Historical overview

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The recognition of velo-cardio-facial syndrome as a specific congenital malformation syndrome is a relatively recent development for so common a disorder. The syndrome has appeared in the medical literature either as a specific and distinct diagnostic entity or as part of a discussion of broader symptoms (such as immune compromise, heart anomalies, or speech disorders) since the 1950s, but the majority of interest in the disorder did not develop until the 1990s. The earliest descriptions of the disorder were based on specific symptomatic presentations to clinicians who found the problems to be common among their caseloads. In 1978, in collaboration with a number of my colleagues, I specifically described “velo-cardio-facial syndrome” (a label I personally constructed) as a genetically caused multiple anomaly syndrome in 12 unrelated cases and one mother–daughter pair (Shprintzen et al., 1978). However, an earlier paper had already reported VCFS as a distinct syndrome in a single family that drew interest because of the presence of congenital heart anomalies and cognitive impairment (Strong, 1968), and descriptions of patients with VCFS from a symptomatic perspective can be found nearly 50 years ago in the Czechoslovakian medical literature (Sedlačková, 1955).

Before going further, it would be useful for those readers who are not clinical geneticists or dysmorphologists to understand what the word “syndrome” connotes. Syndrome is defined as multiple anomalies in the same individual with all of those anomalies having a single cause (Smith, 1982; Shprintzen, 1997). This definition was agreed on by an International Working Group in order to differentiate the root causes of multiple anomaly disorders (Smith, 1982). Outside of the discipline of clinical genetics, the term “syndrome” is often applied in medicine to groupings of symptoms that do not meet the requirements for a multiple anomaly syndrome, such as postviral syndrome or AIDS (acquired immune deficiency syndrome). Familiar groupings of clinical findings are often referred to as syndromes consistent with the Greek roots for the word syndrome: syn meaning together and dramein meaning to run, or roughly translated as things that run together. However, as will be discussed later, not all things that run together meet the stricter criteria for syndrome in a genetic sense.
The failure to recognize velo-cardio-facial syndrome earlier is probably related to a number of factors. The first is that many children with VCFS who had more severe forms of heart anomalies associated with the syndrome, such as tetralogy of Fallot, interrupted aortic arch, and truncus arteriosus, did not survive the neonatal period or infancy. Because many of the findings in VCFS have a later onset (learning disabilities, speech disorders, cognitive impairment, etc.), there would not have been an opportunity to observe these differences in many cases, thus inhibiting syndromic differentiation and the number of cases available for study would have been far fewer. Because approximately 75% of patients with VCFS have congenital heart anomalies, and many are severe, it is possible that the population prevalence of individuals with VCFS may have been quite rare by comparison to today’s figure of 1 : 2000 (Shprintzen, 2001).

Another factor that made recognition of VCFS difficult is that the large majority of children with VCFS are not truly dysmorphic. Although severe manifestations of the syndrome result in abnormal facial features, the large majority of individuals with VCFS are not at all unusual looking. It would be more appropriate to call the typical facial appearance of VCFS to be characteristic without being particularly abnormal. As can be seen in Figure 1.1, children with VCFS look alike without really standing out from the general population. Although individual facial features of VCFS may represent minor anomalies or variants of normal, these minor variations occur frequently enough in the general population so that they are not particularly distinctive. Although VCFS displays a pattern involving over 180 possible congenital anomalies, a high percentage of these anomalies are minor, many of them are behavioral, and many are not obvious nor detectable, such as a single missing or hypoplastic kidney, or a right-sided aortic arch in the absence of structural heart anomalies. Therefore, with many anomalies being difficult to detect without a detailed examination, it becomes more difficult to discern a syndromic pattern.
A third reason why VCFS may not have been recognized as a specific syndrome is that among its clinical presentations are a number of developmental sequences (to be defined and discussed later in this chapter). Sequences are etiologically nonspecific and can occur in association with more than one syndrome. The most common of these sequences that occur secondary to VCFS are Robin sequence and DiGeorge sequence, although several others also have been reported.

Therefore, with the larger pattern of anomalies going undetected as a syndromic association, many earlier clinicians and researchers reported on the individual components of the syndrome as the focus of investigation, such as the speech problems, immune deficiency, endocrine disorders, and heart anomalies.

