Case reports

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REFERENCES

Discordance for Cornelia de Lange syndrome in twins*

Summary. A male infant, the first-born of twins, with features of Cornelia de Lange syndrome is described. His normal twin was discordant for 3 of the 14 blood loci tested. Chromosomes from the affected infant appeared normal. Though the aetiological basis for the Cornelia de Lange syndrome remains obscure, most authorities accept genetic rather than environmental causation.

The present findings of discordance for Cornelia de Lange syndrome in twins support this view but do not clarify the mode of inheritance.

Nearly 300 cases of the Cornelia de Lange syndrome have been reported; they include at least two sets of twins (Choo and Bianchi, 1965; Opitz et al, 1965). In these 2 cases, the twins were concordant for the syndrome and were presumably monogytic. Two additional sets of twins, one concordant and one discordant for Cornelia de Lange syndrome, are known to the authors but have not been published with confirmatory data. It is the opinion of the authors and others (Motl and Opitz, 1971) that twins reported by Kroth do not clearly have the Cornelia de Lange syndrome.

The observation of twins discordant for the Cornelia de Lange syndrome forms the basis of the present report.

Case report

The parents, both normal 21-year-old Caucasians, have no known common ancestors. Their first child is a normal male; their second pregnancy was terminated by elective abortion. No relatives are known to have chromosome abnormalities, skeletal malformations, mental retardation, or features of the Cornelia de Lange syndrome.

Three months before the third pregnancy the mother underwent abdominal surgery to correct a stenotic ureter adjacent to the right renal pelvis. Five months later she had a urinary tract infection which was treated with hexamine mandelate for two weeks. Apart from this treatment and dietary supplements of iron and vitamins, no other drugs were taken during pregnancy. The mother denies any other illness during pregnancy.

The pregnancy was terminated in the thirty-ninth week by caesarian section after prolonged rupture of the amniotic membranes and fetal bradycardia. Twins were not suspected before delivery.

Ta. C. weighed 950 g, had a head circumference of 24.8 cm, and a length of 36.2 cm. A diagnosis of the Cornelia de Lange syndrome was made on the basis of: microbrachycephaly, general hirsutism, synophris, long eyelashes, elongated philtrum, small nose with anteverted nostrils, 'carp-like mouth', micromelia of the upper extremities, with each forearm terminating in a single digit, soft tissue limitation at the elbow, cardiac murmur, poorly differentiated genitalia, with hypoplastic foreskin, chordee, and incompletely descended testes, and cutaneous syndactyly of the right first and second toes (Fig. 1 and 2).

Radiological evaluation showed macrocephaly, bell-shaped rib cage, malformed radius with absent ulna bilaterally, absent carpal bones on the left, and two unidentifiable carpal bones on the right.

The infant's respirations were depressed immediately after birth but improved spontaneously over the first hour of life. Apnoeic episodes, cyanosis with feeding, and hypothermia recurred intermitently until death during an apnoeic episode at 34 hours of age.

At necropsy, the cusps of the pulmonary valve were thickened, a finding of uncertain importance. No gross or microscopical abnormalities other than those noted clinically were detected.

Tr. C. (HH 72-23077), the second born twin, weighed...
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**FIG. 1.** Patient Ta. C. showing features of Cornelia de Lange syndrome and his twin brother (patient Tr. C.) at 2 days of age.

2350 g, had a head circumference of 31.1 cm, and a length of 44.5 cm. No morphological abnormalities were noted. After initial respiratory distress lasting 2 days, the infant began to thrive and was discharged in good condition at 7 days.

The placentas were fused but on microscopical examination showed two chorionic and two amniotic membranes. The section of the placenta belonging to the first twin was approximately one-half the size of the second twin's placenta and had a smaller and shorter cord. Microscopical examination of the smaller placental section showed well-formed chorionic villi, some with partial hyalization and degeneration.

**Other studies.** Chromosome studies, including fluorescent banding, indicated apparently normal chromosomes in Ta. C. Blood typing showed discordance at the D, M, and Fy* loci (Table I).

