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# Cardiofacial Syndrome

## Congenital Heart Disease and Facial Weakness, a Hitherto Unrecognized Association

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In June 1966 an infant with a ventricular septal defect and an unusual form of unilateral partial facial paresis (Fig. 1) was first seen at the Sutter Memorial Hospital. Only the two muscles, the mentalis and the quadratus labii inferioris, innervated by a single branch of the facial nerve, the ramus marginalis mandibulae, were involved, and the weakness was apparent only during crying. Only 2 reports of this unusual type of congenital facial weakness were found in the literature (Hoefnagel and Penry, 1960; Parmelee, 1931). The 6 cases reported by Hoefnagel and Penry (1960) were seen in the Boston area over a span of only 26 months and were not stated to have facial asymmetry or associated anomalies except for one patient with a right-sided esotropia. No reports of the association of congenital heart disease and facial weakness could be found. During the next 6 months 4 further cases of congenital heart disease and unilateral partial facial weakness involving the same two muscles were seen. 3 of these infants also had ventricular septal defects and the fourth had aortic coarctation. When the total group of small infants who were at the Sutter Hospital during 1966 were reviewed, it was found that from a total of 44 small infants with congenital heart defects 5 babies had associated facial weakness. During this same interval no cases of facial weakness were seen in 30 small infants who were examined for functional murmurs. This 'epidemic' was reported (Cayler, 1967) and subsequently 9 further cases have been observed. The present paper reports the total group of 14 cases, and includes analysis of viral and chromosomal data in 3. All were born within a 100-mile radius of Sacramento and the birth dates ranged from August 25, 1965 to May 10, 1967, a 21-month span. The facial weakness in our patients was not associated with facial asymmetry except for one (Case 12) who also had a branchial cleft anomaly, and the weakness has persisted in all cases, with only 3 showing significant improvement.

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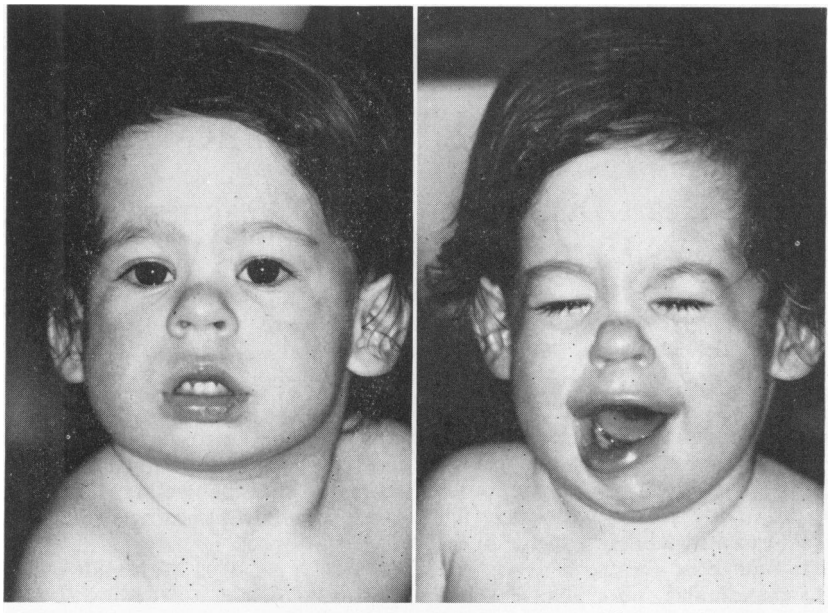
### Material

Table I lists the patients chronologically according to their birth dates. 9 were female and 5 were male. 7 were born in Sacramento and 1 each in Yuba City, San Francisco, Oroville, Willows, Lodi, Walnut Grove, and Stockton. This distribution reflects the ratio of local to outside Sacramento paediatric cardiac referrals seen at the Sutter Memorial Hospital. In only 2 of the 14 cases was the left face involved. The congenital heart lesion was an isolated ventricular septal defect, or included a ventricular septal defect, in 12. One had mild valvar pulmonary stenosis and the other aortic coarctation.