### Speech disorders and VCFS

Speech disorders were among the earliest noted problems to be published. In 1955, Sedláčková, a phoniatrist, published a series of 28 cases of a “syndrome” of congenitally short palate, and followed up that report with an additional 20 cases (Sedláčková, 1967). These cases represented children who had hypernasal speech in the absence of overt palatal clefts. Sedláčková noted a distinctive facial appearance among the children including flaccid facial musculature. The observation led Sedláčková to conclude that the constellation of anomalies was related to embryonic damage of the second branchial arch which was thought to be the origin of the muscles of the velum and the face. In reviewing the article, it is clear that some of the children shown had velo-cardio-facial syndrome while others did not. In these early publications, the intent was to describe the symptom of hypernasal speech that had been unexplained until that point in these cases. Sedláčková suggested that the palate was congenitally short without noting specific anomalies consistent with submucous cleft palate. Occult submucous cleft palate had not yet been described at that time, nor was nasopharyngoscopy in use to observe this anomaly, so Sedláčková’s description was consistent with the state-of-the-art of the time. Few clinicians accept this nomenclature today and the term “congenitally short palate” is rarely applied because of more sophisticated assessments of the palate that followed in later years. Yet it is clear that Sedláčková recognized a difference in at least some children who had unexplained speech abnormality. It is also unfortunate that the publication of the first paper in 1955 was in a Czechoslovakian journal and published in Czech, thus limiting access to it by the large majority of the scientific community. However, Sedláčková’s early reports clearly recognized the existence of VCFS and these early publications preceded the growth of clinical genetics by many years.

In 1975, Kaplan described a palatal anomaly in children with hypernasality but without overt clefts that he called the occult submucous cleft palate, a term still in
use today. Kaplan, a plastic surgeon at Stanford in California reported on four children who had hypernasal speech of unknown origin, much like the cases reported by Sedlácková. Kaplan reported that his patients had normal-appearing palates on oral examination, but when he took them to surgery to correct their speech abnormality, he carefully dissected the soft palate in order to observe the muscle orientation. He found that the muscles of the velum were structurally abnormal, similar to patients with submucous cleft palate. He therefore called the abnormality in his patients the “occult submucous cleft palate” because of the mysterious nature of the defect. Kaplan indicated that the only way this abnormality could be detected was by surgical dissection, but his paper preceded the application of advanced diagnostic techniques that would be able to visualize the defect endoscopically in later years. In his article, Kaplan showed a series of four patients whose facial appearance clearly indicated that they had VCFS, and one patient who clearly did not. Of interest, Kaplan noted a flaccid-appearing facial musculature in his cases, also similar to Sedlácková’s earlier papers. Kaplan’s aim in this important paper was to describe a nettlesome surgical problem from a symptomatic standpoint rather than to describe a genetic syndrome, but he certainly added much to our understanding of the velar anomalies in VCFS and other disorders.

The reports of both Sedlácková and Kaplan are important for describing the unique nature of the speech problems in VCFS specifically related to hypernasality, although more detailed descriptions of the broader speech implications of VCFS would follow (Golding-Kushner et al., 1985; Shprintzen, 2000). Their early recognition that this was a special population has received too little attention, and they should be credited for providing valuable information in the process of syndrome identification.

