Genetic Heterogeneity of Cebocephaly

LEWIS B. HOLMES, SHIRLEY DRISCOLL, and LEONARD ATKINS

From the Genetics Unit, Children's Service and the James Homer Wright Memorial Laboratories and Department of Pathology at the Massachusetts General Hospital, the Department of Pathology of the Boston Hospital for Women, and the Departments of Pediatrics and Pathology and Center for Human Genetics of Harvard Medical School, Boston, USA

Summary. Three infants with cebocephaly with entirely different aetiologies are described: one possibly representing the effect of a single mutant gene, one with apparent E trisomy, and one with D trisomy. In comparison with other reported patients, it is likely that infants with cebocephaly and no associated chromosomal abnormality have few, if any, extracranial malformations.

The malformed infant who dies soon after birth often does not have a careful diagnostic evaluation. In our experience these infants often have genetic diseases the aetiology of which may be a chromosomal abnormality, a polygenic disorder, or a single mutant gene. An example of such a fatal malformation with diverse genetic causes is cebocephaly, a disorder which includes brain and facial anomalies, the most striking of which are holotelencephaly and a cylindrical nose with a single nostril. This disorder has been described in infants who had a normal karyotype (DeMyer, 1964; James and van Leeuwen, 1970; Warkany, 1971 and 1972), as well as in infants with several different chromosomal abnormalities, including 47,XX,+13 (McKusick, 1961; von Bühler et al, 1962; Conen, Erkman, and Metaxotou, 1966), 46,XX,18p− (Uchida et al, 1965; Gorlin, Yunis, and Anderson, 1968), 46,XX, 18r (Neu et al, 1972), and 47,XX, +C (Lejeune et al, 1969). One of the infants with normal chromosomes had a similarly affected sib, raising the possibility that cebocephaly might in some instances be due to a single mutant gene (James and van Leeuwen, 1970).

We have studied three infants with cebocephaly, each of whom had an apparently different genetic aetiology: one infant had a normal karyotype and a sister with holotelencephaly; one had an extra chromosome which may represent (17–18) E-group trisomy although this could not be definitely proven and one had a chromosome D trisomy. The

* Supported in part by grants from the Charles H. Hood Foundation (Boston), and the Massachusetts Developmental Disabilities Council, NIH Special Fellowship Number 1 FG3 HD-53, 606-01 and Children's Bureau Project Number CB-12-HSP-906.
Holmes, Driscoll, and Atkins

FIG. 1. Case 1. Note the hypotelorism, small nose, and absence of philtrum. The clinodactyly of the fifth finger of one hand is also visible.

normal girl and the other a sister with holotelencephaly, who is described below. There is no consanguinity or any other family member with craniofacial anomalies.

The malformed sister of patient 1 was born in 1967. The pregnancy and delivery were uncomplicated. She died soon after birth; birth weight was 1·8 kg, length was 42 cm, and head circumference 25 cm. No photographs were taken of the child. The father recalls that she looked like patient 1, but the pathologist noted that her nose was normal. At necropsy* she had no anomalies, except those involving the cranium and brain. The forebrain was rounded and not divided into hemispheres. The parietal and occipital lobes were smaller than normal. The aqueduct of Sylvius was not present. The peduncles were not differentiated. The lateral fascicles of the medulla oblongata had an abnormal appearance. She also had a patent ductus arteriosus.

Case 2 was born in 1971 to a 25-year-old mother and 24-year-old father. The pregnancy was complicated by vaginal bleeding at 12 weeks' gestation. The infant was delivered by Caesarean section at 36–37 weeks gestation because of a small maternal pelvic inlet. The pla-

* Necropsy findings kindly provided by Dr A. Huaman, Topeka, Kansas.

FIG. 2. Case 1. The brain showing the failure of division of the forebrain and the lack of olfactory bulbs and tracts.
Genetic Heterogeneity of Cebocephaly

centa weighed 120 g and showed no abnormalities other than its very small size. The umbilical cord contained three vessels. The infant had an Apgar of 3 at 1 minute and 2 at 5 min after birth. His respirations were laboured and he died at 4 hours of age. Birth weight was 1·6 kg, crown-rump length 27·5 cm, and head circumference 27·5 cm.

The physical features included: hypotelorism (inner/outer canthal widths = 1-3/4-0 cm), narrow palpebral fissures, a soft tubular nose with a single nostril, small ears with overfolded helices (Fig. 3), no philtrum of upper lip, highly arched palate, short sternum (3·5 cm), an umbilical hernia, a short phallus (1·0 cm), a flat non-rugated scrotum (Fig. 4), tapering fingers, a transverse palmar crease in the right hand, small toenails and short, dorsiflexed great toes (Fig. 5).

