R.C.P.U. NEWSLETTER

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DiGeorge Syndrome/Velo-Cardio-Facial Syndrome

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Historical Overview

The majority of cases of DiGeorge Syndrome (DGS) and Velo-Cardio-Facial Syndrome (VCFS) are now known to be caused by microdeletions of chromosome 22q11.2. Initially, Angelo DiGeorge, MD, an Endocrinologist in Philadelphia, reported on patients presenting early in life with a triad of findings: cardiac defects, hypocalcemia, and immune system deficiencies[1]. These patients were diagnosed with "DiGeorge syndrome". Then in 1978, Robert Shprintzen, PhD, reported on a group of patients with cleft palate, velopharyngeal incompetence (VPI), heart defects, learning disabilities and a characteristic facial appearance. He diagnosed these patients with VCFS[2]. In the early 1980's doctors at The Children's Hospital of Philadelphia began to suspect that DGS and VCFS were related syndromes. But it was not until the advent of *FISH* (Flourescent *in situ* hybridization) analysis in the 1990's that the underlying etiology of the vast majority (>95%) of cases of VCFS and DGS was found to be the same: the 22q11.2 deletion[3].

Genetic Background / Diagnostic Testing

The 22q11.2 deletion spans a 2-3 megabase region which is estimated to contain approximately 30 genes.[5] The majority of patients with DGS or VCFS have the same 3 megabase deletion regardless of their phenotypic presentation. There are a few patients who have been identified with smaller deletions.[4] To date no phenotype-genotype correlations have been made.[5]

The 22q11.2 deletion is believed to effect early embryonic development by disturbing the migration of neural crest cells to the third and fourth pharyngeal pouches.[6] These cells will later develop into the thymus, parathyroid glands and heart of the fetus.

The estimated prevalence of the 22q11.2 deletion is approximately 1/4000 live births.[7] However some researchers believe that because mildly affected individuals are often not diagnosed until much later in life or not at all, the 22q11.2 deletion may be more common in the general population than previously published. Some think the 22q11.2 deletion might even be as common as Down Syndrome (approximately 1/800 live births).[7,8]

If the diagnosis of DGS/VCFS is suspected based on clinical presentation, a 22q11.2 deletion is tested for by fluorescence *in situ* hybridization (*FISH*) using DNA probes from the DiGeorge chromosomal region. This type of testing is widely available for clinical and prenatal diagnosis of DGS/VCFS. Less than 5% of individuals with clinical presentations consistent with DGS/VCFS do not have a 22q11.2 deletion based on *FISH* testing.[3] Research studies are looking for variant deletions in the DiGeorge chromosomal region and at other chromosomal differences which may mimic DGS/VCFS.

Clinical Description

Individuals with DGS/VCFS have a range of findings including congenital heart disease, palatal defects, immune deficiency and learning difficulties.[5,9] The degree of severity of symptoms between patients is highly variable, even for affected individuals within the same family. A good explanation for why some patients are severely affected while others experience very mild symptoms is still lacking. Below is an overview of the numerous systems

that may be affected in individuals with DGS/VCFS.

Cardiac: Congenital heart defects are present in approximately 70-80% of individuals with DGS/VCFS. The majority of these defects involve conotruncal malformations (tetralogy of Fallot (22%), interrupted aortic arch type B (15%), ventricular septal defect (13%) and truncus arteriosus (7%)).[5] Other less common heart defects include: vascular ring, atrial septal defect, and aortic arch anomaly.[5] Also important to note, in one study, 50% of patients with interrupted aortic arch, type B, 34.5 % of patients with truncus arteriosus, 33% of patients with conoventricular septal defects and 16% of patients with tetralogy of Fallot were found to have the 22q11.2 deletion.[10] Thus, patients with these particular heart defects should be screened for the 22q11.2 deletion to provide appropriate medical management.

Palate: DGS/VCFS is the most common syndrome associated with a cleft palate; 8% of patients screened with a cleft palate in absence of a cleft lip were found to have the 22q11.2 deletion.[11] Studies have found that 50-70% of patients with DGS/VCFS have a palatal abnormality including VPI, submucosal cleft palate, overt cleft palate, bifid uvula and cleft lip.[5,9] Some patients may present at the mild end of the spectrum with only hypernasal speech.

Feeding: Many children with DGS/VCFS have difficulty feeding in early childhood (up to 30%).[5] In the most severe cases of dysphagia, gastrostomy tubes or nasogastic tube feedings may be required. It is hypothesized that the underlying reason for these feeding problems is dysmotility of the pharyngoesophagal area, not palate or cardiac defects.

ENT: Hearing loss is noted in approximately 35% of children with DGS/VCFS.[5, 9] The vast majority of hearing loss is conductive and thought to be related to recurrent otitis media, cleft palate or retraction or perforation of the tympanic membrane. Dysmorphia of the ears and nose of individuals with DGS/VCFS is also noted. This includes overfolded helices, cupped, microtic and protuberant ears; prominent nasal root with a bulbous nasal tip and hypoplasic alae nasae.[5] Another important finding is enlargement, medial displacement or abnormal patterning of the internal carotid arteries in approximately 25% of patients.[11] This has implications for palatal surgery.

