22q11.2 SA
Deletion Syndrome Foundation

Understanding 22q11.2 Deletion Syndrome

22q11.2 Deletion Syndrome ("22q11.2") or ("the syndrome) is a genetic disorder that is also referred to as Velo-Cardio-Facial Syndrome ("VCFS"), Shprintzen Syndrome, and/or DiGeorge Syndrome. The syndrome is identified when genetic tests confirm that a small part of a patient's chromosome 22 at the q11 region is missing. The syndrome could lead to cardiac abnormalities, developmental delays, learning difficulties, palate abnormalities, speech and language developmental delays, hypernasal speech, feeding problems during infancy, chronic upper respiratory and middle ear infections – being some of the key characteristics of the syndrome. Expression of the syndrome is highly variable from person to person and no individual has all of the anomalies.

www.22q11sa.org.za

Throughout this brochure 22q11.2 and VCFS are synonymous. The reference to VCFS is being used to remain consistent with the content of the original "Knowlege is Hope" brochure published by the previous Velo Cardio Facial Syndrome Education Foundation (USA).

The diagnosis of 22q11.2 is the first step in getting the answers to your questions. Expression of the syndrome differs from person to person and by age. However, knowing the potential risks allows you to identify problems early and enables you to seek appropriate care.

VCFS / 22q11.2

VCFS / 22q11.2 is a genetic disorder caused by a deletion of a small segment of the long arm of chromosome 22 (hence the name 22q11.2 deletion). It is one of the most common genetic disorders.

The name VCFS is taken from the features that are recognized as part of the syndrome:
Velo = velum or soft palate
Cardio = cardiac or heart
Facial = common facial characteristics
Syndrome = a collection of findings that occur together.

VCFS is known by many names, including DiGeorge Syndrome or Sequence, 22q11.2 Deletion Syndrome, Shprintzen Syndrome, Conotroncal Anomalies Face Syndrome and Sedlacková Syndrome.

Regardless of the stated diagnosis, if the 22q11.2 deletion is present, the diagnosis is VCFS. A diagnosis of the syndrome should not be made unless the deletion is confirmed by genetic testing. Inheritance of the syndrome is autosomal dominant, so a parent who has the deletion has a 50% chance of passing it on to each offspring. However, research has shown that most cases of the syndrome are caused by a new mutation, meaning that neither parent has the deletion. The region on chromosome 22 that is deleted is located at a "hot spot" in the human genome, a place where rearrangements are likely to occur. This is why most cases are new mutations.

DIAGNOSIS

Today there are various chromosome studies that could determine whether a child has a genetic birth defect. A blood test called FISH (fluorescence in situ hybridization) has been used to determine if the critical region of chromosome 22 is missing.

Chromosomal microarray analysis (CMA) is a new laboratory test used to detect chromosomal imbalance at a higher resolution than current standard chromosome techniques.

The deletion must be present to diagnose the syndrome. When a diagnosis of VCFS is suspected, it is very important to have an evaluation by a geneticist because there are many other syndromes that can be mistaken for the 22q11.2 deletion. If the test does not reveal the deletion but the diagnosis of VCFS is still strongly suspected, a lab error should be ruled-out.

MOST COMMON CHARACTERISTICS

More than 180 anomalies have been reported in people with VCFS, but expression of the syndrome is highly variable from person to person and no individual has all of the anomalies. Also, some anomalies are readily apparent and may be recognized at birth while others are subtle and may go unnoticed until much later. Still others are developmental and do not even exist until later on, such as learning disabilities. This explains why a diagnosis of VCFS is sometimes made during the first few days of life, and other times, not until much later. Also, there is great variability in the severity with which characteristics may appear and in the degree to which they cause difficulty. Each of these characteristics occurs in isolation and in other syndromes. It is when two or more of them occur together that a possible diagnosis of VCFS should be considered.

Some of the key characteristics of the syndrome could include:

- Cardiac abnormalities
- Suppressed immune function
- Palate abnormalities (usually submucous cleft palate, but most often not visible by looking in the mouth)
- Characteristic facial appearance (elongated face, prominent nasal bridge and nasal tip, almond shaped eyes, small ears)
- Long tapered fingers
- Feeding problems during infancy (nasal regurgitation of feeds or vomiting through the nose, failure to thrive)
- Chronic upper respiratory & middle ear infections
- Hypotonia
- Delay in achieving developmental milestones
- Delay in speech and language development
- Hypernasal speech
- Dental problems (poor enamel, cavities)
- Leg & foot pain
- Learning difficulties
- Psychological or psychiatric problems
- Kidney abnormalities
- Hernias (umbilical, inguinal, diastasis recti)

WHO SHOULD I CONSULT IF I SUSPECT THE SYNDROME IS PRESENT

You can ask your primary care provider to order a genetic test, but the best way to proceed is to see a clinical geneticist. He or she can perform a complete evaluation, discuss the testing, and arrange for the necessary genetic test to be conducted.

