Understanding DiGeorge
A form of severe combined immunodeficiency, DGS is likely underdiagnosed due to the variability in its characteristics and symptoms, and researchers are still trying to unravel the mystery of why it occurs.

By Ronale Tucker Rhodes, MS

SOME 50 YEARS AGO, Dr. Angelo DiGeorge, an endocrinologist, observed that a subset of patients had similar clinical features, including hypoparathyroidism, an underactive parathyroid gland that results in hypocalcemia (low blood calcium levels), an underdeveloped or absent thymus that results in problems with the immune system, conotruncal heart defects and cleft lip and/or palate. The disorder was coined “DiGeorge syndrome,” or DGS, until the 1970s, when a speech pathologist named Robert Shprintzen, PhD, described a group of patients with similar clinical features and coined the term velo-cardio-facial syndrome (VCFS); others also referred to it as Shprintzen syndrome. Interestingly enough, other children with similar clinical features were diagnosed with the autosomal dominant form of Optiz G/BBB syndrome and Cayler cardio-facial syndrome. It wasn’t until technology was developed in the 1980s that identified the underlying chromosome, 22q11, in over 90 percent of these patients. Thus, it was discovered that different groupings of features were described as separate conditions even though they were part of a single syndrome — 22q11 deletion syndrome — with many possible signs and symptoms. Today, many physicians refer to DGS as 22q11 deletion because it describes the underlying chromosome problem or as VCFS because it describes the main body systems involved.

What Is DGS?

DGS is one of 11 forms of severe combined immunodeficiency (SCID) classifications. It is a common syndrome, occurring in an estimated one in 4,000 to 6,395 newborns; however, researchers and doctors suspect it is more common and is undiagnosed due to its variable features. For instance, DGS may not be identified in people with mild symptoms, and it may be mistaken for other disorders with overlapping features.

DGS is caused by abnormal cell and tissue development during fetal growth. Individuals with DGS are susceptible to infections due to poor T cell production and function and often have altered facial characteristics, abnormal gland development or defects in organs such as the heart. It is a lifelong condition that mostly affects infants and children, who differ in the organs and tissues affected, as well as in the severity of the disease.
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What Causes DGS?

In humans, DNA is organized as 23 pairs of chromosomes. One pair, the sex chromosomes, consists of either two X chromosomes (XX), resulting in a girl, or one X and one Y chromosome (XY), resulting in a boy. The other 22 pairs of chromosomes, referred to as autosomes, are numbered 1 through 22. Each chromosome has two or three parts: a short arm (which is not present in some), a central portion and a long arm. The long arm is called by the number of the autosome and “q.” Therefore, the long arm of chromosome 22 is called 22q. The arms also have sections that are numbered and appear as light and dark bands. 22q11 is the 11 band (pronounced one-one) on the long arm of chromosome 22.5

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Most cases of DGS result from a deletion of chromosome 22, but a small number of cases of DGS have defects in another chromosome, notably 10p13.6 Every person has two copies of chromosome 22, one inherited from each parent. In persons with DGS, one copy of chromosome 22 is missing a segment that includes an estimated 30 to 40 genes, which haven’t been clearly identified and aren’t well understood. The region of chromosome 22 that’s deleted in DGS is known as 22q11.2. This deletion usually occurs as a random event in the father’s sperm or in the mother’s egg, or it may occur early during fetal development. It is rarely an inherited condition passed to a child from a parent who also has deletions in chromosome 22 but may or may not have symptoms.7

Symptoms of DGS

Symptoms of DGS vary greatly from patient to patient depending on what body systems are affected and how severe the defects are. And, while some symptoms may be apparent at birth, others may not be apparent until later in infancy or early childhood.8 Characteristics of DGS include underdeveloped facial characteristics, parathyroid gland abnormalities, heart defects and thymus gland abnormalities. These characteristics can lead to a number of symptoms, including cleft palate, poor function of the palate, delayed acquisition of speech, difficulty feeding and swallowing, bluish skin due to poor circulation of oxygen-rich blood, twitching or spasms around the mouth, hands or throat, frequent infections, delayed growth, failure to gain weight, poor muscle tone, delayed development, learning disabilities, behavioral problems and hyperactivity.8,9

