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The DiGeorge Syndrome

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A single mother arrives at the emergency room of her local hospital with her 3 month old baby, George, who presents with a high fever, dry cough, and difficulty breathing—symptoms characteristic of pneumonia. The mother informs the triage nurse that his symptoms began several days ago. The nurse notes that baby George seems rather small for his age, in both size and weight. To determine whether George has pneumonia, the attending physician takes a sputum sample, orders several routine blood tests, and sends the patient to receive a CT scan. Test results return several hours later, revealing that George has Pneumocystis pneumonia caused by Pneumocystis carinii, an opportunistic fungus that usually causes illness in HIV patients who have compromised immune systems. Blood tests report low levels of naïve T cells, but normal levels of other blood cells, including double-negative T cells. Upon the return of the CT scan, the physician notes that George's thymus is absent, and orders a FISH analysis to determine whether baby George has DiGeorge syndrome so that proper treatment can be established.

DiGeorge syndrome (DGS) is a congenital primary immune deficiency disorder associated with the abnormal development of cells arising from the pharyngeal apparatus (neck area) during growth and differentiation of the fetus (Figure 1). The risk is the same across gender and is estimated to occur in 1 out of 4000 live births, making it one of the most common genetic disorders (Oskarsdottir, Persson, Eriksson, & Fasth, 2005; Lindsay, 2001). In the mid-1960s, an endocrinologist recognized that certain clinical features often presented together and, thus, made the assumption that they belong to one disorder, which was coined after the discoverer, Dr. Angelo DiGeorge (2003). In the 1970s, a speech pathologist, Dr. Robert Shprintzen, gave the term velo-cardio-facial syndrome (VCFS) or Shprintzen syndrome to a similar group of features (2003). A decade later, it was found that over 90% of patients diagnosed with either DiGeorge or Shprintzen syndrome had a common genetic deletion on the long arm of the 22nd chromosome in the q11.2 position (Lindsay, 2001). Hence, although described by two independent researchers, DGS and VCFS are united by a common microdeletion: 22q11 deletion syndrome or CATCH-22 (Cardiac defects, Abnormal faces, Thymic hypoplasia, Cleft Palate, Hypocalcaemia, Chromosome 22) (Markert et al., 2003).

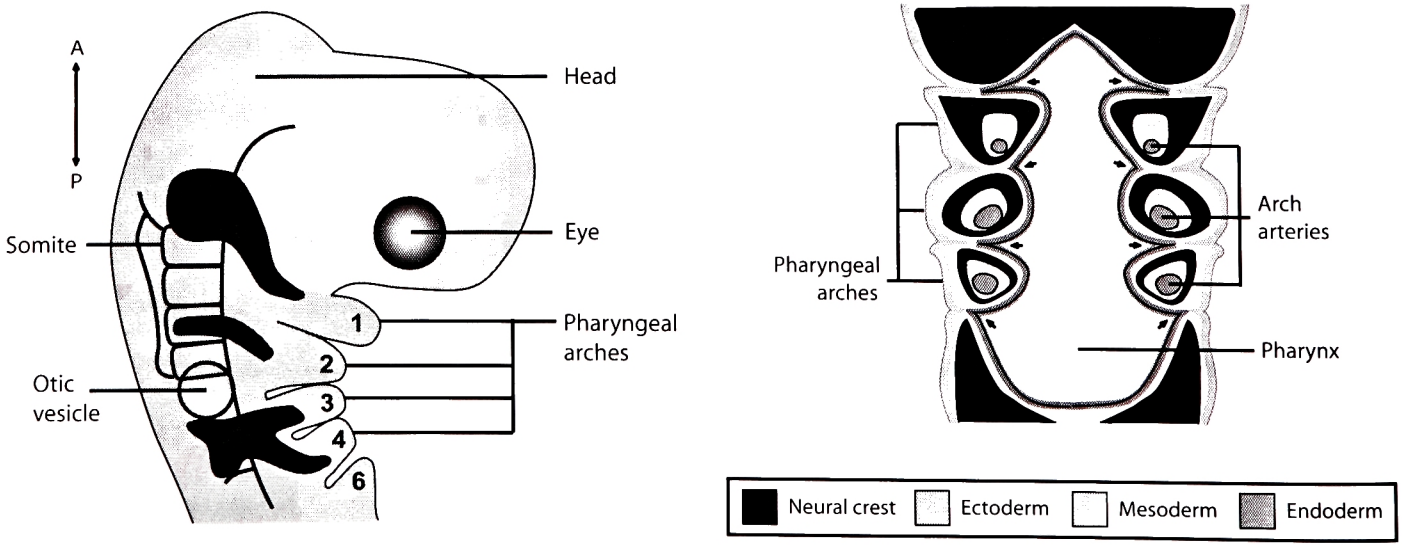
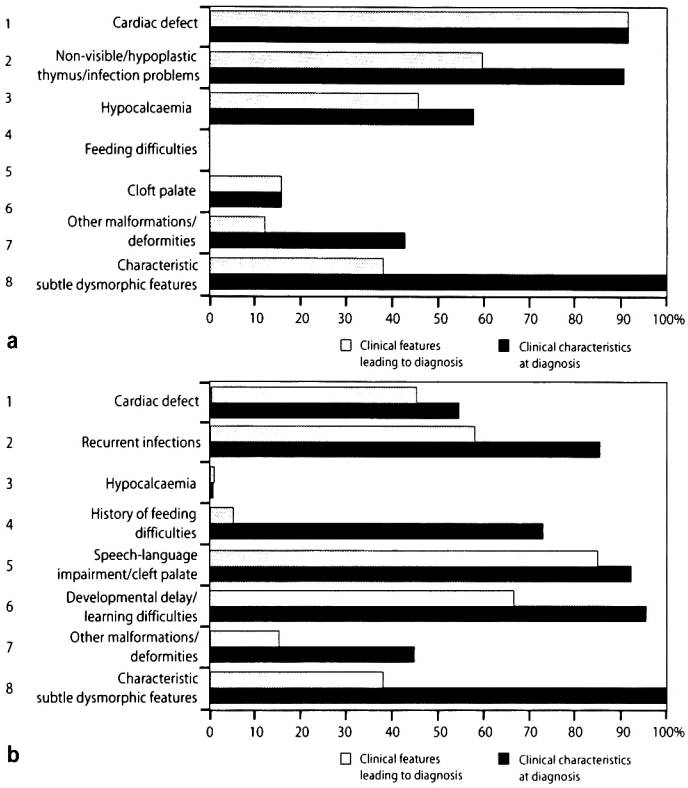