TREATMENT

There is no "cure" for VCFS, but there are ways to treat the various problems associated with the syndrome. It is important to realize that people with VCFS do not always respond to the same treatments as people with similar problems who do not have VCFS. Some treatments are even syndrome specific. Therefore, it is important for professionals caring for children and adults with VCFS to be knowledgeable about the syndrome.

Palate, speech, immune system and attention issues are several areas in which treatment may differ.

WHERE TO BEGIN

Whether the diagnosis is made prior to birth or after, it is important to consult a doctor with knowledge of the syndrome. There is a lot of information available on what evaluations need to be done. After results are obtained, a specific, individualized treatment plan can be developed.

WHO SHOULD MANAGE THE CARE WITH SO MANY SPECIALISTS INVOLVED?

Your primary care doctor or paediatrician should help you coordinate treatments, medications and visits with other specialists. It is important that your primary care doctor be knowledgeable about the syndrome because the evaluations needed are sometimes different for individuals with the syndrome than for others with similar problems.

WHO SHOULD BE PART OF THE MEDICAL TEAM?

This decision is based on the individual's needs but may include:

Paediatrician/Developmental Paediatrician: With an infant, weight gain may be an immediate concern. Many babies with VCFS have nasal regurgitation (sometimes incorrectly called "nasal reflux"). This is usually due to velopharyngeal insufficiency (VPI). It is not a feeding disorder and is not harmful or painful to the baby. Children with the syndrome often have delays in achieving developmental milestones. If motor development is delayed, referral for evaluations by a physical therapist, occupational therapist, or both should be considered.

For both medical and developmental problems, earlier treatment usually results in a better outcome.

Geneticist: A medical geneticist is the most highly qualified person to discuss the condition and all the ramifications of this diagnosis. These include the risk of associated medical problems, both present and future, the likelihood that other family members may have the syndrome, and why this occurred. Sometimes, a geneticist coordinates overall care.

Cardiologist: A typical workup includes a clinical examination, an electrocardiogram (EKG), and an echocardiogram. Even if cardiac issues are not apparent, each person should have a full evaluation because minor cardiac findings can go undetected without a thorough examination.

Immunologist: Compromised immune function is common in VCFS and individuals may experience difficulty fighting common infections or receiving certain vaccines. An immunology evaluation will facilitate proper management of early childhood illnesses.

Audiologist: A complete audiological evaluation should be performed because mild conductive hearing loss is common in VCFS.

Speech-Language Pathologist: SLPs are experienced in evaluating feeding, speech, and language. Sometimes there are simple adjustments in feeding technique that may alleviate feeding problems for infants. Delayed speech and language, hypernasality and articulation disorders are very common in VCFS. It is important to have an evaluation by a certified speech-language pathologist who is familiar with the syndrome during the first year of life. Many children with VCFS require speech therapy to learn to articulate sounds correctly and this treatment is specialized. Surgery may be needed to eliminate hypernasality. To plan the surgery, the SLP participates in the nasopharyngoscopy and multi-view fluoroscopy examinations when the child can cooperate, usually between the ages of 3 and 5 years. Most individuals with VCFS achieve completely normal speech through a combination of aggressive speech therapy and surgery. Language therapy may be needed over a longer period of time due of the nature of language, which becomes more complex and sophisticated.

Ear, Nose & Throat Specialist: Ear infections and fluid in the middle ear may not be symptomatic but are common in VCFS. Therefore, the ears should be monitored closely. ENT surgeons sometimes repair cleft palate and perform surgery to correct VPI. A submucous cleft palate or occult submucous cleft palate (not visible by looking in the mouth) is common in VCFS. Tonsillar hypertrophy (enlarged tonsils) is very common in VCFS. The tonsils may look normal on oral examination, but may be enlarged lower in the airway. Nasopharyngoscopic examination allows the tonsils to be seen in the airway. This is critical because enlarged tonsils may cause feeding, choking, sleeping and speech problems.

Endocrinologist: A calcium deficiency (hypocalcemia) may cause seizures or muscle spasms. Thyroid dysfunction (most common before the onset of puberty) is common. Small stature is also a frequent finding. A complete endocrine workup should be considered.

Craniofacial/Cleft Surgeon: Specialists in a number of disciplines perform cleft palate repair and surgically treat VPI, including ENT surgeons, plastic surgeons, oral and maxillofacial surgeons, and paediatric surgeons. It is vital to have magnetic resonance angiography (MRA) to map the arteries in the neck prior to pharyngeal flap or other pharyngoplasty because displaced carotid arteries is a common finding in VCFS.

