients with DGS.

Patients with DGS may have any or all of the following:

Unusual facial appearance - Features may include an underdeveloped chin, eyes with heavy eyelids, ears that are rotated back and small upper portions of their ear lobes. These facial characteristics vary greatly from person to person and may not be prominent in many patients.

Heart defects - These include a variety of heart (or cardiac) defects. The defects usually involve the aorta and the part of the heart from which the aorta develops. In some patients, heart defects may be very mild or absent.

Thymus gland abnormalities - The thymus is crucial in the development of the cellular (T-cell) immune system. It is normally located in the upper area of the front of the chest behind the breastbone. 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 in front of 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 those with a normally sized thymus. T-lymphocytes are essential for protection against infections. Some T-lymphocytes, the cytotoxic T-lymphocytes, directly kill viruses. T-lymphocytes also help B-lymphocytes to develop into

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antibody producing plasma cells. Patients with DGS may have poor T-cell production compared to their peers, and as a result, have an increased susceptibility to viral, fungal and bacterial infections.

As with the other defects in DGS, the T-lymphocyte defect varies from patient to patient. In a very small number of patients with DGS the thymus is completely absent, so the number of T-cells is severely low. These patients require prompt medical attention since they are severely immunocompromised. The majority of patients with DGS have less severe or mild deficiencies.

Autoimmunity - Patients with DGS develop autoimmune disease at a rate that is higher than in the general population. Autoimmune disease occurs when the immune system inappropriately attacks its own body. *(See chapter titled "Autoimmunity in Primary Immunodeficiency.")* It is not known why this happens in people with T-lymphocyte problems. The most common autoimmune diseases in DGS are idiopathic thrombocytopenia purpura (antibodies against platelets), autoimmune hemolytic anemia (antibodies against red blood cells), autoimmune arthritis, and autoimmune disease of the thyroid gland.

Parathyroid gland abnormalities - These glands may be underdeveloped in patients with DGS, causing 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. People with DGS may have trouble maintaining normal levels of calcium, and this may cause seizures (convulsions). In some cases, the parathyroid abnormality is not present at all, relatively mild or only a problem during times of stress such as severe illness or surgery. The parathyroid defect often becomes less severe over time.

Miscellaneous clinical features - Patients with DGS may 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, psychiatric disorders and hyperactivity. For example schizophrenia occurs at a higher rate in patients with DGS compared to the rate in the general population.

Diagnosis of DiGeorge Syndrome

The diagnosis of DGS is made on the basis of signs and symptoms that are present at birth, or develop soon after birth, along with confirmatory genetic testing. Some infants may have facial features that are characteristic of DGS. Affected infants may also show signs of low blood calcium levels as a result of hypoparathyroidism. This may show up as low blood calcium on a routine blood test, or the infant may be "jittery" or have seizures as a result of the low calcium.

Affected infants may also show signs and symptoms of a heart defect. These may include a heart murmur that is detected 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. Affected infants may also develop infection because of their low T-lymphocyte levels.

In some children, all of the classical features are present and the diagnosis of DGS is made very early. In

(Diagnosis of DiGeorge Syndrome continued)

other people, all of the different organs and tissues may not be affected, and the organs and tissues that are involved may be impaired to different degrees so that the presentation is more subtle and the diagnosis is not made until later on in life when a speech delay, feeding problems or autoimmune disease are noted.

In the past, the diagnosis of DGS was usually made when all the characteristic findings described above were present without obtaining a confirmatory genetic test. Unfortunately, this caused many mild cases to be missed. In recent years, the genetic test has been more widely used.

Approximately 90% of patients with the clinical diagnosis of DGS have a small deletion of a specific portion of chromosome number 22 at position 22q11.2, called a microdeletion. This is usually identified by a blood test called a FISH analysis (for Fluorescent In Situ Hybridization). The FISH test has made the diagnosis of DGS more precise and more common.

Approximately 90% of 22q11.2 deletions occur spontaneously and have not been passed on from the mother or father of the child. But once the diagnosis has been made, genetic counseling is critically important and testing should be offered to parents and other family members.

DGS is the most common microdeletion syndrome. The rate of occurrence is estimated at approximately 1 in 4,000 people. For patients who do not have the 22q11 microdeletion, a DGS diagnosis can still be made on the basis of the characteristic combination of clinical features and by excluding a diagnosis of other syndromes.

Therapy for DiGeorge Syndrome

Therapy for DGS is aimed at correcting the defects in the affected organs or tissues. Therefore, therapy depends on the nature of the different defects and their severity. In general, patients with DGS have the same response rates to therapies as do the general population.

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. Surgery can be performed before any immune defects are corrected. If there is a problem with the T-cells, precautions must be taken as with other children with congenital T-cell immunodeficiencies. These include irradiating all blood products to prevent graft vs. host disease and ensuring the blood products are free of potentially harmful viruses. *(See discussion of General Treatment in the chapter titled "Severe Combined Immune Deficiency and Combined Immune Deficiency.")*

The need for therapy of the T-lymphocyte defect varies. Most people with DGS have normal T-lymphocyte function and do not require therapy for immunodeficiency. Other children initially have mild defects in T-lymphocyte function that improve, as they grow older. In these cases the small amount of thymus tissue present provides adequate T-lymphocyte function.

Management of DiGeorge Syndrome

Immunologic care for patients with DGS includes monitoring the overall immune system including the numbers and function of T-lymphocytes. Patients who have initially been deemed immunocompetent but then develop frequent, severe or unusual infections should have their immune system reevaluated.

Between 1-2% of patients with DGS completely lack T-cells. This is a serious, potentially fatal, condition that is similar to Severe Combined Immune Deficiency *(See chapter "Severe Combined Immune Deficiency and Combined Immune Deficiency.")* This is sometimes called "complete" DiGeorge syndrome and is usually associated with severe low blood calcium causing seizures. In this situation, T-cells must be reconstituted for the infant to survive. This can be achieved with a thymus transplant (available only on a research basis) or by stem cell transplantation.

In some patients with DGS, 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, the result is simply a delay in the production of antibodies. Immunoglobulin replacement therapy is sometimes required.

Expectations for Patients with DiGeorge Syndrome

The outlook for people with DGS depends on the function of each affected organ system. The severity of heart disease is usually the most important determining factor. With the improvements made in cardiac surgery and management of immunodeficiency, the infant mortality rate in DGS is estimated to be relatively low at approximately 4%. Early diagnosis is important and optimal management of patients with DGS requires a multidisciplinary approach including an immunologist as part of the team of specialists.