The severity of the cardiac lesions and those with congestive failure and poor growth are listed in Table II. 5 had minor, haemodynamically insignificant, cardiac lesions. 3 had tetralogy of Fallot and 2 of these had right aortic arch. Additionally, one of the patients with a ventricular septal defect had a right aortic arch. 8 developed congestive failure and 2 had pulmonary artery banding with improvement. In 5 growth failure was marked (weight centile less than the 3rd) and in 4 others the weight centile persisted between the 3rd and the 10th. None have died.

Table III is a summary of the pertinent maternal and prenatal data. The ages of the mothers ranged from 18 to 38 years. 5 were primiparas. One had had a previous miscarriage. There was no history of congenital anomalies in the 19 sibs. One of the mothers was epileptic and one was a chronic diabetic. There was no history of rubella during pregnancy or any other exposure to known



1a 1b

FIG. 1.—*Photographs of Case 3 at rest and during crying. The lower left facial weakness is evident only during crying, when the lower lip is pulled toward the normal or functioning side. Except for variations in the side and the severity of weakness, the facial lesion was identical in all patients.*

teratogenic agents or disease. The gestational ages, birthweights, and types of delivery for the 14 cases are listed on Table IV. All were spontaneous occipital anterior deliveries in which outlet forceps were used in only 3 cases. 2 were premature and 5 were underweight for their gestational ages.

Table V lists the other anomalies found in these patients. 4 had no other anomaly, 3 had major central nervous system disorders, 4 had associated skeletal deformities, 4 had gastro-intestinal anomalies, and there were anomalies of other organs in 5 of the patients.

Viral and chromosomal studies were performed in 3 patients (Cases 5, 11, and 13) and the results are listed in Table VI. Since only one baby was

TABLE I
*Patients with Cardiofacial Syndrome*

| Case No. | Sex | Birth Date | Birth Place | Side of Facial Paresis | Cardiac Lesion |
|---|---|---|---|---|---|
| 1 | F | 25 Aug. 65 | Sacramento | R | Pulmonary stenosis* |
| 2 | F | 19 Nov. 65 | Sacramento | R | Tetralogy, ductus* |
| 3 | F | 16 Mar. 66 | Sacramento | L | Ventricular septal defect* |
| 4 | F | 17 Mar. 66 | Sacramento | R | Ventricular septal defect† |
| 5 | F | 8 April 66 | Yuba City | R | Atrioventricularis communis†‡ |
| 6 | M | 10 July 66 | San Francisco | L | Coarctation†‡ |
| 7 | F | 25 Oct. 66 | Oroville | R | Ventricular septal defect* |
| 8 | F | 30 Oct. 66 | Willows | R | Ventricular septal defect* |
| 9 | F | 8 Feb. 67 | Sacramento | R | Tetralogy, right aortic arch† |
| 10 | M | 26 Feb. 67 | Lodi | R | Single ventricle†‡ |
| 11 | F | 7 Mar. 67 | Walnut Grove | R | Atrial and ventricular septal defects† |
| 12 | M | 11 Mar. 67 | Stockton | R | Tetralogy, right aortic arch† |
| 13 | M | 7 May 67 | Sacramento | R | Ventricular septal defect, rt. aortic arch* |
| 14 | M | 10 May 67 | Sacramento | R | Ventricular septal defect* |

Diagnosis made by *Clinical, †Catheterization and ‡Operation.