Figure 1: The pharyngeal apparatus consists of all three layers of embryonic tissue (ectoderm, mesoderm and endoderm) and gives rise to the thymus, parathyroid, parts of the jaw, and the arch arteries (vessels of heart) (Lindsay, 2001).

Figure 2: Clinical findings at time of diagnosis of DiGeorge syndrome in (a) 26 infants (median number of characteristics per infant = 4), and (b) 74 children and teenagers (> 2 years old) (median number of 6 clinical characteristics found per patient) (Oskarsdottir et al., 2005).



Causes and Pathophysiology of DiGeorge Syndrome

Prior to recent research, which identified the 22q11 deletion, DiGeorge syndrome was believed to be caused by teratogens—agents associated with developmental defects in the embryo—due to the presence of similar clinical features that were linked to prenatal exposure to retinoic acid (Accutane), maternal diabetes, and fetal alcohol syndrome (Lindsay, 2001; Porth, 2005). However, research suggests that microdeletion of 22q11 occurs de novo in all but 10-15% of cases in which DGS is inherited from a mildly affected parent (Oskarsdottir et al., 2005). Since a microdeletion of only one chromosome is required to develop the clinical features, DGS is classified as an autosomal dominant disorder and those affected have a 50% chance of passing the syndrome to their offspring (Oskarsdottir et al., 2005).

In 90% of cases, the same thirty genes are deleted from chromosome 22, however, it is not yet known how many of these genes are responsible for the clinical features of DGS (Lindsay, 2001). In a mouse study, researchers knocked out the Tbx1 gene which is normally located in the 22q11 region The gene is highly expressed in the pharyngeal apparatus during embryonic development, and may initiate the segmentation of the entire pharyngeal apparatus (Lindsay, 2001). They found that the heterozygous loss of the Tbx1 gene does not affect embryo viability (which explains why a fetus with DGS often makes it to the end of the third trimester) but that the homozygous loss of the gene can affect the development of the entire pharyngeal apparatus and results in perinatal lethality (Jerome & Papaioannou, 2001). Hence, the loss of Tbx1 can account for the abnormal formation of some of the structures that arise from the pharyngeal arches. For instance, Tbx1 knockout mice have been found to have persistent truncus arteriosus, lack thymus and parathyroid glands, and have jaw abnormalities, common clinical features of DGS. Although Tbx1 deletion has elucidated its role in DGS, it is still unknown whether the Tbx1 gene alone is sufficient to induce the deficits associated with this disorder or if signals from other genes are required (Lindsay, 2001).