**Discussion**

The clinical features in the first born twin (Ta. C.) fulfilled the diagnostic criteria for Cornelia de Lange syndrome suggested by Berg et al (1970). Erythrocyte antigen studies and examination of the placenta acknowledge the dizygotic origin of the twins. A tabular comparison of known cases of Cornelia de Lange syndrome in twins is given in Table II.

The aetiology of the Cornelia de Lange syndrome is not clear. No consistent prenatal environmental insult has been seen nor would this aetiology be consistent with the findings in the present case. Most investigators accept a genetic basis for the condition but there is little agreement on the particular mode of inheritance. Both single gene mutation as well as chromosomal imbalance have been suggested without conclusive supporting evidence.

Recessive transmission, suggested by Opitz and associates (1965) and Opitz and Gross (1971), does not fit the total experience with Cornelia de Lange syndrome (Berg et al, 1970: McArthur and Edwards, 1967). The pronounced variability of clinical features, as well as the prominence of structural deformities, argue against recessive inheritance.

**FIG. 2.** Patient Ta. C. showing facial and limb abnormalities of Cornelia de Lange syndrome.
Case reports

TABLE I

RESULTS OF BLOOD TYPING OF MOTHER AND TWINS

<table>
<thead>
<tr>
<th>Group</th>
<th>D</th>
<th>E</th>
<th>C</th>
<th>c</th>
<th>e</th>
<th>K</th>
<th>M</th>
<th>N</th>
<th>P</th>
<th>S</th>
<th>s</th>
<th>Fy*</th>
<th>JK*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother 1.2</td>
<td>O</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ts. C. 11.2</td>
<td>O</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tr. C. 11.3</td>
<td>O</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
</tbody>
</table>

TABLE II

REPORTS OF CORNELIA DE Lange SYNDROME IN TWINS*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Twin</th>
<th>Sex</th>
<th>Birthweight (g)</th>
<th>Chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choo and Bianchi (1965)</td>
<td>A</td>
<td>Female</td>
<td>1980</td>
<td>Apparently normal</td>
</tr>
<tr>
<td>Opitz et al (1965)</td>
<td>B</td>
<td>Female</td>
<td>1890</td>
<td>Apparently normal</td>
</tr>
<tr>
<td>Present cases</td>
<td>A</td>
<td>Male</td>
<td>950</td>
<td>Apparently normal</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Male</td>
<td>2350</td>
<td>—</td>
</tr>
</tbody>
</table>

* Twins concordant for Cornelia de Lange syndrome were reported by Stewart et al at the 1974 Birth Defects Conference at Newport Beach, California (June, 1974). Twins discordant for Cornelia de Lange syndrome have been reported in a personal communication to Dr John Opitz by Dr Gerston Carakushansky of Rio de Janeiro, Brazil. Substantial reports of these two cases have not been made. Twins reported by Kroth (1965) may represent a condition other than Cornelia de Lange syndrome (Motl and Opitz, 1971).

Transmission of the abnormality by means of a dominantly expressed mutant gene or by a minute chromosome abnormality appears more likely (McArthur and Edwards, 1967). In less than 5% of the cases a structural abnormality of the chromosomes has been seen. However, the nature of the chromosome abnormality has varied greatly; hence, assignment of an aetiological role to the chromosome defect, even in these cases, would not seem warranted. The presence of structural defects, as well as the frequently variable manifestations, would be consistent with either a chromosome anomaly or with a dominant mutation. In the present case there is insufficient historical, clinical, or cytogenetic evidence to assign any particular mode of inheritance.

We wish to thank Doctors Marjorie Shaw and Charleen Moore for chromosome studies on patient Ta. C.

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REFERENCES


The de Lange syndrome in one of twins*

Summary. A pair of female monozygotic twins, one of them affected by the de Lange syndrome, is described for the first time. Monozygosity was established by most of the accepted standards in use at the present time. Speculation is offered as to whether the discordance in the manifestation of the syndrome provides any clues for understanding its

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