Facial characteristics include an underdeveloped chin, eyes with heavy eyelids, ears that are rotated back and defective upper portions of the earlobes. With hypoparathyroidism, DGS patients may have trouble maintaining normal calcium levels, which can cause them to have seizures. Heart defects all involve the aorta and the part of the heart from which the aorta develops. The thymus controls the development and maturation of T lymphocytes, as well as helps B lymphocytes develop into plasma cells and produce immunoglobulins (antibodies). The smaller the thymus, the fewer T lymphocytes will be produced. T lymphocytes are essential for resistance to certain viral and fungal infections. Therefore, DGS patients are at increased susceptibility to viral, fungal and bacterial infections.9 Recurrent infections tend to decrease in late childhood and adulthood, with approximately one-third of affected adults having mild recurrent infections.5

Diagnosing DGS

Typically, DGS is diagnosed at birth or in infancy based on clinical observation. Historically, the diagnosis of DGS was made when at least three of the characteristics described previously were present, which caused many mild cases of DGS to be missed.6

Today, a variety of tests can help to diagnose DGS. Lab tests include a complete blood cell count and serum calcium and parathyroid hormone studies. Tests that evaluate T-cell count and function include flow cytometry, reverse-transcriptase polymerase chain reaction assay to assess thymic T-cell count for detection of TCR excision circles and antibody response studies. Imaging studies to diagnose thymic and cardiovascular abnormalities in 22q11.2 include radiography, magnetic resonance imaging, computed tomography scanning, echocardiography, and angiography and magnetic resonance angiography. Genetic studies can also be conducted, including the chromosomal microarray analysis or array comparative genom ic hybridization, TBX1 gene study, multiplex ligation-dependent probe amplification and fluorescent in situ hybridization (FISH).10 The FISH test is the technology (previously mentioned) developed in the 1980s that can identify
deletions of 22q11 that are too small to be seen under the microscope. Today, FISH is the most definitive of the diagnostic genetic tests. It is not routinely conducted for every amniocentesis or from every blood sample from patients; instead, it is performed only when physicians suspect a 22q11 deletion in a person or a fetus.\(^5\)

If a 22q11 deletion is detected in a child, both parents are offered the FISH test to determine if the child’s deletion is inherited. In approximately 10 percent of families, the deletion is inherited. And, an individual with a 22q11 deletion has a 50 percent chance with each pregnancy of passing it on to their child.\(^1\)

It should be noted, however, that a child may still have DGS even if the FISH test is negative. As noted previously, this technology only tests positive in approximately 90 percent of DGS patients. A small percentage of DGS patients have a deletion affecting the short arm of chromosome 10 that can be tested with a different FISH. But, most DGS patients who have a negative FISH test have no chromosomal abnormality that can be found currently. Therefore, if a child is diagnosed with DGS on the basis of certain characteristics, the diagnosis remains true even if the FISH test is negative.\(^1\)

**Treating DGS**

Treatment of DGS patients differs depending on their specific symptoms, and many physicians will likely be involved. For instance, heart defects will be evaluated by cardiologists, cleft lips or palates will be evaluated by plastic surgeons and speech pathologists, feeding difficulties will be evaluated by speech and gastrointestinal specialists, and T-cell disorders and recurrent infections will be evaluated by immunologists.\(^1\)

Critical problems of DGS can usually be corrected with treatment. Hypoparathyroidism can typically be managed with calcium and vitamin D supplements. Cleft palate can be repaired with surgery. Surgery is also required to repair heart defects and to improve the supply of oxygen-rich blood.\(^11\)

If there is limited thymic function, infections are treated as they would be for all children, and the normal vaccine schedule is followed. The immune system function normally improves with age for those with moderate thymic impairment. If there is severe thymus impairment, treatment requires a transplant of thymus tissue, specialized cells from bone marrow or specialized disease-fighting blood cells.\(^11\) In rare cases in which the T-lymphocyte defect of the thymus is significant enough to cause the B lymphocytes to fail to make sufficient antibodies, immune globulin (IG) replacement therapy is required.\(^9\)

In 2012, researchers on behalf of the International DiGeorge Syndrome Immunodeficiency Consortium conducted an evaluation of the records of 1,023 DGS patients with a mean age of 5.5 years, 885 of which had immunoglobulin data available. The researchers examined immunoglobulin levels according to age, and found that low levels of immunoglobulin are present in a significant minority of patients and, overall, between 2 percent and 3 percent of those patients were receiving immune globulin replacement therapy. From that study, the researchers concluded that DGS is associated with significant humoral immune deficiency.\(^12\)

Many DGS patients also experience developmental, mental health or behavioral problems that can be treated with speech therapy, occupational therapy and developmental therapy.\(^11\)

**DGS Research**

Much more needs to be understood about DGS to treat these patients and improve their outlook.