Ocular: Some patients have been noted to have tortuous retinal vessels, posterior embryotoxin, strabismus, small optic nerves, amblyopia, and titled discs. [5, 11]

Endocrine: One of the first symptoms recognized in many infants with DGS/VCFS is hypocalcemia. Most times, hypocalcemia is transient and resolves in the neonatal period or in early childhood.[9] Short stature is seen in about 1/3 of patients with DGS/VCFS, and a small percentage of patients have been identified with a growth hormone deficiency.[12]

Immune: During the first year of life, children with DGS/VCFS are at the most risk for serious infection due to the reduced thymic production of T cells. In many patients the thymus gland is very small or non-existent.[5] There is also an increased incidence of autoimmune disease including juvenile rheumatoid arthritis (JRA), idiopathic thrombocytonpenia (ITP), vitiligo (spontaneous irregular depigmentation of skin), and Graves disease. [5, 13] Preliminary studies have suggested that adults with DGS/VCFS are at risk for immune senescence and a decreased number of T-cells later in life. The clinical implications of this are not yet known. [13]

Skeletal: Significant cervical spine abnormalities have been identified in approximately half of all patients examined; this includes cervical spine malformations and cervical spine instability.[14] Other skeletal abnormalities include polydactyly, club foot, and vertebral anomalies such as butterfly vertebrae, hemivertebrae and rib anomlalies.[15]

Renal: About 1/3 of patients with DGS/VCFS have kidney abnormalities including absent, dysplastic and multicystic kidneys, obstructive abnormities, vesicourecteric reflux, nephrocalcinosis, and duplex kidney. [5,9]

Psychological/Child Development: Although the vast majority of individuals with DGS/VCFS have a learning disability, there is a wide range of learning differences. In one study assessing toddlers mental development, 22% were average, 32% were mild delayed and 46% were significantly delayed. In motor development, 8% were average, 13% were mildly delayed and 79% were significantly delayed. The same study assessed preschoolers and found, for mental development, 33% were average, 33% were mildly delayed and 33% were significantly delayed. [5] In total language skills, 16% were average, 44% were mildly delayed and 40% were significantly delayed. [16] IQ testing on school-age children with DGS/VCFS showed a full scale IQ range from the normal to the moderately retarded range (mean IQ 71.2). The mean verbal IQ (77.5) was significantly higher than the mean performance IQ (69.1); this is evidence for a non-verbal learning disability.[17] Further evidence for a non-verbal learning disability in these individuals includes stronger verbal than visual memory skills and stronger reading than math skills.

Psychiatric: Studies of adults with DGS/VCFS have shown very variable incidences of psychiatric illness in the population ranging from 10% to as high as 64%. (The prevalence of psychosis in the general population is 5%.)[7,11] Other studies have reported increased behavioral problems in children with DGS/VCFS including attention deficit disorder, psychosis and mood changes. [9,17]

Other: A variety of other anomalies have been associated with the 22q11.2 deletion including hematological abnormities such as ITP and Bernard-Soulleir syndrome.[5] Other findings include inguinal and umbilical hernia, accessory spleen, imperforate anus, cyrptorchidism, hypospadias, constipation, leg pain, and craniosynostosis. [5]

Genetic Counseling

DGS/VCFS caused by a 22q11.2 deletion is inherited in an autosomal dominant manner. For parents of an affected child, the recurrence risk depends if the deletion was inherited from one of the parents (familial) or was a new deletion in the child (*de novo*). Approximately 90% of cases of the 22q11.2 deletion are *de novo* and, in these cases, the recurrence risk is small, less than 1%.[5] Nevertheless, the small possibility of germ line mosaicism still exists and must be explained to families.[3] For familial cases of DGS/VCFS, the recurrence risk is 50%. Parents must be made aware of this high recurrence risk and the extreme clinical variability that exists between different individuals affected with DGS/VCFS. Prenatal diagnosis using *FISH* is now available using either chorionic villus sampling (CVS) at 10-12 weeks gestation or amniocentesis at 16 weeks gestation. Other non-invasive tests, like a fetal echocardiogram can also be offered to families who are at risk to have a child with the 22q11.2 deletion. Unfortunately, no known factors can predict the clinical severity of DGS/VCFS.

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Support Groups

There are many support groups nation wide for DGS/VCFS. Two of the larger foundations in the United States focusing on families affected by DGS/VCFS are:

Velo-Cardio-Facial Syndrome Educational Foundation, Inc.
PO Box 874
Milltown, New Jersey 08850
(732) 238-8803 or 1-866-VCFSEF5
info@vcfsef.org
Webpage: www.vcfsef.org

The International 22q11.2 Deletion Syndrome Foundation, Inc.
P.O. Box 15
Haddon Heights, NJ USA 08035
(877) 739-1849
info@22q.org
Website: www.22q.org

About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20 of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health, Children's Medical Services.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

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The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large. The RCPU Newsletter is funded by the Raymond C. Philips Research and Education contract with the Department of Health, Children's Medical Services.

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