A New Syndrome Involving Cleft Palate, Cardiac Anomalies, Typical Facies, and Learning Disabilities: Velo-Cardio-Facial Syndrome

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This report describes a pattern of similarities among 12 patients which are felt to represent a *newly recognized congenital malformation syndrome.* The symptoms shown most consistently by the 12 patients were overt or submucous *clefts* of the *secondary palate, ventricular septal defects,* typical *facies,* and *learning disabilities.* Other symptoms were noted with varying frequency. The occurrence of velopharyngeal insufficiency in all twelve patients reflected poor motion in the lateral pharyngeal walls, thus necessitating specific forms of treatment. Treatment was often dependent on the extent of cardiac lesions.

Twelve patients who were recently evaluated at the Center for Cranio-Facial Disorders (CCFD) of Montefiore Hospital and Medical Center had very similar patterns of symptoms. All but two of the patients were referred to CCFD after the age of four years because of velopharyngeal insufficiency (VPI), the two exceptions were newborns referred with clefts of the velum and suspected Robin Anomalad. Complete evaluation of these twelve children led to the conclusion that they had similar patterns of congenital anomalies which probably represent a newly recognized malformation syndrome. It is the purpose of this report to describe this new syndrome and to discuss its implications for treatment.

Description of Symptoms

Six of the patients were referred to CCFD because of hypernasality of unknown origin. During evaluation, it became evident that these patients had submucous clefts of the soft palate. These submucous clefts were characterized by a slight diastasis of the velar musculature along the midline. Nasopharyngoscopic examinations showed a prominent midline groove along the superior surface of the velum and the absence of a uvular muscle mass. Lateral videofluoroscopic views indicated that the velum was quite thin and hypoplastic. Five of the patients had overt clefts of the velum only. Three had been repaired prior to referral and these three patients were severely hypernasal. Two patients were referred as infants with unrepaired clefts of the velum. One patient had an obvious submucous cleft velum, bifid uvula, and notching of the posterior hard palate.

Of interest were the findings from the multi-view videofluoroscopy and nasopharyngoscopy. Videofluoroscopic examination of the velopharyngeal sphincter in lateral, frontal, base, and left and right oblique projections showed that, of the eleven speaking patients, nine had no observable motion in the lateral pharyngeal walls. Two had very poor lateral wall motion. There was some motion

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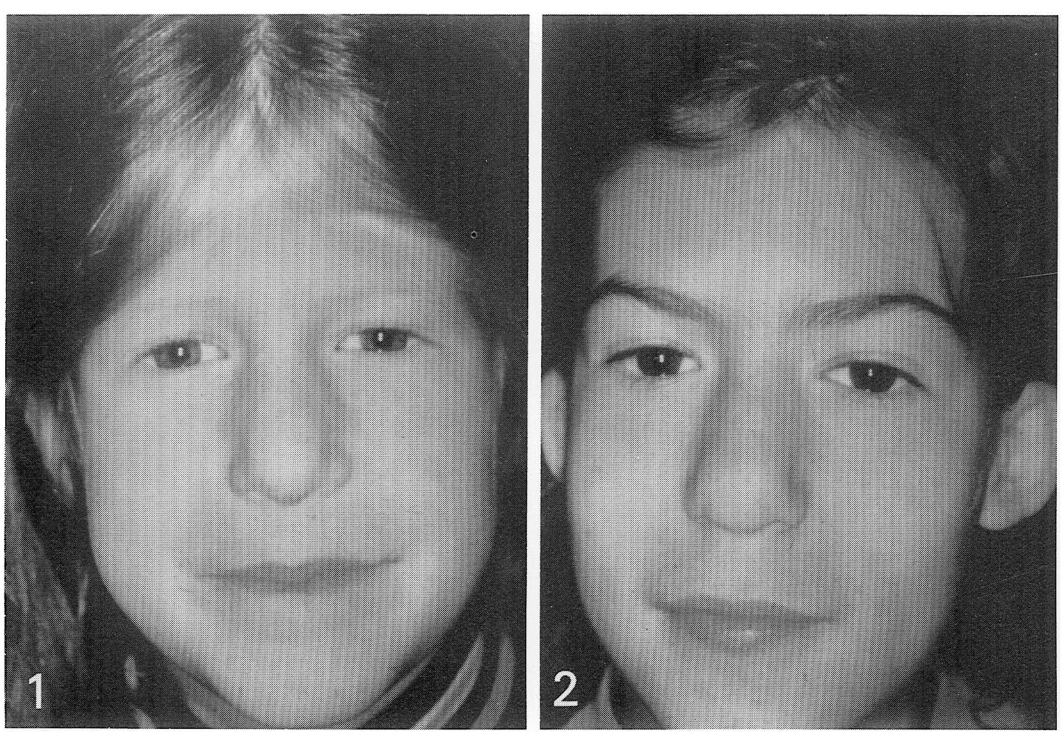
in the velum, but this was generally limited. Nasopharyngoscopy confirmed that narrowing of the velopharyngeal sphincter occurred only in the antero-posterior direction with little or no observable medial motion of the lateral pharyngeal walls.