TABLE II

*Severity of Cardiac Lesion*

| Case No. | Cardiac Lesion | Severity of Lesion | Congestive Failure | Failure to Thrive* |
|---|---|---|---|---|
| 1 | Pulmonary stenosis | Mild | 0 | 0 |
| 2 | Tetralogy, ductus | Moderate | 0 | + + |
| 3 | Ventricular septal defect | Moderate | + | + |
| 4 | Ventricular septal defect | Moderate | + | + + + |
| 5 | Atrioventricularis communis | Large | + | + + + |
| 6 | Coarctation | Severe | + | + + |
| 7 | Ventricular septal defect | Small | 0 | 0 |
| 8 | Ventricular septal defect | Small | 0 | 0 |
| 9 | Tetralogy | Moderate | + | + + + |
| 10 | Single ventricle | Marked | + | + + + |
| 11 | Atrial and ventricular septal defects | Marked | + | + + + |
| 12 | Tetralogy | Moderate | + | + + |
| 13 | Ventricular septal defect | Small | 0 | 0 |
| 14 | Ventricular septal defect | Small (spont. closure) | 0 | 0 |

* + mild; + + moderate; + + + severe.

diagnosed during the first week of life (Case 13), the timing of the viral studies was not optimal and therefore interpretation is limited. Poliomyelitis Type 2 virus was found in the stool culture from one infant (Case 11) who had had prior oral immunization. Serological studies seemed to rule out rubella or cytomegalovirus. For the chromosomal studies a microtechnique was employed (TC-Chromosome Micro-test Kit–Difco) resulting in metaphase spreads of lymphocytes in mitosis. Karyotyping showed all 3 cases to be euploid diploid, 2 genotypical and phenotypical females and 1 genotypical and phenotypical male. All 3 showed chromosomes of altered form, consistent with fractures or breaks and deletions, usually involving the terminal portion of the long arm (Fig. 2). In all 3, 50% or more of the cells photographed showed one or more chromosomes with shortened arms. In no instance were both chromatids of a pair affected. There was no constancy as to the group, or number within the group, of chromosomes affected, though pair No. 3 of group A was affected more than others. In one instance the fracture and deleted fragment were visible (Fig. 2). A detailed statistical analysis of all 14 cases and their mothers is in process and will be reported later (Blumenfeld and Cayler).

TABLE IV

*Gestational Age, Birthweight, and Delivery*

| Case No. | Gestation (wk.) | Birthweight (g.) | Delivery |
|---|---|---|---|
| 1 | 32 | 1785 | Spontaneous |
| 2 | 38 | 3175 | Forceps |
| 3 | 39 | 2834 | Spontaneous |
| 4 | 38 | 2409 | Spontaneous |
| 5 | 40 | 2494 | Forceps |
| 6 | 34 | 2409 | Spontaneous |
| 7 | 40 | 2777 | Spontaneous |
| 8 | 39 | 3189 | Spontaneous |
| 9 | 40 | 3089 | Spontaneous |
| 10 | 39 | 3939 | Spontaneous |
| 11 | 42 | 3798 | Forceps |
| 12 | 38 | 2578 | Spontaneous |
| 13 | 39 | 3317 | Spontaneous |
| 14 | 38 | 3061 | Spontaneous |

TABLE III

*Maternal and Prenatal Data*

| Case No. | Mother | | | | Prenatal Complications |
|---|---|---|---|---|---|
| | Age (yr.) | Gravida | Para | Abnormalities | |
| 1 | 26 | 4 | 4 | None | None |
| 2 | 25 | 1 | 1 | None | None |
| 3 | 20 | 2 | 2 | None | None |
| 4 | 18 | 1 | 1 | Epilepsy | Spotting, drugs (phenobarbitone phenytoin) |
| 5 | 18 | 1 | 1 | Diabetes | Diabetes |
| 6 | 19 | 1 | 1 | None | None |
| 7 | 38 | 6 | 6 | None | Pneumonia (40th wk.) |
| 8 | 22 | 3 | 3 | None | Cystitis (12th wk.), salpingitis (16th wk.), 'flu' (24th wk.) |
| 9 | 27 | 3 | 3 | None | None |
| 10 | 20 | 2 | 2 | None | None |
| 11 | 19 | 1 | 1 | None | None |
| 12 | 22 | 2 | 2 | None | None |
| 13 | 28 | 4 | 3 | None | Anaemia |
| 14 | 26 | 2 | 2 | None | None |