Necropsy findings included: fused frontal bones, holotelencephaly with a single cerebral ventricle, hypoplasia of the cerebral peduncles, and small cerebellum, pontine fibres, temporal horns, and hippocampus. Microscopic examination of the pituitary gland showed no abnormalities. The adrenal glands weighed 3-5 g (expected weight 5 g [Potter, 1961]). The internal genitalia showed two immature testes located in the abdomen,
two epididymes, two oviducts, and a unicorne uterus with a single cervix. The heart was dextroposed, had a ventricular septal defect, hypoplastic left atrium, and anomalous pulmonary venous return. Radiology showed a small cranium, orbital hypotelorism, shallow orbits, abnormal sternal ossification, and ossification of each calcaneus.

Chromosome analysis was performed on lymphocytes obtained shortly before death. Unfortunately, only four metaphase plates were adequate for evaluation. Each showed an extra chromosome (Fig. 6) in the E (17–18) group (47,XX,+E). Unfortunately, it was not possible to study the E-group chromosomes with either quinacrine fluorescence or other staining techniques. Chromosome analysis from leucocytes of the parents showed no abnormalities.

Case 3, a stillborn female, was born in 1961. Her mother, age 23 years, developed 'acute hydramnios' at 34 weeks gestation and delivered this infant spontaneously at that time. A previous pregnancy had resulted in a normal child.

The placenta was small and oedematous. The umbilical cord was short and contained two vessels (one artery and one vein). Birth weight was 1·5 kg, crown-rump length 29 cm, and head circumference 28 cm. The necropsy findings included: brain weight 77 g, holotelencephaly with a single cerebral ventricle, absence of the olfactory bulbs and tracts, optic nerves and chiasm, circle of Willis, cerebral peduncles and pyramids, an incomplete sella turcica, microphthalmia, a single nostril 1·5 cm long, a ventricular septal defect and patent ductus arteriosus, lack of fixation of the caecum, a universal mesentery, and a bicornuate uterus. The pituitary was present, but no histological examination was performed. The combined weight of the adrenal glands was 9·2 g (expected weight 5 g together). Radiographs showed that the anterior fossa was more oblique.
than usual. Chromosome analysis using skin fibroblasts showed D trisomy (47,XX,+D) in all metaphase preparations.

**Discussion**

All of the reported infants with cebokocephaly (McKusick, 1961; Bühler et al, 1962; DeMyer, 1964; Uchida et al, 1965; Conen et al, 1966; Gorlin et al, 1968; Lejeune et al, 1969; James and van Leeuwen, 1970; Warkany, 1971; Neu et al, 1972; Warkany, 1972), as well as our three patients, have had holotelencephaly and the associated cerebral abnormalities often found in individuals with holotelencephaly (Yakovlev, 1959). In addition, infants with cebokocephaly often have absence, and abnormal development, of the pituitary; endocrine gland; hypoplasia, genital underdevelopment that is most noticeable in males, and a cleft or highly arched palate (Table I). Presumably the small adrenal and thyroid glands and the small penis and undescended testes of males are the result of hormonal deficiencies. Deficiencies of pituitary hormones have not been proven in infants with cebokocephaly, but have been documented in infants with a similar malformation, holotelencephaly with cleft lip and palate (Hintz, Menking, and Sotos, 1968). The cleft palate is apparently a feature of the abnormal craniofacial development in infants with cebokocephaly.

In evaluating infants with cebokocephaly it is their associated extracranial anomalies which seem to reflect their different genetic aetiologies. Each of the four infants with a normal chromosome karyo-