Perhaps the most striking feature of these patients was the similar facies of all twelve. The facies was characterized by a large, fleshy nose with a broad nasal bridge, flattened malar region, narrow palpebral fissures with a downward obliquity, deep overbite with a class II malocclusion and retruded mandible, mild synophrys, abundant scalp hair, and a vertically long face. It was noted by the team at CCFD that all twelve were quite similar in appearance (Figure 1-4). Only one patient had any resemblance to a parent, and that parent also had a submucous cleft palate, hypernasal speech, and learning disabilities.

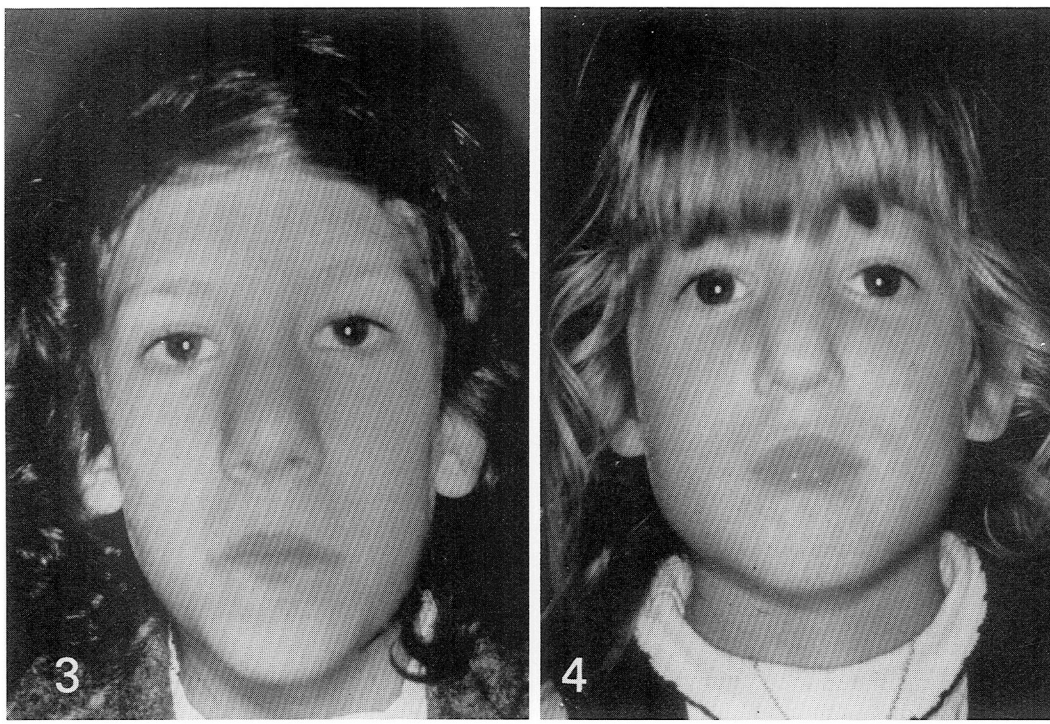
Nine of the patients were found to have ventricular septal defects (VSD) diagnosed by cardiac catheterization and confirmed at surgery in four cases. Eleven of the patients have exhibited specific learning disabilities, usually involving the ability to form abstractions, mathematical ability, and visual-motor capacity. The twelfth patient (the infant) has shown some signs of slight motor development delay. However, only two of the patients are significantly retarded. IQ scores have ranged between 78 and 104, with the exception of the two retarded patients who are both educable.

Several other problems were noted in each of the patients with varying frequency (Table I). These included hypotonia in infancy, poor fine motor coordination, pyloric stenosis, hypospadias, inguinal hernia, undescended testes, anomalous pinnae, hyperextensibility of the large joints, other cardiac malformations, laryngeal web, conductive hearing loss, and unilateral sensorineural hearing loss.