TABLE V

*Central Nervous System, Skeletal, Gastro-intestinal, and Other Associated Anomalies in 10 Cases*

| Case No. | CNS | Skeletal | Gastro-intestinal | Miscellaneous |
|---|---|---|---|---|
| 2 | | | Umbilical hernia | Lop ear (R) |
| 4 | ? Dysplasia microcephaly | Aplasia 5th distal phalanx; occipital moulding | | |
| 5 | | Arthrogryposis knees | | |
| 6 | | | | Hypertension ( ?renal artery stenosis) |
| 8 | | | Umbilical hernia | |
| 9 | Microcephaly, convulsive disorder, retardation | | | |
| | | | Anal stenosis | Fusion labia minora |
| 10 | | | | Lacrimal duct obstruction (L), 2° AV block (ECG) |
| 11 | Convulsive disorder, retardation | | | |
| 12 | | Aplasia radius (R) | | Aplasia kidney (R), branchial cleft anomaly (R) |
| 13 | | Aplasia radius (R) and proximal phalanx thumb (R) | Imperforate anus | |
| 14 | | | | |

## Discussion

The aetiology of the association of facial weakness and congenital heart disease is unexplained, but the data in the 14 cases observed suggest the possibility of a first trimester infection, probably viral. The fact that none of the mothers gave a history of any significant infectious illness during the first three months of pregnancy is not unusual, as half of the patients in the prospective studies of Brown and Evans (Brown and Evans, 1967, Evans and Brown, 1963; Brown, 1965) had subclinical disease, i.e. there were no symptoms during the interval when paired sera showed serological evidence of viral infection. 9 of the pregnancies in our 14 cases started during the summer months when enteroviral disease is of highest incidence. There were no viral epidemics in California during the summers of 1965 and 1966 (R. L. Magoffin, 1967, personal communication). The chromosomal aberrations observed in our cases could be of viral aetiology, as it has been shown experimentally and clinically that viral infections can produce at least three types of chromosomal damage: (1) breaks, (2) pulverization, and (3) cell fusion and spindle abnormalities (Cohen and Shaw, 1965; Nichols, 1966). The relation of the chromosomal aberrations to the aetiology of the congenital anomalies is speculative at present. The breakages and deletions were not inherited nor did they appear in the zygote. No clones were established. Similar aberrations have been noted in 4 autosomal recessive diseases, Bloom's syndrome (Cohen, Hirschhorn, and Frosch, 1967), Fanconi's anaemia (Cohen *et al.*, 1967), ataxia telangiectasia

TABLE VI

*Viral and Chromosomal Studies*

| Case No. | Age at Time of Studies | Titres (baby/maternal) | | | Virus Isolation | Chromosomes |
|---|---|---|---|---|---|---|
| | | Rubella | | Cytomegalovirus | | |
| | | CF | HI | | | |
| 5 | 12 mth. | 1:4/1:32 | 1:8/1:1024 | | No growth | Euploid diploid female* |
| 11 | 3 mth. | 1:4/1:4 | 1:16/1:64 | 1:4/ ? | Polio type 2 | Euploid diploid female* |
| 13 | 12 dy. | 1:4/1:4 | 1:32/1:64 | 1:32/1:32 | No growth | Euploid diploid male* |

*See text. CF = complement-fixation. HI = haemagglutination inhibition. ? = not done on mother.