Complications

Although the majority of patients diagnosed with DGS share a common deletion on chromosome 22, the phenotype of this syndrome has variable expression and severity (Figure 2) (Oskarsdottir et al., 2005). The structures affected by DGS such as the thymus, parathyroid, part of head and neck, and heart, may appear to be unrelated in a developed infant, but they stem from the same fetal tissues in the pharyngeal apparatus that develops before the twelfth week of gestation (Porth, 2005). For normal development, cells must migrate out of the pharyngeal apparatus to their respective locations. However, in DGS, the development and/or migration of these tissues is abnormal (Winkelstein, Winkelstein, Bass, & Patterson, 2001).

Heart Defects

In a study of 100 children with DGS, 92% had a congenital heart defect (Oskarsdottir et al., 2005). Common heart defects due to 22q11 deletion involve the aorta and part of the heart from which the aorta develops (Oskarsdottir et al., 2005). For instance, the truncus arteriosus may develop in which a single vessel exits the heart, due to the failure of septum formation that normally separates the truncus into an aorta and a pulmonary trunk (Porth, 2005). This leads to the mixing of oxygenated and deoxygenated blood. Another common congenital heart defect is a ventricular septal defect characterized by a hole in the interventricular septum of the heart. Blood shunts from the side of higher pressure to lower pressure (left-to-right shunt), resulting in an increased amount of mixed blood pumping through the pulmonary trunk and into the lungs (FIRSTConsult,

2005). Thirdly, the combination of certain defects, such as pulmonary stenosis, overriding aorta, ventricular septal defects, and right ventricular hypertrophy are given the collective name: "Tetralogy of Fallot," a severe condition that causes cyanosis within the first few years of life, breathlessness upon exertion, aortic ejection click, and ejection systolic murmur (FIRSTConsult, 2005). Each of these cardiovascular defects arises from an abnormal development of the cardiac outflow tract and of the pharyngeal arch artery IV (Lindsay, 2001). In instances of severe defects, the patient may experience restricted growth and a failure to gain weight (Lindsay, 2001).

Hypoparathyroidism

The parathyroid consists of four small glands located in the neck area on the posterior surface of the thyroid gland, and arises from the third pharyngeal pouch (Lindsay, 2001; Tortora, 2006). These glands increase extracellular calcium levels when they fall below the normal range (Tortora, 2006). Deletion of genes that control the development of the pharyngeal pouches, as with DGS, results in impaired or failed development of the parathyroid glands and the loss of calcium regulation (Lindsay, 2001). Failure to control the normal metabolism and blood levels of calcium in patients with DGS may trigger seizures, muscle spasms and cramps, confusion, heart failure, and arrhythmias, symptoms characteristic of hypoparathyroidism (Tortora, 2006; Choi et al., 2005).

Thymus Gland Abnormalities

The thymus gland is a bilobed organ that plays an important role in adaptive immunity. The thymus develops from the third pharyngeal pouch and descends to its destined location behind the sternum and between the lungs in the mediastinum (Tortora, 2006). Immature T lymphocytes produced in the bone marrow, from hematopoietic stem cells, migrate to the thymus where they undergo somatic diversification and selection (Janeway, Travers, Walport, & Shlomchik, 2005). Although the thymus is only 20 grams at birth, it may grow to 70 grams and is largest during infancy (Tortora, 2006). It begins to atrophy after puberty at which point the repertoire of immune cells is well established. Although it continues to involute during adulthood (~3g), the thymus still produces enough new T lymphocytes to sustain immune functions (Tortora, 2006). Due to the 22q11 deletion, a patient with DiGeorge syndrome, however, may have a hypoplastic thymus or an absent thymus, rendering the patient immunodeficient. Although it is rare for a patient to have complete absence of the thymus, this severe form of DGS may only be determined on the basis of laboratory data since imaging studies or physical examination of the mediastinum may not detect a small ectopic thymus (Markert et al., 2003). Through flow cytometry, lab results can be obtained to determine the number of mature T cells and other derivatives (Janeway et al., 2005). A patient with no thyroid function is considered to be "athymic".