Dermatoglyphic analysis showed that four of the patients had whorls on all ten digits, and three more patients had whorls on five or more digits. Of a total of 120 digits for all twelve patients, 64 digits, or 53 per cent had whorl patterns. This is in comparison to established norms which show that 25.43 per cent of digits have whorl patterns while 69.72 per cent have loops (Cummins and Midlo,



FIGURES 1 and 2



FIGURES 3 and 4

1961). Four patients had inflated total ridge counts. One patient had bilateral simian lines; one patient had bilateral sydney lines, and one patient had a bridged simian line on the left hand.

All twelve patients were somewhat small in stature. Height and weight were below the twenty-fifth percentile for all twelve children, at the third percentile for six of the patients, and below the third percentile for two. Head circumference was below the fiftieth percentile for all twelve patients, below the twenty-fifth percentile for four of the children, and below the third percentile for two.

Since the features which called attention to the similarities between these children initially were the clefts of the secondary palate and velopharyngeal insufficiency (VPI), ventricular septal defect, and typical facies, this syndrome has been labelled Velo-Cardio-Facial Syndrome, or VCF.

Case Reports

To illustrate the symptoms reported above in VCF Syndrome, two cases will be described in more detail below.

CCFD #638. This white female (birth date 1/25/70) was the third child born to a then 28-year-old gravida 2 para 2 ab 0 mother and a 29-year-old father, both of Russian Jewish descent. The parental union was nonconsanguineous. She was referred to the CCFD at the age of three because of severely hypernasal speech and poor language development. Evaluation revealed multiple congenital anomalies including a small VSD, coarctation of the aorta, pulmonary stenosis, and laryngeal web. Intra-oral examination showed the velum to be hypoplastic at the midline with a small muscular diastasis. The facies was marked by a large fleshy nose with a broad nasal bridge, flattening of the malar region, mild synophrys, long face, deep overbite, abundant scalp hair, and narrow palpebral fissures with a downward slant. She was somewhat small for her age (height and weight were at approximately the tenth percentile), but within normal limits.

Developmental landmarks were slightly delayed, and a mild hypotonia was noted in the first three years of life. Psychological testing revealed specific learning disabilities, and

TABLE I

	Date of birth	*Race and sex*	*Submucous cleft, secondary palate*	*Overt cleft, secondary palate*	*Hypernasal speech*	*VSD*	*Specific learning disability*	*Poor fine motor coordination*	*Hypotonia in infancy*	*Overbite, retruded mandible*	*Flat malar region*	*Long face*	*Large nose*	*Anomalous ears*	*Other*
CCFD #579	11/19/67	W ♀	+	−	+	+	+	+	+	+	+	+	+	−	unilateral sensorineural hearing loss mild synophrys
CCFD #610	11/30/72	H ♀	−	+	+	+	?	−	−	+	+	+	+	−	language impairment, conductive hearing loss umbilical hernia
CCFD #638	1/25/70	W ♀	+	−	+	+	+	+	+	+	+	+	+	−	laryngeal web, coarctation of aorta mild synophrys, hyperextensibility
CCFD #722	3/22/74	W ♂	−	+	+	+	?	+	+	+	+	+	+	+	left inguinal hernia, left undescended testis
CCFD #741	9/11/69	W ♀	+	−	+	+	+	+	+	+	+	+	+	−	patent ductus, conductive hearing loss
CCFD #759	2/4/70	W ♀	+	−	+	−	+	+	+	+	+	+	+	−	
CCFD #772	8/26/63	W ♀	−	+	+	−	+	+	−	+	+	+	+	+	unilateral sensorineural hearing loss mild synophrys
CCFD #864	9/23/70	H ♀	+	−	+	+	+	+	+	+	+	+	+	−	conductive hearing loss hyperextensibility
CCFD #917	12/20/61	W ♂	−	+	+	+	+	+	+	+	+	+	+	−	hypospadias
CCFD #942	5/12/71	H ♀	−	+	+	+	+	+	+	+	+	+	+	+	pyloric stenosis, synophrys sleep apnea
CCFD #978	1/31/64	W ♂	+	−	+	+	+	+	+	+	+	+	+	−	
CCFD #984	1/31/70	W ♂	+	−	+	+	+	+	+	+	+	+	+	−	bilateral epicanthi

W = White.
H = Hispanic.

speech evaluation showed a language disorder, including deficient vocabulary recognition and deviant syntax. There were numerous misarticulations related to VPI. Neurological examination was essentially within normal limits with no evidence of neurologic disease or lesions. Hyperextensibility of the large joints was found. Dermatoglyphics showed whorls on all ten digits and an a-b ridge count of 28 on the left hand and 27 on the right hand for a total of 55. The atd angle was 43° on the left hand 40° on the right. The pedigree, environmental history, prenatal and natal histories were negative for known teratogens or genetic disorders. Her karyotype was normal female 46XX with conventional staining.