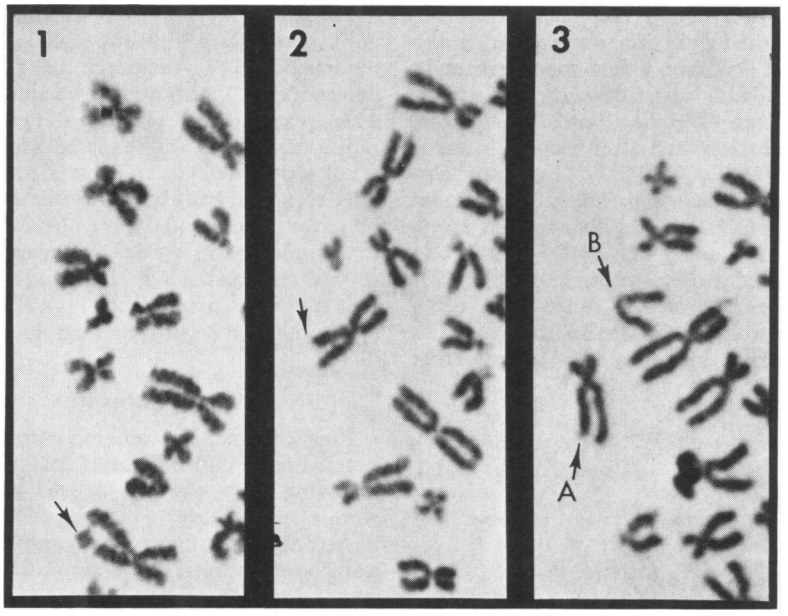



FIG. 2.—*Illustrated are portions of chromosome spreads from 3 patients. (1) Fracture of long arm of chromosome A2 with the deleted fragment still present (at arrow). (2) Deleted long arm, one chromatid of chromosome A3 (at arrow). (3) Possible deletion of a group B chromosome (at arrow A) and possible deletion of both short arms of a group D chromosome (at arrow B).*

(Cohen *et al.*, 1967), and recently, fibrocystic disease (Smith *et al.*, 1968). It is of additional interest that patients with three of these syndromes show a high propensity to neoplasm, and that cells of neoplastic origin frequently show chromatid breaks. De Haan (1967) notes that the rubella virus occasionally disrupts development of the ventricular septum, and cites experimental studies showing disturbance of mitotic control associated with viral infections. Emerit *et al.* (1967) noted a 12% incidence of chromatid breaks in 100 children with cardiac and other major malformations who did not have a known syndrome or a familial history of congenital heart disease. In a similar group of children Rohde (1966) noted no chromosomal aberrations in 34 children. Cohen *et al.* (1967) reported a high frequency of chromosome breaks in 2 of 4 newborns of mothers taking LSD. These babies did not have recognizable malformations; however, Zellweger, McDonald, and Abbo (1967) reported a case of unilateral fibular aplastic syndrome in a child of parents taking LSD. Father, mother, and child showed an increased incidence of chromatid breaks. Again it should be noted that the significance of these minor abnormalities of karyotype is not established, and it must be remembered that Court Brown, Jacobs, and Brunton (1965) noted a 3% incidence of minor chromosome change in a group of randomly chosen normal men and women.

It is puzzling why there should have been such a high incidence of congenital heart disease associated with facial weakness during the past 16 months, and this may represent 'clustering', as observed by Day (1966), for aneuploid chromosomal anomalies (Down's syndrome and sex chromosome abnormalities) and by Rutstein, Nickerson, and Heald (1952) for persistent ductus. It is also puzzling why the association of facial weakness and congenital heart disease has not hitherto been recognized. This is perhaps related to the fact that the facial weakness is partial and not apparent when the baby is quiet and therefore easily overlooked. A new syndrome, perhaps due to a new virus or recent viral mutation, is of course possible.

Though many viral diseases occurring during pregnancy have had untoward effects on the fetus, only 2, rubella and cytomegalovirus, have been proved to be associated with an increased incidence of anomalies in the fetus (Wright, 1966; Gregg, 1941). There is also recent evidence indicating that Coxsackie virus B, Types 3 and 4 (Brown and Evans, 1967; Evans and Brown, 1963; Brown, 1965), and mumps virus (St. Geme, Noren, and Adams,

1966) can result in a higher incidence of cardiac anomalies if maternal infection occurs during the first trimester. There are a few case reports in which maternal rubeola was followed by the birth of defective children (Wright, 1966). Congenital cataracts have been reported after maternal herpes zoster infection (Duehr, 1955). There are also two reports of anomalies occurring after maternal epidemic hepatitis (Kåss, 1951; Blattner and Heys, 1961). Though Wilson *et al.* (1959) showed no significant difference in the incidence of anomalies after Asian influenza, Kaye, Rosner, and Stein (1953) have reported 3 infants with anomalies whose mothers had influenza during the first trimester.