Secondary complications due to an absent/ineffective thymus involve increased susceptibility to viral, fungal, and bacterial infections since T cells are essential for cell-mediated immunity as well as in activating humoral-mediated immunity (Janeway et al., 2005). In addition, patients with DGS are more susceptible than the normal population to infectious and opportunistic diseases, such as pneumocystis pneumonia and other pulmonary diseases (Deerojanawong, Chang, Eng, Robertson, & Kemp, 1997). The respiratory tract is a vulnerable site of entry for infection and a challenge to protect in the absence of a functional immune system. Warning signs of primary immunodeficiencies include: (a) eight or more ear infections in one year, (b) two or more months on antibiotics with little effect, (c) two or more pneumonias within one year, (d) failure of the infant to gain weight or grow normally, and (e) a need for intravenous antibiotics (Greenberg, 2005). Moreover, depending on the severity of the thymic deficiency, further complications may be induced through the delivery of vaccines that contain even small concentrations of live, attenuated viruses, such as the measles-mumps-rubella-varicella (MMR) vaccine and through contact with persons who have contagious infections (FIRSTConsult, 2005; Perez, Bokszczanin, Donald-McGinn, Zackai, & Sullivan, 2003).

Craniofacial Anomalies

A separation in the upper lip is called a cleft lip, while a similar birth defect in the roof of the mouth, the palate, is called a cleft palate. Although the soft tissues and bony and cartilaginous structures of the lip, nose, and soft and hard palates all develop from the first and second pharyngeal arches, they develop separately (Lindsay, 2001; FIRSTConsult, 2005). Thus, it is possible for an infant to have a cleft lip, a cleft palate, or variations of both. Together, these deformities are the most prevalent craniofacial anomalies of DGS (Lindsay, 2001). Severe malformations of lips and soft and hard palates may cause significant speech, feeding, and swallowing difficulties, and may result in airway obstruction prompting surgical correction (FIRSTConsult, 2005).

Deletion of 22q11 can also be associated with atypical facial appearance: upward bowing of their mouth (small), underdeveloped chin, hooded eyes that slant downward, low set ears that are defective in the upper lobes (Porth, 2005).

Other Considerations

A neurobehavioural phenotype may result from DGS, which manifests into learning and cognitive disabilities, hyperactivity, and psychiatric disorders, such as schizophrenia and bipolar disorder. The basis of these complications, however, has not yet been established (Lindsay, 2001). Those affected with DGS who survive and enter into adulthood most often require academic assistance throughout school and long term care for their individual psychiatric needs (2003).

Diagnosis

Diagnosis of DiGeorge syndrome is usually based on symptoms that are present at or soon after birth. However, milder cases of this disorder may result in diagnoses made well into infancy or childhood when complications are encountered. A hospital-based study of 100 patients, comprised of children and adolescents with DiGeorge syndrome, found that only 26% of patients were diagnosed during infancy (Oskarsdottir et al., 2005). Diagnosis remains a challenge and is often delayed due to varying degrees of presentation and severity (Oskarsdottir et al., 2005; Lindsay, 2001). Before the discovery of a genetic basis for this disorder, a patient only needed to present with at least three of the characteristics symptoms to be diagnosed with DGS (Winkelstein et al., 2001). However, this method of diagnosis missed cases with mild or latent clinical presentations. Presently, a FISH analysis (Fluorescent In-Situ Hybridization) is conducted to detect whether or not there is a microdeletion on chromosome 22 (Driscoll, 2001). Since almost all diagnoses made in infancy are associated with cardiac defects, newborns with cardiac defects born in some European hospitals are routinely screened for the 22q11 deletion neonatally using FISH analysis (Oskarsdottir et al., 2005).

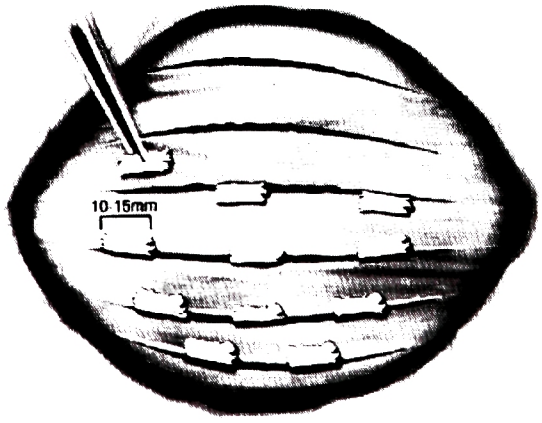


Figure 3: Artist rendition of surgical implantation of thin slices of thymus tissue into the quadriceps muscle (Rice et al., 2004).