**Immune and endocrine disorders**

The isolation of unusual symptoms in children with VCFS was not restricted to speech disorders. In 1965 when Angelo DiGeorge participated in a panel discussion of a colleague’s paper relating to immune disorders in children, the proceedings of the meeting were published in the *Journal of Pediatrics*. DiGeorge described athymia and immune disorder in a child with a right-sided aortic arch during the question and answer session. Several years later, he published a series of cases in the birth defects literature that expanded the phenotype to include conotruncal heart anomalies (DiGeorge, 1968). The cases were described with the perspective of congenital absence of the thymus and its immunologic consequences, as well as the concurrence of congenital hypoparathyroidism, an uncommon finding in VCFS. The majority of the cases described by DiGeorge were infants, and many did not
survive infancy because of the severity of their heart anomalies and the inability to repair many of these major malformations at the time. Therefore, these valuable observations of athymic neonates or infants with hypoparathyroidism could not account for the expansive phenotype in VCFS because of the absence of long-term follow-up. Photographs of the cases were not included in the early reports of DiGeorge. A pivotal article in the delineation of the phenotype came from Kretschmer et al. in 1968. Three cases of “DiGeorge’s syndrome” were described, and one was shown in photographs with an obvious expression of VCFS. Kretschmer described a pattern of facial dysmorphism, although review of the photograph from this article shows a somewhat more severely affected individual than is typical in the syndrome. Of the three cases described, one died in the neonatal period and the other two were young children. The article described these cases in relation to the finding of absent thymus, but the finding of normal polymorphonuclear leukocyte function, normal immunoglobulins, and normal antibody formation. Of the two cases who survived, there were features that were clearly consistent with VCFS. Case 1, the case for whom photographs were published and who clearly had VCFS, a bifid uvula, umbilical hernia, hypotonia, right-sided aortic arch, and aberrant left subclavian were present. This case was reported as having frequent upper respiratory infections. Case 2, the other surviving infant, had what was reported as a bifid nose, high arched palate, and seizures that were reported to be hypocalcemic in origin. Although the article by Kretschmer focused on the immunologic and endocrine features of these three athymic children, this was the first paper to firmly link facial patterns to at least one, if not more, children with DiGeorge sequence.

**Congenital heart anomalies**

The earliest descriptions of VCFS came from Strong (1968) and Cayler (1969). Strong may have actually been the first person to truly describe VCFS as a distinct genetic syndrome. He reported a single family with an affected mother and three affected siblings (two girls and a boy) and two suspected cases amongst an anencephalic stillborn child and an infant who died at 10 months of complications from heart anomalies. Strong listed multiple anomalies in his sample including mental retardation, congenital heart disease, microcephaly, facial asymmetry, hypotonia, and inguinal hernias. Although there were a number of other incidental findings listed that are not considered typical in children with VCFS, review of the photos in Strong’s article leaves no doubt that his cases represent VCFS. Conspicuously absent from Strong’s list was cleft palate or submucous cleft palate. However, Dr. Strong indicated that although none of his cases had overt clefts, all of the children in the family “sounded as if they had clefts” (Strong, personal
communication). Although not often credited for having delineated the syndrome, Strong’s recognition of the pattern of anomalies is not sufficiently acknowledged.

Cayler published two articles describing a symptom complex he labeled cardiofacial syndrome. In his first paper (Cayler, 1969), a single case was shown in photographs and this patient did not appear to have the facial phenotype of VCFS, although asymmetric crying facies was present. In a follow-up article (Cayler et al., 1971), Cayler showed a larger number of photographs of cases from among 30 described in the article. Of the cases shown, several clearly had VCFS, although others clearly did not, and in the review of the clinical features, it was obvious that some of the cases could not have had VCFS because some of the major anomalies reported are inconsistent with the diagnosis. Cayler’s descriptions are based primarily on symptomatic associations in terms of focusing on asymmetric crying facies and congenital heart anomalies. Therefore, the article did not specifically delineate a new syndrome, but did include VCFS among the cases described.

Kinouchi et al. (1976) began the focus in Japan on the association between abnormal facial appearance and conotruncal heart anomalies, a focus that was refined in the Japanese literature in subsequent years with the label conotruncal anomaly face syndrome applied by other Japanese clinicians and researchers (Takao et al., 1980; Momma et al., 1996). Although some of the earliest cases described in the Japanese literature represented multiple anomaly syndromes other than VCFS, it is clear that the refinement of the phenotype over time has yielded a description in the Japanese literature of the same exact disorder described in the earliest reports from this author. This development ran essentially in parallel with the focus in the Japanese literature through the 1980s being on heart anomalies, while in the American literature the emphasis was on craniofacial disorders, communication disorders, and behavior. However, although the name for this disorder in the Japanese literature is different, the syndrome is exactly the same as VCFS.

Another probable description of VCFS was published by Stern et al. (1976). They described many cases with VCFS in a case report series published in the Birth Defects Original Articles Series. Although no photographs were shown in the published version of the presentation made at the annual March of Dimes Birth Defects meeting of 1975, it is very likely that many if not most of the cases described by Stern had VCFS. Stern described a series of 26 cases ascertained from a cardiology clinic with hypernasal speech in the absence of cleft palate (except for incomplete clefts of the palate in two cases). Nearly half of the cases had unusual cervical spine fusions, another anomaly that is probably common in VCFS, although it also occurs in other syndromes associated with conotruncal heart anomalies.
Several years after we had delineated VCFS, the pediatric cardiologist at our institution, Dennison Young reported on a series of 27 consecutive children with VCFS who were evaluated regardless of a past history of detectable heart anomalies (Young et al., 1980). Of the 27 cases, 23 (85%) had heart anomalies. He reported that three of the subjects who had no apparent cardiac malformations (based on routine clinical examinations) had right-sided aortic arch that required imaging procedures for detection.

