There has been much discussion and some confusion over the issue of the various diagnostic names attached to patients who have deletions of chromosome 22q11. This discussion has appeared on the pages of several medical journals, but more often than not, it is the subject of questions from patients who have been given a diagnosis from one source only to be given another by a different professional. In 1995, I wrote an explanatory article for *CHASER News*, an excellent publication for parents of children with congenital heart disease (CHASER is an acronym for Congenital Heart Anomalies Support, Education, and Resources, Inc.). My article had been prompted after I had seen several *CHASER* Newsletters with pictures of many children with VCFS who had not been diagnosed previously, or who had been given the label of DiGeorge syndrome. Because the “name game” issue has appeared in print in a number of places, I thought it was about time that it appeared in this Newsletter which is the official publication of the VCFS Educational Foundation.

In clinical genetics, syndromes are named in a number of different ways. In some cases, syndromes are named after those who first described them in honor of their scientific contribution. Sometimes syndromes are described symptomatically, by the use of several key findings which appear frequently in affected patients. Some syndromes have been named using acronyms, using the first letters of clinical features associated with the syndrome. In syndromes which are caused by chromosome rearrangements, syndromes may be named by the type of rearrangement and the chromosome involved. There have been a small number of syndromes which have been named in other ways, including using the name or initial of the first known patient, after the place or institution where it was first described, or by a specific metabolic defect associated with the syndrome. There is no general consensus on the best naming system, and as a result, some syndromes are known by more than one name or system. For example, Down syndrome is named after John H. Langdon Down, a British physician in the 19th century who described children with this common syndrome as “mongoloid idiots.” This unfortunate reference (mongoloid) by Down was derived from a theory about differences in racial intellect which were unmistakably racist in his 1866 article, *Observations on an Ethnic Classification of Idiots*. Therefore, many scientists feel uncomfortable about honoring Down by using his name to designate the syndrome, and prefer to refer to it by the most common form of chromosome rearrangement found in children with the disorder, trisomy 21 (an extra chromosome 21).

It is also important to define just what a syndrome is when referred to by clinical geneticists (Figure 1). When multiple congenital anomalies occur together in the same individual, it is typically suspected that they are related and caused by a common factor. It is unrealistic to believe that a child born with a cleft palate, heart malformations, and inguinal hernias has those things occurring together by chance. The odds of this type of chance co-occurrence would be overwhelmingly high because each anomaly by itself is relatively rare. When multiple anomalies in the same person have a common cause, we call that a syndrome. There are thousands of multiple anomaly syndromes, some like Down syndrome and VCFS being fairly common (with frequencies
Figure 1: Schematic representation of a syndrome where a single causative factor, such as a genetic deletion, causes a series of anomalies, all of which can be traced back to this causative factor.

Some syndromes have a limited number of anomalies, others like VCFS, may have many anomalies. At last count, VCFS has over 180 separate anomalies. The expression of these anomalies is variable from person to person. There is no single anomaly which is found in every person with VCFS, though some have a higher frequency than others. This phenomenon is known as **variable expression**. The more variable the expression of a syndrome, the more likely it is that confusion will develop over diagnostic labels because the possible combinations of the many anomalies becomes greater. Thus, it is possible for someone with VCFS to have heart anomalies, hypotonia, inguinal hernias, and hypocalcemia, but no cleft palate, and another person with VCFS to have cleft palate, a small lower jaw, and club foot. While these may seem to be two separate syndromes, all of the features mentioned commonly occur within the VCFS phenotype (presentation). Therefore, two individuals with the same syndrome may, to a clinician inexperienced with a particular disorder, seem to have different diagnoses. This is often the case with the confusion over DiGeorge and VCFS. What has typically been referred to as “DiGeorge syndrome” is based on a 1965 publication in the *Journal of Pediatrics* which was a discussion of a paper by Dr. Angelo M. DiGeorge, a pediatric endocrinologist at St. Christopher's Hospital in Philadelphia. In his discussion of *A New Concept of the Cellular Basis of Immunity*, Dr. DiGeorge described a proposed mechanism of immune deficiency related to hypothesized abnormalities in a specific region of the developing embryo, the 3rd and 4th pharyngeal pouches involving the thymus and parathyroid glands. The immune disorder Dr. DiGeorge was describing was not proposed as a genetic syndrome, but the approach was one of a mechanism for the development of this particular immune and endocrine disorders. In subsequent years, other papers from Dr. DiGeorge and a variety of researchers reported on other clinical findings in patients with “DiGeorge syndrome,” such as heart anomalies and facial abnormalities. The name **DiGeorge syndrome** became attached to the profile of thymic aplasia, hypoparathyroidism, immune disorders, hypocalcemia, and heart anomalies to honor Dr. DiGeorge’s important contribution to the pediatric literature.