Multi-view videofluoroscopy was performed in lateral, frontal, base, and left and right oblique projections. Lateral view confirmed that the velum was thin and hypoplastic with fair motion but a poorly defined velar eminance during speech. Velopharyngeal closure did not occur between the velum and adenoid pad or posterior pharyngeal wall as described by Skolnick et al. (1975). In frontal and oblique views, no lateral pharyngeal wall motion was demonstrable. Base view confirmed a gross VPI with narrowing of the velopharyngeal portal occurring only in an antero-posterior direction.

CCFD #579. This white female (birth date 11/19/67) was the second child born to a then 31-year-old gravida 1 para 1 ab 0 mother and a 30-year-old father, both of Armenian descent. The union was nonconsanguineous. She was referred to the CCFD at the age of four because of a life-long history of hypernasality. She was noted to be hypotonic at birth. The proband's mother had severe nausea and vomiting during the first trimester and was given Bendectin and Tigan from approximately the fourth week of pregnancy until the sysptoms subsided. She also had severe headaches and took three or four Bufferin daily during this period of early pregnancy. Evaluation showed the presence of a large VSD, a submucous cleft of the soft palate, a moderate unilateral sensori-neural hearing loss, and learning disabilities specific to reading and math. Language deficits included depressed vocabulary recognition scores and grammar below normal for chronological age. There were numerous articulation errors related to VPI. Intra-oral examination showed the velum to be hypoplastic with a muscular diastasis at the midline. This submucous cleft was quite narrow and had not been previously diagnosed. The facies was marked by a large fleshy nose with a broad bridge, flattening of the malar region, mild synophrys, abundant scalp hair, long face, deep overbite, and the palpebral fissures were narrow and had a slight downward slant. Multi-view videofluoroscopy and nasopharyngoscopy showed fair velar mobility, but essentially motionless lateral pharyngeal walls. Dermatoglyphics were not unusual. Pedigree analysis showed that the mother's sister had Down Syndrome.

Discussion

The rather unusual combination of symptoms in the twelve patients described above becomes difficult to explain in relation to the timing of fetal development. The symptoms common to most or all of the patients are velopharyngeal anomalies, cardiac anomalies, typical facies, learning disabilities, and speech and language impairment. Can the relationship of these symptoms be accounted for on the basis of an interruption of fetal development at a specific point in time? Facial development begins at approximately three weeks of gestation and is essentially complete by eight weeks (Stark, 1961). Palatal development begins at approximately six weeks and is complete by approximately nine weeks (Stark, 1961). Development of the brain continues throughout the gestational period (Langman, Rodier, and Webster, 1975), but it is not clear if there is any relationship between learning disabilities and either brain damage or an error in neural development. Cardiac development occurs between approximately three and seven weeks of gestation with closure of the intraventricular foramen occurring between six and seven weeks (Patten, 1968). It is possible that some factor may have been in operation at approximately six to eight weeks of gestation to cause the above mentioned combination of symptoms. What this factor might be is unclear at present. Pedigree analysis has not shown the presence

of any teratogenic, environmental, or genetic factors consistently expressed by the parents of the twelve patients. A familial link has been established for two patients, one whose mother also expresses the syndrome and a second who has a brother with a submucous cleft velum.

The coincidence of cardiac anomalies and unusual facies (Linde, Turner, and Sparks, 1973; Yurchak and Fallon, 1976) and the association of cardiac abnormalities with orofacial clefting (Shah, Pruzansky, and Harris, 1970) has been previously reported. Linde, Turner, and Sparks (1973) described the association of small stature, elfin facies, mental retardation, and cardiac lesions including supravalvular and subvalvular aortic stenosis. None of the children described by them or by Yurchak and Fallon (1976) as having "cardio-facial syndrome" had a VSD or facies similar to those reported above.