After the burst of interest in VCFS in 1992, a larger number of studies began to appear detailing the heart anomalies associated with VCFS, including a number of studies that screened populations of children with conotruncal heart anomalies in order to determine the frequency of 22q11.2 deletions in the population of children with congenital heart anomalies (Ryan et al., 1997). Although statistics vary somewhat from study to study, it is clear that a high percentage of children with conotruncal heart anomalies have VCFS, and screening this population if conotruncal anomalies are present in the absence of other obvious diagnoses (such as Down syndrome) is certainly indicated.

As molecular genetics research moved forward, a number of candidate genes for the development of heart anomalies were identified. UFD1L generated significant excitement as a candidate gene for both heart and craniofacial malformations based on mouse studies (Yamagishi et al., 1999), but more recently, TBX1 has become the focus as the major candidate for the development of cardiovascular anomalies (Merscher et al., 2001).

### Development of interest in the 1990s

Prior to 1992, the majority of the scientific literature related to VCFS was coming from a small number of sources, but in 1992, two important events occurred that gave impetus to the study of VCFS in multiple locations around the world. The first was the confirmation that individuals with VCFS have deletions on chromosome 22 at the q11.2 band. This developed in two separate studies. The first was the outcome of a collaboration between several clinical programs including my own and the research laboratory of Peter Scambler in London (Scambler et al., 1992; Kelly et al., 1993). DiGeorge sequence had become associated with chromosome rearrangements at 22q11.2 in 1981 by de la Chapelle and in 1984 (Greenberg et al., 1984). Both of these early identifications of chromosome rearrangements on 22q involved unbalanced translocations and focused on the heart anomalies and immune deficiencies. The family reported by de la Chapelle had a 20;22 translocation, while the Greenberg et al. (1984) cases had an unbalanced 4;22 translocation. However, the association between DiGeorge sequence and VCFS was first noted in 1985 (Goldberg et al., 1985) and reported at the American Society of Human Genetics meeting that year. We noted that DiGeorge
sequence was a clinical finding associated with VCFS in a minority of cases and our hypothesis was that the DiGeorge developmental sequence was triggered by the primary etiology of VCFS. We therefore initially contacted Dr. Scambler and provided him with DNA samples from a series of patients clinically diagnosed with VCFS. These samples were analyzed in Dr. Scambler’s laboratory on a blind basis, and other samples from Newcastle and London were also analyzed. In all, 12 cases clinically diagnosed with VCFS were found to have deletions at 22q11.2. Two of the cases did not have congenital heart anomalies or other clinical findings consistent with DiGeorge sequence. This therefore supported the hypothesis that DiGeorge sequence was a secondary developmental field sequence caused by the deletion that was at the root of VCFS (Kelly et al., 1993). As a follow-up to this initial study, we later contributed a number of blood samples to the laboratory at the University of Pennsylvania in a study published shortly after (Driscoll et al., 1992). As in the previous study, the DNA contributed came from subjects with and without DiGeorge sequence, but all had VCFS. The findings from this second investigation confirmed the findings from Dr. Scambler’s laboratory. The confirmation that DiGeorge sequence was a secondary developmental sequence in VCFS indicated that the expansive phenotype of VCFS was likely to result in a number of secondary developmental sequences, consistent with our earlier report of Robin sequence as a consequence of VCFS (Shprintzen et al., 1978).