In North America, pre- and post-natal testing is available in select hospitals, only two of which are Canadian (University of Washington, 2005). Prenatal testing using FISH analysis can be performed at 15-18 weeks of gestation by sampling fetal cells through amniocentesis or as early as ten weeks of gestation by using CVS for high-risk fetuses (Driscoll, 2001; University of Washington., 2005). In lower-risk pregnancies where there is no known family history for 22q11 deletion, findings of cleft palate or congenital heart disease by routine ultrasound will lead to further testing for the genetic deletion by FISH analysis (Driscoll, 2001). In either case, early diagnosis can prepare health care professionals and parents for the management, treatments, and surgical procedures that lie ahead.

Although FISH analysis is the gold standard procedure for diagnosing DiGeorge syndrome, other diagnostic tests may be ordered to determine the severity of the disorder. In addition, other tests and procedures may be performed before the differential diagnosis of DGS is considered. For instance, ultrasound examination of the fetus during the second trimester may visualize cardiac and palatal anomalies. Additionally, if the patient presents with a recurrent or prolonged infection after birth, a complete blood count may be done to determine if the bone marrow is working normally. A white blood cell count (WBC) may demonstrate decreased white cell values, indicative of infection (University of Iowa, 2005). However, since a WBC test is not specific to the type of cell in the sample, a WBC differential test may be performed to determine the proportion of neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Decreased lymphocyte counts may lead to further testing to determine which subsets of lymphocytes are low (Tortora, 2006; University of Iowa, 2005). Furthermore, echocardiograms and Doppler tests may be used to evaluate the structure and function of the heart and its valves, while CT scans may be conducted to visualize the presence and size of the thymus.

Treatment and Therapy

Due to the genetic nature of DiGeorge syndrome and the striking variability in clinical expression, treatment is aimed at correcting the defects in the organs or tissues affected. For instance, surgical intervention can be performed to treat facial deformities. Plastic surgery techniques have made great advances in treating children with cleft lips and palates and are available worldwide. Surgery for a cleft is generally done when the child is about ten weeks old, while a procedure for cleft palate is performed on infants of at least nine months of age, since the latter operation involves more extensive surgery.