Learning/Educational Specialist: Many children with VCFS have specific learning disabilities. Math and abstract reasoning are typically most difficult. It may be helpful to place children in classes with fewer students within a program that can offer individualized instruction in areas of difficulty. Students' needs change over time as the curriculum becomes more complex and abstract.

Psychiatrist, Psychologist, and Neuro-psychologist: Individuals with VCFS are at increased risk for a variety of psychiatric disorders including ADHD, mood disorders, anxiety disorder and obsessive-compulsive behaviours. Other behavioural and cognitive issues are also common in people with VCFS. Some adolescents and young adults develop psychotic disorders. Signs of psychosis (hallucinations and delusions) and other psychiatric symptoms should be identified and treated early. In general, individuals with VCFS are more sensitive than the general population to side effects of psychiatric medications. A routine psychiatric assessment, at least once every two years before adolescence and once a year during adolescence, is currently recommended. A neuropsychological assessment can be very helpful in terms of making appropriate educational and lifestyle adjustments, as well.

WHAT DOES THE FUTURE HOLD FOR INDIVIDUALS WITH THE SYNDROME?

With the appropriate care and intervention, most children with the syndrome become productive and successful individuals who are capable, self-sufficient, and have careers and families of their own. Diagnosing the syndrome is the first step toward obtaining effective treatment. Characteristics differ from person to person and by age. Being aware of potential risks associated with the syndrome will help families and care providers identify challenges and determine the appropriate care.

GLOSSARY OF TERMS OFTEN ASSOCIATED WITH VCFS / 22q11.2

Anomaly: Any deviation from normal structure, form, or function that is considered to be abnormal.

Articulation: Pronunciation; the process by which structures of the speech mechanism (lips, tongue, teeth, etc.) approach or contact each other to produce different speech sounds. Misarticulations may include substitutions, distortions, omissions, or even additions of sounds.

ASD (Atrial Septal Defect): A hole between the two upper chambers of the heart permitting oxygen-poor blood from the right ventricle to mix with oxygen-rich blood from the left ventricle.

Chromosomes: The part of a cell nucleus that contains the genes. Every human cell contains 23 pairs of chromosomes. One set is inherited from each parent.

Cleft Palate: The failure of embryonic fusion of the hard and/or soft palate (roof of the mouth and floor of the nose) resulting in an opening in the roof of the mouth after birth. Fusion normally occurs during the first 8 weeks of pregnancy. See also submucous cleft palate and occult submucous cleft palate.

Conductive Hearing Loss (CHL): Hearing disorder caused by a disruption in the sound-conducting mechanism of the outer or middle ear so that a reduced level of sound is heard. Sound is not distorted. Middle ear fluid and infections that may cause CHL are common in cleft palate and VPI. See also sensori-neural hearing loss.

DiGeorge Sequence: A combination of thymic aplasia, immune deficiency, hypocalcemia, and congenital heart anomalies. It is sometimes, but not always, associated with the 22q11.2 deletion.

DNA (Deoxyribonucleic Acid): The molecule that encodes genetic information.

FISH (Fluorescence in situ hybridization): An approach to mapping human genes using fluorescein radioactive tags. This procedure is used to detect the 22q11.2 deletion.

Gene: Segment of DNA that controls inheritance of a trait.

Genetic Deletion: A segment of the DNA string that is missing from a chromosome. Deletions can be very tiny or very large. With a larger deletion, more genetic material is missing. The absence of these genes on one copy of the chromosome can cause problems depending on the gene that is deleted. Although another copy of the gene is present on the other copy of the chromosome, it may take two genes to perform the task adequately. VCFS is known as a microdeletion syndrome because the deletion is typically too small to be seen under a microscope.

Hypernasality: A resonance disorder in which a person's speech sounds too nasal. In English, air is only supposed to come out of the nose during production of the sounds m, n, and ng. On every other sound, the palate and muscles of the throat move together and close so air cannot

escape through the nose (velopharyngeal closure). When this closure is incomplete, air vibrates in the nose and mouth, rather than only in the mouth (velopharyngeal insufficiency). Hypernasality is perceived when there is too much nasal resonance during production of vowels. It is not the same as nasal emission.

Magnetic Resonance Angiography (MRA): MRA is a technique for visualizing blood vessels in very fine detail without exposure to ionizing radiation (x-rays). MRA works by using radio waves and a very powerful electromagnet that detects differences in the vibration (resonance) of the protons in the nuclei of the atoms in tissue. The resonance characteristics are analysed by a computer, which forms two- or three-dimensional images that can be viewed on a TV monitor.

Mutation: Any heritable change in DNA sequence.

Nasal Emission: The escape of air through the nose during speech. It may be silent or audible and occurs during production of pressure consonant sounds. It is usually caused by VPI or an opening (fistula) in the palate.