Shah, Pruzansky, and Harris (1970) suggested several possible explanations for the concordance of congenital heart disease and orofacial clefting. Since there is little overlap between cardiac and palatal development, it was not considered probable that a single, short-acting agent would cause both types of anomalies. It was considered possible, however, that a teratogenic action might be prolonged over a two-week period to cause both cardiac and palatal malformations. It was also hypothesized that variability in the timing of fetal development may cause more overlap than usual in cardiac and palatal anomalies for certain embryos. It should be noted that Shah, Pruzansky, and Harris (1970) described a wide spectrum of cardiac anomalies in association with clefting including tetrology of Fallot, coarctation of the aorta, patent ductus, ASD, and VSD.

Two of the 12 patients apparently affected with VCF Syndrome were not found to have cardiac lesions at the time of initial examination (CCFD #759 and CCFD #772). It should be pointed out, however, that these patients were referred to the CCFD after the ages of five and 12 respectively. On the basis of the examinations performed, a VSD which had spontaneously closed during late fetal life or early postnatal life, could not be ruled out. It is also possible that these two patients have an incomplete expression of the syndrome.

Several factors have led to the conclusion that these twelve children share a common malformation syndrome. Certainly, the symptoms presented by the twelve children are quite consistent. The facies, velar, cardiac, and neurological pictures presented by the children are strikingly similar. Also, cardiac lesions in association with clefting have been reported to be relatively rare (McKeown and Record, 1960; Shah, Pruzansky, and Harris, 1970). The addition of learning problems and other symptoms to the cardiac and palatal anomalies with such consistency would seem to be beyond the realm of chance.

It is important to note that the characteristic facies of the patients described in this report is a congenital feature and not a feature which developed as the result of exogenous conditions in the postnatal period. The clefts detected in these children were either overt or submucous clefts of the secondary palate. The primary palate was not involved in any of the patients. Ten of the patients had not had any surgery which could in any way account for a change in facial development prior to evaluation at CCFD. All operations performed on these 12 children involved intraoral soft tissues only (for velar repair or pharyngeal flap), with the exception of cardiac surgery which was not performed before the age of five in any of the children.

Treatment for velopharyngeal insufficiency has varied for the 12 patients with VCF Syndrome mostly in relation to the seriousness of the cardiac disorder. In two instances, surgical intervention to improve speech had to be deferred until cardiac surgery was performed. In all other cases, cardiac clearance was given for surgery. For four of the patients, cardiac surgery was performed to repair the ventricular septal defects and other cardiac anomalies.

Pharyngeal flap surgery has been performed in ten of the patients. Two of the patients had pharyngeal flap surgery done prior to the use of multi-view videofluoroscopy and nasopharyngoscopy. The pharyngeal flaps constructed in these two patients were "standard" type flaps in that large enough lateral gutters were left to facilitate breathing and mucous drainage and to prevent hyponasality. However, speech remained hypernasal following surgery for these two

patients since the absence of lateral pharyngeal wall motion resulted in a failure to close the lateral gutters.

Those patients evaluated with multi-view videofluoroscopy and nasopharyngoscopy received obliterating type pharyngeal flaps. The speech results were excellent. The pharyngeal flaps constructed for these seven patients left only slit-like lateral gutters, thus effectively obstructing air flow through the velopharyngeal portal. The one patient who had an unrepaired overt cleft of the velum (CCFD #917) had a primary pharyngeal flap done at 18 months of age since:

1. The cleft of the velum was rather wide.
2. The patient had a rather large VSD, and it was desirable to keep the number of surgical procedures to an absolute minimum.
3. Poor lateral pharyngeal wall motion would make a simple palatal repair insufficient for the attainment of normal speech.

One patient (CCFD #942) who had a pharyngeal flap at the age of four developed respiratory problems post-operatively. Several days after the operation, sleep apnea was diagnosed. The initial post-operative problems subsided completely, and the patient was discharged in good health. Four weeks after discharge, the patient died in her sleep following an upper respiratory infection with a 104° fever, apparently of an apneic episode. The possible presence of sleep apnea in the other patients is being explored.

It should be noted that the educational needs of all of the school-aged children except one have been satisfactorily met in regular classrooms with special help (remedial reading, math tutoring, etc.). In all other respects, these children are functioning well within their home environments.

The reporting of syndromes involving cleft palate facilitates progress in identifying specific factors underlying the predispositions to clefting. Certainly, an accurate diagnosis must precede any discussion of recurrence risk figures and mental and physical prognosis.

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