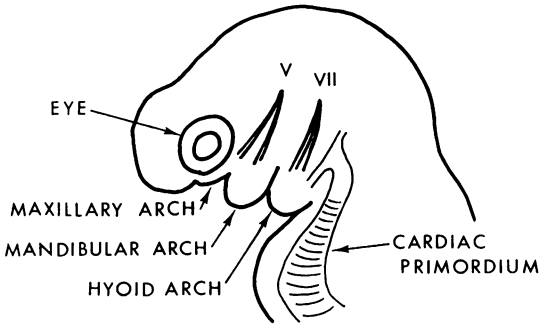



FIG. 3.—*Diagrammatic representation of the 6 mm. (approximately 30-day) embryo, showing the close anatomical relation of the 7th cranial nerve, the hyoid arch, and the cardiac primordium.*

It is of interest that during early embryogenesis the cervical region of the body is scarcely present, and as a result the hyoid arch (from which the facial structures are derived) is in close proximity to the cardiac primordium (Fig. 3). An agent attacking the heart at this state of embryonic life would, therefore, be very close to the caudal segment of the hyoid arch and could very well involve branches of the facial nerve, particularly those branches that are distributed to the lower part of the face and neck. The afferent and efferent fibres of the facial nerves have been observed in the human embryo as young as 6 mm. (approximately the 30th gestational day) (Wilson, Windle, and Fitzgerald, 1941), and it is possible that innervation of the facial muscles takes place during the 33rd to 38th day of gestation at the same time as cardiac septation is largely completed (R. L. DeHaan, 1967, personal communication). Two of the cases reported in this paper also had aplasia of the right radius which begins its embryonic development during the 5th week (28th to 35th day) (Harris and Osborne, 1966). These authors reported a 30% incidence of ventricular septal defects (1 of 3 with a right aortic arch) in patients with aplasia or hypoplasia of the radius (ventriculoradial dysplasia). The association of secundum atrial septal defects and digital anomalies ('finger-like' thumb: atrio-digital dysplasia) has also been observed (Holt and Oram, 1960). The so-called 'hand and wrist syndromes' were recently completely summarized by Feingold (1967), and it is striking that approximately one-third of these syndromes have associated cardiac lesions.

## Summary

Fourteen patients are reported with congenital heart disease and unilateral partial facial weakness involving only the lip depressors. These cases were observed over a 16-month period and were born between August 1965 and May 1967. All were born within a 100-mile radius of Sacramento, and 9 were conceived during the summer months of 1965 and 1966. All but 2 had ventricular septal defects or anomalies which included ventricular septal defects. 10 had other major system anomalies. Viral studies were negative in 3 patients except for poliomyelitis virus recovered in the stool of one previously immunized infant. Chromosomal studies in 3 showed a high frequency of breaks of the terminal portions of the long arms of many chromosomes. Though there was no constancy as to group, pair No. 3 of group A was affected more than others. The association of cardiac and facial anomalies may be related to the proximity of the hyoid arch to the cardiac primordium and/or to the chronologically close embryonic development of facial innervation and cardiac septation. It is postulated that the syndrome may be due to a subclinical viral infection occurring in the mother during the 5th week of pregnancy. The facial weakness is partial and not apparent while the infant is quiet and at rest. Since 9 of our 14 cases had serious cardiac anomalies, 8 developing congestive heart failure, the physician is urged to examine all newborns very carefully for this subtle facial sign, and to be highly suspicious of a major cardiac anomaly in newborns who show unilateral partial facial weakness of the lower lip depressors.

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