Nasal Regurgitation: The escape of food or liquid through the nose during eating; decreases in time and does not require treatment. Upright positioning and modifying placement of the nipple while feeding may help.

Nasopharyngoscope (Endoscope): A fiber optic instrument that can be inserted through the nose to see the pharynx and larynx (voice box) during uninterrupted speech. The images and sound of the examination should be recorded and saved to allow for review and comparison before and after treatment.

Nasopharyngoscopy: A diagnostic procedure used to assess laryngeal and velopharyngeal function during unimpeded speech.

Occult Submucous Cleft Palate: A cleft palate in which the palate looks normal on oral examination but there is an abnormality on the nasal surface of the palate. An occult (hidden) cleft can be diagnosed with nasopharyngoscopy.

Palate: The roof of the mouth and floor of the nose. The anterior two-thirds of the palate contains bone and is called the hard palate. The posterior third contains muscle, but no bone and is called the soft palate or velum.

Pharyngeal Flap: One type of a surgical procedure to eliminate hypernasal speech by creating a permanent separation between the nose and mouth. Soft tissue is elevated from the back wall of the throat and inserted into the top surface of the palate. The spaces on either side of the flap (lateral ports) remain open during breathing but close during speech so air cannot escape into the nose.

Pharynx: The throat, i.e., the tube extending from the larynx to the nostrils. It is composed of several large muscles that are active but move differently during speech and swallowing.

Phenotype: The observable physical and behavioural characteristics of a person. They may be "observable" on physical examination, or by use of special diagnostic tests, such as lab tests, x-rays, IQ tests, or physical measurements. Height, ear size, head shape, learning ability, and temperament are all phenotypic features.

Reflux: Gastroesophageal reflux is commonly referred to as GER (GERD adds the D for disease meaning the condition is chronic). Reflux causes stomach acid to go from the stomach into the oesophagus causing a condition that was previously referred to as "heartburn." If the acid and stomach contents come out of the oesophagus into the back of the throat, this is known as "extra-oesophageal reflux." This should not be confused with "spitting up" which is common in babies, or with "emesis" which really means vomiting up larger amounts of gastric contents. It should also not be confused with "nasal regurgitation" which is common in VCFS and related to issues involving the palate and pharynx.

Sensori-Neural Hearing Loss: A hearing disorder caused by a problem in the inner ear (cochlea) or auditory nerve. This results in both a reduced level of sound heard and distortion of the sound heard. See Conductive Hearing Loss (CHL).

Submucous Cleft Palate: A variant of a cleft palate in which only the surface tissue (mucosa) of the palate is fused together so there is not an obvious opening in the palate. Three signs that are usually present include bifid

(split) uvula, zona pellucida (blue central discoloration), and a notch in the hard palate that can be seen or felt with a finger. None of the signs are present in an occult submucous cleft palate.

Syndrome: A group of problems that occur together and have a common cause.

Tetralogy of Fallot (TOF): The association of four congenital heart anomalies: pulmonary valve stenosis, ventricular septal defect (VSD), an overriding aorta, and enlargement of the right ventricle (right ventricular hypertrophy). This combination of defects can cause decreased blood flow to the lungs and the mixing of oxygen-rich blood with oxygen-poor blood inside the heart.

Velopharyngeal Insufficiency (VPI): Failure of the muscular portion of the soft palate (velum) and the throat (pharynx) to close completely during speech. VPI causes hypernasality and nasal emission.

Velum: Posterior part of the palate containing muscle but not bone. During speech, the soft palate moves up and back and contacts the back and sides of the pharynx to open and close the nasopharynx to prevent hypernasal speech. The process of the velum and pharynx moving together is referred to as velopharyngeal closure.

Videofluoroscopy: A diagnostic procedure using x-rays to obtain and record a three dimensional view of velopharyngeal function during uninterrupted speech. Barium contrast is used to help see the movements of the speech musculature. At least two different views must be obtained for adequate diagnosis. As with endoscopy, the images must always be recorded with sound.

Ventricular Septal Defect (VSD): A hole between the ventricles or two bottom chambers of the heart, permitting oxygen-poor blood from the right ventricle to mix with oxygen-rich blood from the left ventricle.

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The 22q11.2 Deletion Syndrome Foundation South Africa NPC (K2015/299095/08) ("the Foundation"), is a non-profit company, incorporated by parents of children who have been diagnosed with 22q11.2, to drive awareness and education around 22q11.2 in South Africa.

This publication is designed to provide general information with regard to the subject matter covered. The Foundation is not engaged in rendering medical, psychological, or other professional advice or services. This publication should not be utilized as a substitute for professional services.

KNOWLEDGE IS HOPE

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