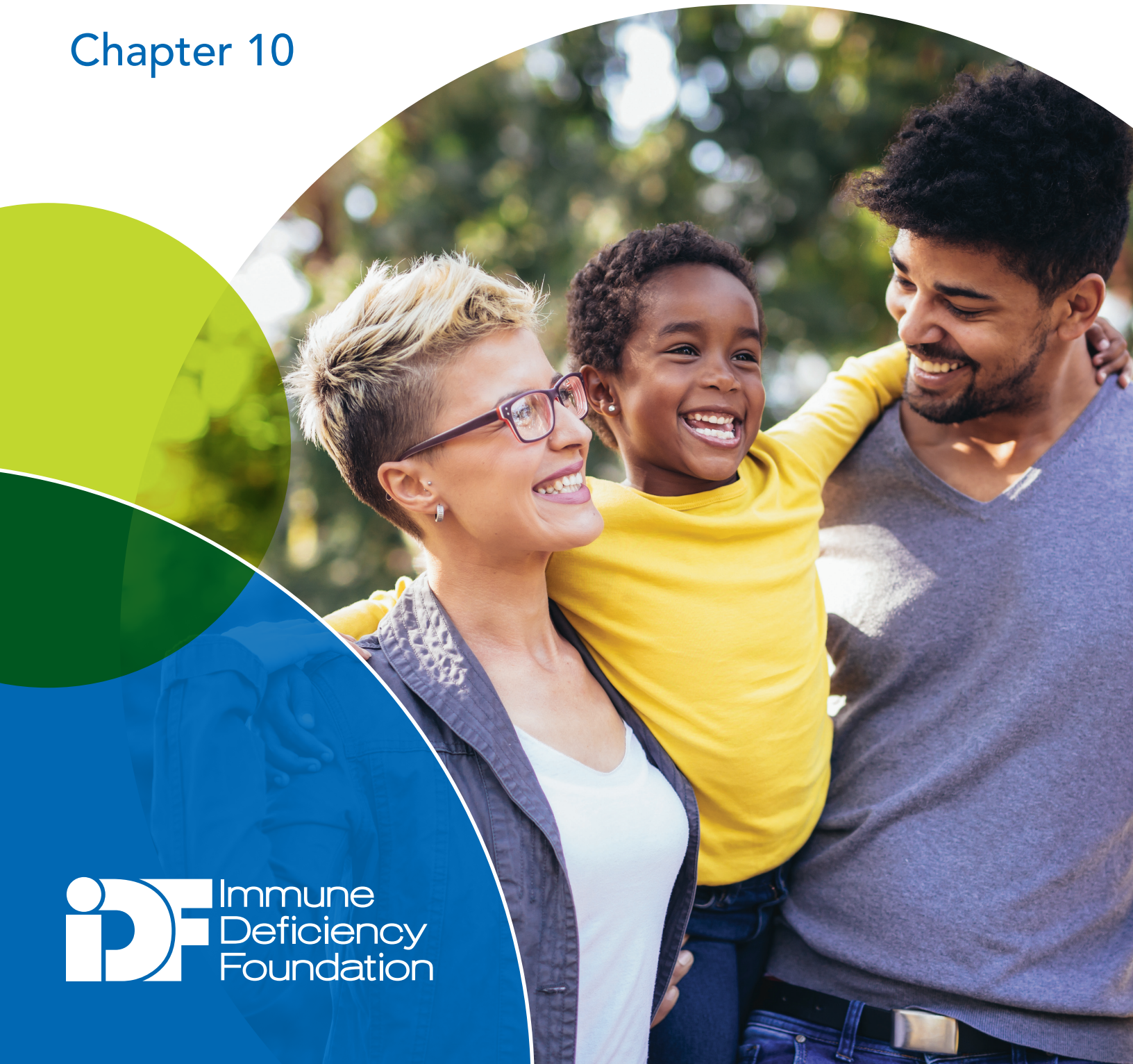
Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 10



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Chapter 10
DiGeorge Syndrome

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Introduction

DiGeorge Syndrome (DGS) was first described by Dr. Angelo DiGeorge who described the syndrome consisting of low T cells, recurrent infections, and heart defects. DGS is a form of primary immunodeficiency disease (PI) characterized by:

- Heart defects,
- Small or absent parathyroid glands that control calcium levels, and
- Small or absent thymus gland that makes T cells (a type of white blood cell that fights infections).

Infants born with heart defects may require surgery. If the parathyroid glands are small, calcium levels in the blood can be dangerously low resulting in seizures (patients require treatment with calcium supplements). If the thymus size is small, infants may have lower T cell numbers than normal. In the rare situation in which the thymus is absent at birth (1% of cases), the infant will not have any T cells to fight infections and have a life-threatening immunodeficiency.