Researchers are trying to identify the 30 to 40 missing genes on chromosome 22, many of which have not been well-characterized, that contribute to the variability in DGS characteristics and symptoms. For instance, they have found that the loss of a particular gene on chromosome 22, TBX1, is likely responsible for many of the DGS characteristic signs such as heart defects, cleft palate, distinctive facial features, hearing loss and low calcium levels, as well as behavioral problems. And, the loss of the COMT gene may also help to explain the increased risk of behavioral problems.\(^2\)

**Critical problems of DGS can usually be corrected with treatment.**

In 2013, an international team of researchers described a new mechanism by which most human cells can avoid being bombarded by DNA fragments. DGS is characterized by absence of the “microprocessor” protein complex, which means patients lack a “vigilante” gene to watch out for repeated sequences and, therefore, are potentially susceptible to being bombarded by DNA fragments. These researchers are now conducting studies, using an embryonic model of induced pluripotent stem cells donated by patients with DGS, to determine the impact of the repeated sequences during the embryonic stage. By examining
the deletion that causes this pathology, they believe these studies will clarify the molecular base for DGS, as well as permit the long-term development of new therapies for its treatment.\textsuperscript{13}

**Much more needs to be understood about DGS to treat these patients and improve their outlook.**

In 2014, researchers discovered information about the pathogenesis of feeding and swallowing difficulties often found in children with neurodevelopmental disorders. Using an animal model of DGS, the researchers found clear signs of early feeding and swallowing disruption and underlying changes in brain development, known as pediatric dysphagia. “A lot of children with pediatric dysphagia tend to be sicker from birth onward. Making the health of these kids as stable as possible from birth onward would allow clinicians to pick up on developmental signs sooner, which are often masked by more immediate problems like having ear or respiratory infections, not sleeping or not gaining weight,” said Anthony-Samuel LaMantia, PhD, professor of pharmacology and physiology at the GW School of Medicine and Health Sciences and director of the GW Institute for Neuroscience. “The physical stress caused by the complications of dysphagia early on likely exacerbates the fundamental behavior issues that will emerge later. A happy, healthy baby is often able to focus on observing and gathering information to drive important experience-dependent changes in the brain. A sick baby has less time to do so, possibly making cognitive outcomes even worse.”\textsuperscript{14}

Researchers at the University of California, Davis, have found that for children with DGS, anxiety (but not intelligence) is linked to poorer adaptive behaviors such as self-care and communications skills that affect daily life. The study evaluated 78 children with DGS, ages 7 years to 15 years, with a battery of standardized tests related to behavior, anxiety, adaptive functioning and intelligence. Thirty-six typically developing children with no known genetic syndromes were also evaluated for comparison. Many anxiety scores were found to be significantly higher in children with DGS than in typically developing children. Fifty-eight percent of children with DGS were found to have at least one elevated anxiety score, although only 19 percent had previously been diagnosed with an anxiety disorder. In addition, higher anxiety scores correlated with lower adaptive function among children with DGS. The study findings suggest that helping children cope with fear-based symptoms may be the best strategy for increasing independence and protecting against psychiatric problems later in life.\textsuperscript{15}

**DGS Outlook**

Until more is known, the outlook for DGS patients depends on the degree to which the organ systems are affected. The most important determining factor is the severity of heart disease. The deficit in T-cell production is also important, although the infection pattern appears optimistic since most patients don’t suffer from recurrent infections in adulthood.\textsuperscript{9}

Tragically, a small percentage of children with DGS with severe heart defects and immune system problems won’t survive the first year of life. Those with less acute problems, who receive proper treatment, will survive into adulthood. Many will need extra help and long-term care for their individual health needs, as well as for their behavioral conditions.\textsuperscript{16} But with continued research, there is potential for better understanding and treatments. And when the mystery of DGS is better understood, a cure cannot be far behind. ■

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**References**