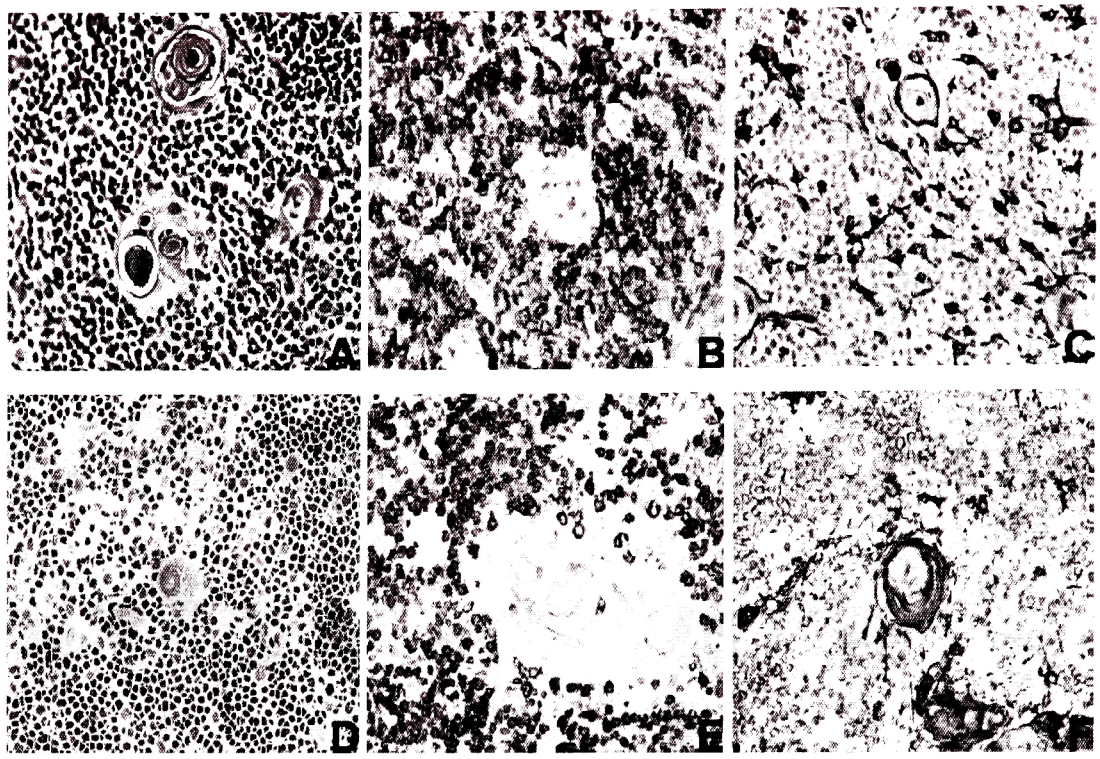


Figure 4: Immunohistochemistry comparing biopsies of normal thymus tissue (A, B, C) compared to biopsy of transplanted tissue 218 days after surgery (D, E, F). Reactivity with CD3 shows T cell in graft (Rice et al., 2004).

Surgical care for more severe heart defects may be immediately essential for survival. In milder cases of ventricular septal defects, the physician may delay surgery to see if the hole closes on its own as the myocardium continues to develop in infancy (FIRSTConsult, 2005). However, if the interventricular hole is greater than 0.5 cm^2, surgery is quickly scheduled since it is unlikely that the defect will self-repair (FIRSTConsult, 2005).

Some children have mild defects in T cell function, which improve as they grow older. This is related to an initially tiny but otherwise normal thymus gland. The tiny thymus ultimately grows enough to provide adequate T cell function. However, in 25% of cases the thymus is completely absent or never grows enough to develop adequate numbers of T cells (Markert et al., 2003). This defect may be significant enough to cause B cells to fail to generate enough antibodies. Of those with complete DiGeorge syndrome (athymic), 27% will live to their first birthday and none will survive past two years of age without treatment (Markert et al., 2003). Thus, thymus transplants, introduced and successfully completed as early as 1968, are essential to prolonging the lives of these individuals. In this procedure, donor thymuses are sliced into 0.5 mm sections, matched for HLA type between donor and recipient, and grafted bilaterally into both quadriceps muscles (Figure 3) (Markert et al., 2003; Rice et al., 2004). The efficacy of thymic transplantation depends on HLA matching between donor and recipient, length of tissue cultured, and amount of thymus tissue transplanted (thymus transplantation). One study reported that 218 days after thymic transplantation, immunohistochemistry performed on biopsies of thymic tissue were comparable to those from normal thymuses in terms of activity and number of T lymphocytes (Figure 4) (Rice et al., 2004). However, the success rate of thymic transplants has been questioned since it is not possible to determine how many children would have improved spontaneously without the procedure due to a small thymus that may grow to a size that is able to sustain normal function.

Besides surgery, pharmacological agents may be used to alleviate underlying symptoms of DGS. Therapeutic calcium supplementation and replacement of parathyroid hormone can restore the homeostatic balance that is offset by hypoparathyroidism. In addition, infections, such as pneumonia, should be treated with the proper antibiotics, such as Trimethoprim (TMP) and sulfamethoxazole (SMX), which are very effective anti-PCP drugs when taken together (FIRSTConsult, 2005). Preventive management, such as maintaining good hygiene and proper hand-washing, can reduce the number of viral, bacterial, and opportunistic infections (Deerojanawong et al., 1997).

Closing Remarks

A FISH analysis for 22q11 deletion was not ordered during baby George's neonatal period, because he did not have any obvious craniofacial abnormalities. Hence, he was not

diagnosed with DGS. However, baby George soon fell ill to an opportunistic pathogen, pneumocystis carinii, which a healthy individual can usually fight off without experiencing any symptoms. After ordering routine blood tests, it became evident that George's naïve T cells were low while he had a normal amount of double-negative T cells, indicating a nonfunctional or absent thymus. At this point, physicians ordered a FISH analysis for 22q11 deletion to confirm that he had DGS. Although antibiotics may be prescribed to treat his current infection, recurrent infections are likely to occur since his immune system cannot produce mature T lymphocytes. This, in turn, prevents B lymphocyte activation and antibody production, leading to the loss of proper immune response (Janeway et al., 2005). Hence, in baby George's case, a thymic transplant was a likely consideration.

Severe cases of immunodeficiency and congenital heart defects (complete DGS) require thymic and cardiac transplants for survival. It has been documented that a small percentage of children with severe heart defects and immune problems will not survive their first year of life. With proper treatment for heart defects, immune system disorders, and other health problems, many will survive and grow into adulthood (Greenberg, 2005). Therefore, it is vital that health care professionals regularly screen newborns that present with symptoms of DiGeorge syndrome for early diagnosis so that optimal medical care can be provided. M

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