DGS most commonly occurs in children with 22q11.2 deletion syndrome, CHARGE syndrome, and infants of diabetic mothers. Other names for DGS include:

- Velocardiofacial syndrome
- 22q11.2 deletion syndrome
- Shprintzen syndrome
- Conotruncal anomaly face syndrome.

Some children, however, do not have any genetic syndromes or mothers with diabetes.

Overview

Children with DGS can have a wide range of presentations and can range from having mild to severe immunodeficiency. The term DGS is used most commonly for individuals with T cells below the 10th percentile for age. DGS occurs in four main groups of children:

1. The most common cause is due to a genetic defect called 22q11.2 deletion syndrome (22q11.2DS). In children with 22q11.2DS, a piece of chromosome 22 is missing.
2. Patients with CHARGE syndrome. CHARGE syndrome is usually caused by mutations (changes) in the gene CHD7. Children with CHARGE have many of the same problems as those with 22q11.2DS, but they have additional problems, especially involving the eyes, nose, and ears. Children with CHARGE syndrome who have low T cells are said to also have DGS. Developmental delay is found in both 22q11.2DS and CHARGE syndrome.
3. Infants of diabetic mothers who do not have any genetic defects.
4. Infants without any genetic defects or whose mothers do not have diabetes.

Of children with DGS, only 1% have no thymus and thus no T cells. These patients are said to have Complete DGS. These children have life-threatening infections and need a transplant to give them T cells. The transplant can be a hematopoietic stem cell transplantation (bone marrow transplantation) or an experimental thymus transplant.

Immunobiology

It is helpful to understand how the thymus works. The thymus acts as a schoolhouse for developing T cells (the students). First, white blood cells called stem cells leave the bone marrow and go to the thymus to learn to become T cells. The developing T cells have to learn two key lessons and pass a final test in order to graduate and leave the thymus. The first lesson is how to fight infections. The second lesson is to how not to attack the body and cause autoimmune disease. The majority of T cells (90%) fail the final test and die without leaving the thymus. The 10% that pass the test leave the thymus as mature T cells. They are able to protect the body from infection but also do not attack the body.

Clinical Presentation

Infants with DGS do not all present in the exact same way. For example, some have severe heart problems; some have none at all. Some have parathyroid disease; some do not. To be called DGS, most people would say that the T cell counts in the blood should be low (in the bottom 10th percentile for age). Individuals with DGS due to 22q11.2 deletion may have many other findings. They may have a unique facial appearance such as a small chin, eyes with hooded eyelids, and ears that are rotated back with small upper portions of the ear lobes, cleft palate, and floppy outer part of the ear (the pinna). Infants with DGS secondary to CHARGE syndrome may have additional defects beyond those found in 22q11.2DS. Parts of the eye may be missing leading to partial blindness. The inner ear area (semicircular canals) may not be properly formed leading to balance problems and deafness. Individuals with DGS can have autoimmune disease resulting in low platelets (which causes bleeding problems), low neutrophils (white blood cells that also fight infection), and low red blood cells that carry oxygen in the blood. Individuals can also develop thyroid disease (and need to take thyroid medication). Some develop arthritis. Individuals with DGS may have a variety of other abnormalities including cleft palate, delayed speech, and difficulty in feeding and swallowing. Some have learning disabilities, behavioral problems, psychiatric disorders (such as schizophrenia), and hyperactivity.

Diagnosis

The diagnosis of DGS is made on the basis of findings that are present at birth, or develop soon after birth, in particular, heart defects and low calcium. Babies with heart defects are often screened for 22q11.2DS by a blood test, commonly a FISH assay, a method using a fluorescent signal to visualize the presence of the genetic region on one of two copies on chromosome 22. Other newer tests are available to analyze gene mutations and chromosome deletions to make a diagnosis of DGS. Children with CHARGE are usually identified at birth because of their physical findings. Even though children with 22q11.2DS or CHARGE often have normal T cell numbers, these children should be followed by a geneticist who can provide guidance for the other issues that are common problems for children with DGS.

Newborn screening (a drop of blood from a heel stick) for Severe Combined Immunodeficiency (SCID) may identify a child as having low T cells. If the test indicates that a child has low T cells, an additional blood test is done to determine the actual number of T cells. An immunologist reviews the data and lets the parents know if the T cell numbers are low and if the child needs additional follow up.