In 1978, I published a paper in *The Cleft Palate Journal* titled **A New Syndrome Involving Cleft Palate, Cardiac Anomalies, Typical Facies, and Learning Disabilities: Velo-Cardio-Facial Syndrome**. This paper described a dozen patients and was specifically meant to delineate a new syndrome. At the time, approximately 20 clinical features were recognized, far fewer than the more than 180 we know of today. In 1980, the late Dennison Young, the pediatric cardiologist working with my team at the time, described the heart anomalies in a larger sample of
children with VCFS, including the heart problems typically associated with the so-called DiGeorge syndrome. By 1985, we realized that some of the children with VCFS had the endocrine and immunologic features typically associated with “DiGeorge syndrome” and a paper was presented at the American Society of Human Genetics meeting that year titled *Phenotypic Overlap Between Velo-Cardio-Facial Syndrome and the DiGeorge Sequence*. You might well ask, “What is a sequence? I thought it was DiGeorge syndrome?” It is well understood in clinical genetics that the presence of one anomaly often precipitates the development of other anomalies. In other words, it is possible when a group of symptoms are present that all of the findings are secondary to a single malformation. Without that malformation, the others would not have occurred. This is analogous to the following scenario. I am driving along in my car on a familiar route to the grocery store. On the way, I smell a strong odor of antifreeze and check under the hood to find a leaking radiator hose. Knowing that my car could overheat, I decide to alter my route to go to my service station. Along the way to the service station, a car runs a red light and slams into my car causing me to break a leg and sending me to the hospital. In this scenario, the crash and broken leg would never have happened had I not altered my route to get to the service station. Therefore, the leaking radiator hose triggered a sequence of events resulting in the injurious consequences. In genetic terms, the trigger is not a leaking radiator hose, but rather the presence of some type of anomaly which interferes with subsequent development of other structures. A common sequence is the **Robin sequence**, often mistakenly referred to as **Pierre Robin syndrome**. Robin sequence is the association of a small lower jaw, cleft palate, and upper airway obstruction with failure to thrive. At about 9 weeks after a pregnancy is established, the palate begins as two halves which are physically separated by the tongue within a small embryonic mouth. As the lower jaw develops, the mouth enlarges which permits the tongue to drop down from between the two palatal halves. These halves are then free to grow towards the midline where they fuse. If the lower jaw does not grow sufficiently, the tongue can not descend from between the halves of the palate. If the tongue remains in that position beyond approximately 11 weeks gestation, the potential for fusion is lost because the palate is beyond its preprogrammed growth stage. After birth, babies are programmed to be nose breathers and keep their mouths closed unless eating. With the lower jaw small and the mouth closed, the tongue may drop back and obstruct the airway causing both breathing and feeding problems. Robin is a sequence because it is the small lower jaw which results in the cleft palate, upper airway obstruction, and failure to thrive.
However, many different syndromes can result in a small lower jaw. There are literally hundreds of genetic or chromosomally caused syndromes, as well as a few disorders caused by teratogens (substances or infections which interrupt normal fetal development) which have a small or retruded jaw as a part of the symptom complex, including VCFS. Therefore, it should become obvious that sequences are not specific to one cause (this is known as etiologic heterogeneity), and that sequences are often (most often, in fact) secondary symptom complexes to other syndromes. In fact, Robin sequence occurs in about 17% of babies with VCFS, and VCFS is the second most common cause of Robin sequence. This rather long-winded explanation (a sort of clinical genetics 101) leads us back to DiGeorge. DiGeorge, the combination of thymic aplasia, immune deficiency, hypocalcemia, and congenital heart anomalies, is a sequence...not a syndrome. How do we know this? Because there are multiple syndromes which have thymic aplasia, hypoparathyroidism, hypocalcemia, immune deficiency, and heart anomalies as a component of their symptom complexes. These include VCFS (the most common cause of DiGeorge sequence), fetal alcohol syndrome, a deletion of the short arm of chromosome 10 (which does not cause VCFS), to name a few. In my own patients with VCFS (which number over 500), fewer than 10% meet the clinical criteria for DiGeorge sequence. More of my patients have Robin sequence. This may represent what is known as an ascertainment bias because most of my early patients were seen in a craniofacial center. However, I now see patients from a large variety of sources, and the frequency of DiGeorge sequence has not risen dramatically.