<table>
<thead>
<tr>
<th>Reference Source</th>
<th>Sex</th>
<th>Pituitary and Adrenal Glands</th>
<th>Small Penis and Cryptorchidism</th>
<th>Palate Either Cleft or Abnormal</th>
<th>Extracranial Anomalies</th>
<th>External</th>
<th>Internal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cebokocephaly with normal karyotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>James and van Leeuwen (1970)</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Inguinal hernia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeMyer (1964)</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Bilateral simian crease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warkany (1971; 1972)</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Hydronephrosis due to ureteral narrowing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present case 1</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Clinodactyly of fifth fingers</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cebokocephaly with abnormal karyotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C trisomy</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lejeune et al (1969)</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td>Malformed ears; small chin; elongated thorax; enlarged liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 trisomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McKusick (1961)</td>
<td>F</td>
<td></td>
<td></td>
<td>Anophthalmos; deformed ears</td>
<td>Ventricle septal defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buhler et al (1962)</td>
<td>F</td>
<td></td>
<td></td>
<td>Polydactylly; ulnar deviation of hands</td>
<td>Ventricle septal defect; diaphragmatic hernia; septate uterus; intestine incompletely rotated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conen et al (1966)</td>
<td>M</td>
<td></td>
<td></td>
<td>Scalp defects; malformed eyes and ears</td>
<td>Multiple cardiac anomalies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D trisomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present case 3</td>
<td>F</td>
<td></td>
<td></td>
<td>Microphthalmia; single umbilical artery</td>
<td>Venticular septal defect; universal mesentery; bicorionate uterus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uchida et al (1965)</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>Inverted feet; dorsiflexed little toes</td>
<td>Fissured spleen and accessory spleen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorlin et al (1968)</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>Microphthalmia</td>
<td>Colon incompletely rotated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18q</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neu et al (1972)</td>
<td>F</td>
<td></td>
<td>+</td>
<td>Large ears; partial aniridia</td>
<td>Small thymus; multiple cardiac anomalies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E(17–18) trisomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present case 2</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>Small ears; short sternum; umbilical hernia; tapering fingers; simian crease; short dorsiflexed great toes</td>
<td>Two testes; two oviducts; unicorne uterus; ventricular septal defect; anomalous pulmonary venous return</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A plus sign is used to indicate some of the features; the absence of the plus sign indicates lack of information in original report.
type had only one associated malformation two of which were minor in nature [transverse palmar creases (James and van Leeuwen, 1970) and clinodactyly of the fifth fingers–bilateral in the present case] and two were major [inguinal hernia (DeMyer, 1964) and unilateral hydronephrosis (Warkany, 1971 and 1972)]. In assessing the significance of a single minor anomaly, it should be noted that in one study (Marden, Smith, and McDonald, 1964) 13% of normal newborns had one minor anomaly. By contrast, the nine patients with chromosomal abnormalities had two or more different external and internal malformations (Table I). This general distinction based on there being only one or no extracranial anomalies between infants with ceboccephaly and a normal chromosome karyotype and those with associated chromosomal abnormalities was first suggested by DeMyer (1964). The practical value of this observation is in terms of genetic counselling. Based on the findings of two affected children in the family of patient 1 and the family reported by James and van Leeuwen (1970), it is possible that these infants have ceboccephaly as a result of their being homozygous for an autosomal recessive mutant gene. If future experience confirms these observations about associated extracranial malformations and the mode of inheritance, genetic counselling to a family can be more specific after the birth of the first infant with ceboccephaly and no demonstrable chromosome abnormality.

We know that the sib of case 1 also had holotelencephaly, but we do not know if she also had ceboccephaly. There is evidence that sibs with holotelencephaly need not have the same craniofacial abnormality. They may have either ceboccephaly, cyclopia (fused eyes with a proboscis located above the eye), ethmoencephaly (two eyes with a proboscis between them), or hypotelorism with cleft lip and palate (Hintz et al., 1968). In 1921 Klostock reported a family in which one male infant had ceboccephaly and his brother had cyclopia. The parents in this family were closely related. A family in which one infant had cyclopia and another had ceboccephaly was described by Welter in 1968.

The associated external anomalies of case 2 (Table I) are similar to those reported for infants with chromosome 18 trisomy (Taylor, 1968). However, the abnormal internal genitalia are unusual. The presence of oviducts and a uterus in association with cryptorchid testes and epididymes is a rare form of hermaphroditism. The reported patients have usually normal external genitalia, inguinal herniae, and a normal chromosome karyotype (Morillo-Cucci and German, 1971). The extracranial anomalies of case 3 are typical of the features of infants with chromosome 13 trisomy, although she does not have some of the well-known features such as cleft lip and palate, postaxial polydactyly, and scalp defects.

The data on these three infants were made available by the assistance of Drs J. Cohen, J. Meeker, E. T. Hedley-Whyte, M. Rogers, A. E. Szulman, and P. Yakovlev.

REFERENCES


Warkany, J. (1972). Personal communication.


Genetic Heterogeneity of Cebocephaly

Lewis B. Holmes, Shirley Driscoll and Leonard Atkins

doi: 10.1136/jmg.11.1.35

Updated information and services can be found at:
http://jmg.bmj.com/content/11/1/35

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/