**Psychiatric manifestations**

At the time researchers were focusing on the molecular genetics of VCFS, there was also the beginning of research interest into the psychiatric disorders associated with VCFS. The initial report documenting psychiatric illness in VCFS was actually a letter to the editor of *Am. J. Med. Genet.* that described the occurrence of psychiatric illness in individuals whom we had reported on many years earlier and who had been discharged from follow-up following the surgical resolution of their speech problems (Shprintzen et al., 1992). We labeled the onset of psychiatric illness as “late onset” only because we had been following these patients for many years without obvious evidence of their predisposition towards psychosis. Approximately one-third of the patients we contacted reported the onset of psychiatric illness in adolescence or early adult years. In this initial description of psychiatric illness in a small number of cases, we accepted the diagnoses from a number of private psychiatrists who had been assessing and treating these cases. The diagnosis of schizophrenia had been applied to a number of the cases and was reported in that article. Presuming that people with VCFS were prone to schizophrenia, we established a collaboration with Ann Pulver and her colleagues at Johns Hopkins to prospectively study 20 late adolescents and young adults with VCFS (Pulver et al., 1994). Of the 20 subjects studied, four were found to have
either schizophrenia or schizoaffective disorder. As an extension of our collaboration with Dr. Pulver, we also reviewed a sample of 100 individuals who were being followed up longitudinally for schizophrenia in Maryland. Photos of these patients were examined for physical features that might be consistent with a diagnosis of VCFS. Molecular analysis showed that two of 100 cases studied had 22q11.2 deletions indicating that among people diagnosed as schizophrenic, there were likely to be individuals with VCFS.

We then established a collaboration with Demitri Papolos who was in our own institution and was conducting molecular genetics research on individuals with psychiatric illness. After examining a number of patients with VCFS, Dr. Papolos concluded that the psychiatric disorders observed in these cases were more consistent with a form of bipolar disorder rather than schizophrenia, and that the progression of the illness in the most severe cases resulted in schizoaffective disorder and symptoms that could be interpreted as consistent with schizophrenia. A second prospective study was implemented with 25 cases being examined with standardized tests and interviews. Papolos et al. (1996) reported that 16 of the 25 subjects studied met criteria for the spectrum of bipolar disorders.

In the years following these early publications, the debate over the nature of psychiatric disorders in VCFS ensued. It was also suggested that the psychiatric illness seen in individuals with VCFS was syndrome-specific and therefore was atypical for both schizophrenia and bipolar disorder (Vogels et al., 2002). To date, there is no definitive answer to the debate, but it is clear that the study of psychiatric illness in a syndrome with a known genetic deletion continues to focus attention on the genes in the commonly deleted area as possible candidates for psychiatric illness.

Secondary sequences

As mentioned earlier, not every multiple anomaly disorder represents a syndrome. In true genetic syndromes, all of the anomalies seen in the individual are caused by some primary etiology that is in effect from the earliest stages of embryonic development. Therefore, the presence of chromosome rearrangements, genetic mutations, or teratogenic exposures will result in a series of anomalies that can all be traced back to their effects. Another type of multiple anomaly disorder is the sequence. Sequences are defined as the presence of multiple anomalies in a single individual, but many of the anomalies are secondary to the presence of an anomaly that interfered with the normal developmental process. For example, a genetic mutation may give rise to a tetralogy of Fallot. The presence of the tetralogy subsequently causes poor growth, poor peripheral perfusion, small stature, clubbing of the fingernails, circumoral cyanosis, and other anomalies. The small stature, clubbing, cyanosis, and other anomalies would not have been present
were it not for the tetralogy, so the presence of the tetralogy was the structural anomaly that secondarily caused the other anomalies. However, tetralogy of Fallot is etiologically heterogeneous. Tetralogy of Fallot can be one of the features of VCFS, but it also occurs in fetal alcohol syndrome, CHARGE association, Down syndrome, and many other disorders. Therefore, sequences are etiologically heterogeneous, and sequences may be caused secondarily by syndromes. The difference between a syndrome and a sequence is demonstrated in Figure 1.2.

VCFS has a number of developmental sequences that are set into motion as the result of its spectrum of anomalies. The finding of both Robin sequence and DiGeorge sequence in association with VCFS indicated that many early cases of VCFS were not diagnosed properly because they had a well-recognized malformation sequence as a secondary finding. Although DiGeorge is the secondary

Figure 1.2 Schematic representation of the difference between a syndrome and a sequence. Syndromes (upper left) have a single known cause and all of the anomalies in the affected individual can be traced back to that cause. Sequences represent an interruption in the normal developmental process caused by the presence of an anomaly that causes other anomalies in a cascading manner (upper right). At lower center, it is shown that an individual feature of a syndrome can set a sequence into motion, so that sequences can occur secondary to syndromes.