Inheritance

Most cases of 22q11.2 DS occur spontaneously. DGS is caused by a large deletion from chromosome 22. This deletion means that several genes from this region are not present in those with DGS. It appears that the variation in the symptoms of the disease is related to the amount of genetic material lost in the chromosomal deletion. Many of the manifestations of DGS have been linked to deletion of the T-box transcription factor 1 *(TBX1)* gene on chromosome 22q11, which plays a role in neural crest cell migration, pharyngeal arch (PA) development and formation of the pharyngeal pouches. *TBX1* interacts with many genetic molecular pathways leading to craniofacial defects and aberrant neural crest cell migration and survival.

Once a child is found to have 22q11.2 deletion, it is recommended that all parents be tested to determine if they or their other children are at risk. Affected parents or siblings may not have obvious symptoms of DGS.

All described cases of CHARGE syndrome due to CHD7 mutation have occurred spontaneously. There are no known parents with CHARGE syndrome. It is extremely unlikely for any couple to have more than one baby with CHARGE syndrome.

Treatment

The treatment of a child with DGS varies depending on the infant's immune status and the medical problems that the child has. For the 1% of infants with DGS who on newborn screening are found to have no T cells, transplant of thymus is recommended because of the high risk of infection and death. Because the defect in T cell development is due to a lack of thymus, hematopoietic stem cell transplantation (bone marrow transplantation) is not effective. These infants should be kept in strict isolation to avoid infection until T cells develop after thymus transplantation.

For all infants with DGS, a multidisciplinary team is the preferred form of care. One example of such a team would be a clinic specializing in 22q11.2DS with multiple medical specialists needed for any child with DGS (whether or not the child has 22q11.2DS). The table below lists specialists who may be needed to care for infants with DGS. When a team is not available, the pediatrician, geneticist, or immunologist caring for the child should be asked to arrange for the appropriate doctors to be consulted for care for the child.

Team Member	Medical Focus
Geneticist, genetic counselor	Counseling for the child and other family member and coordination of care
Immunologist	T cell counts, immunization schedule
Speech therapist	Speech therapy and feeding
Physical and occupational therapist	Physical skills such as rolling over, sitting, crawling, walking and activities of daily living
Cardiologist	Heart abnormality if present and blood pressure
Kidney doctor	High blood pressure, single kidneys, abnormalities of the urine system
Pulmonology	Treatment of breathing problems, tracheostomy care if necessary
Gastroenterologist and nutritionist	Tube feeding, growth, constipation management
Ears/nose/throat doctors	Cleft palate, tubes in ears
Orthopedic surgeons	Scoliosis (curved spine)
Endocrinologists	Calcium management, thyroid disease
Pediatric psychologists or psychiatrists	Behavioral problems and psychiatric disease

Expectations

For the 99% of infants with DGS who have T cells, the immune system is not a major problem. An immunologist will determine if the T cells are high enough for administration of live vaccines such as the rotavirus vaccine; the measles, mumps, rubella virus vaccine; and the varicella (chickenpox) vaccine. An immunologist should assess each child periodically to confirm that the T cell numbers remain adequate.

T cells help another white blood cell called the B cell make antibody responses to vaccines. In about 10% of individuals with 22q11.2 DS, they have difficulty with production of immunoglobulins or vaccine responses. Some of these individuals require immunoglobulin replacement therapy. (See Immunoglobulin Replacement Therapy Chapter.)

There is great variability in the other problems that a child with 22q11.2 DS may have.

Some children with very mild forms of DGS are diagnosed later in life due to speech abnormalities or other subtle findings, while others have varying degrees of impairment in any combination of the following aspects of DGS.

The heart defects at birth often need to be repaired by heart surgery. Cardiac follow up will be needed depending on the type of heart defect. The cardiologist may also provide guidance for high blood pressure (if present.)

Low calcium levels from a poorly functioning parathyroid gland usually improve, and most children do not need calcium replacement for more than one year. The exception is the group born with no T cells—these children often remain on calcium for life. It is important that calcium levels be followed by the pediatrician because on rare occasions the calcium levels may drop in a child who previously had been able to come off of calcium replacement.

The thyroid should be checked annually in children with DGS because thyroid disease is very common. By the time an individual with DGS is 40 years old, 1 of 5 have thyroid disease and are treated with thyroid medication.

Learning disabilities are common. Most children with DGS take longer than usual to learn to talk. Math is particularly difficult. Working with school officials, including the school nurse, to develop an Individualized Education Program (IEP) and/or an Individual Healthcare Plan (IHP) can be very helpful.

Psychiatric disease can develop in adolescents and adults. Two common conditions are schizophrenia and bipolar disorder in individuals with 22q11.2DS. Family and school support are very important for children with DGS to enhance their development as best as possible. Staying connected to others through the Immune Deficiency Foundation, the 22q11.2 Society, and the CHARGE Syndrome Foundation can be helpful for families.

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