In practical terms, this means that a small segment of patients with VCFS has the DiGeorge sequence as a secondary symptom complex. They may have other sequences as part of their symptom complexes, as well. I have already mentioned Robin sequence. Last year, Devriendt and colleagues from Belgium published a report on patients with VCFS who had Potter sequence (after having first presented this data at the 2nd Annual VCFSEF Meeting), a symptom complex which occurs secondary to kidney anomalies which is fatal. Two other sequences, CHARGE and holoprosencephaly, have also been reported.

Therefore, all patients who have the symptoms of DiGeorge sequence who are found to have 22q11 deletions have VCFS. However, not all patients who have VCFS (and therefore have 22q11 deletions) have DiGeorge sequence. If a patient with DiGeorge does not have a 22q11
deletion, it is likely that the DiGeorge sequence was caused by one of the other known genetic, chromosomal, or teratogenic syndromes which are known to be associated with it.

What about other names which have been applied to VCFS? There are actually quite a few. In Japan, the disorder is referred to as Conotruncal Anomalies Face Syndrome, or CAFS. This is because Japanese researchers, Drs. Kinouchi and Takao, described a pattern of facial appearance in patients with congenital heart anomalies in 1980. In that series, some, but not all, had VCFS. Cayler syndrome refers to facial asymmetry and “asymmetric crying facies” in babies with heart anomalies (so-called cardiofacial syndrome). Again, approximately 15% of babies with VCFS have asymmetric crying facies. CATCH 22 is a term which has been applied and decried. CATCH is an acronym for Cardiac defects, Abnormal facies, Thyroid hypoplasia, Cleft palate, and Hypocalcaemia. Many readers will recognize CATCH 22 as an attempt at humor because it refers to Joseph Heller’s black comedy novel of the same name. The term catch 22 itself refers to a paradoxical dilemma for which the solution is as big a problem as the dilemma. In other words, a catch 22 refers to a completely illogical or preposterous situation. Therefore, this term has unmistakably pejorative connotations and its application to patients in its attempt to be humorous is regrettable. It has no place in our lexicon, a position articulated admirably by Wulfsberg in a brief article last year. Some researchers prefer to call the syndrome “22q11 deletion syndrome” or some variant thereof for obvious reasons, though this has clearly not been the favored way to designate the syndrome. Some Europeans have referred to VCFS as “Sedlačková syndrome” after the Czechoslovakian plastic surgeon who describe a syndrome of congenitally short palate. Some of the children in that report in 1967 had VCFS, others did not. Finally, in 1982, my dear friend and mentor Dr. M. Michael Cohen suggested the eponym “Shprintzen syndrome” which was acknowledged by another early mentor and friend, David Smith in the 1982 edition of his book Recognizable Patterns of Human Malformation, and this name has continued in use in subsequent editions of this text.

M. Michael Cohen Jr., who is one of the true giant intellects in the field of clinical genetics, has said in his lectures on many occasions, “Geneticists would rather share their toothbrushes than their terminology.” The case of this “name game” certainly bears him out. It is clear that some have staked out a personal interest in a particular name, in some cases it is geographic, and in others, an attempt to honor particular individuals. It is likely that only time and usage will resolve this issue. It is too bad that it comes at the expense of confusion of both scientists and the lay public. From my personal perspective, I favor velo-cardio-facial syndrome for the following reasons:

1. Our article in 1978 was specifically written to delineate a new genetic syndrome, unlike the earlier works of DiGeorge, Sedlačková, and others. This comment in not meant in any way to diminish the considerable and landmark work of Dr. DiGeorge, for which he has been recognized and honored frequently (and deservedly).

2. The other earlier publications and diagnoses, such as conotruncal anomalies face syndrome, Cayler syndrome, and Sedlačková syndrome, focused on components of the syndrome and did not describe the more global manifestations of VCFS. Behavioral manifestations such as speech, psychological, and learning problems, and many physical anomalies such as hernias, hypospadias, vascular, and brain malformations were all recognized to be a part of VCFS.

3. Other symptomatic descriptions, such as DiGeorge, Robin, and CHARGE are all secondary sequences which are etiologically heterogenous, whereas VCFS has only been
related to 22q11 deletions and no other cause has been isolated as yet.

The “name game” is bound to continue unabated because people have developed a fondness for one term or another. I hope this article has helped to clarify some of the reasons for the confusion and the history of the various labels applied to children with VCFS.

REFERENCES


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