A Probable Case of Incomplete Trisomy of a Chromosome of the 13-15 Group

J. ISHMAEL and K. M. LAURENCE

From the Department of Paediatric Pathology, Welsh National School of Medicine, Llandough Hospital, Penarth, Glamorgan

It is now recognized that the presence of a portion of an extra chromosome may be associated with some of the features characteristic of one of the autosomal trisomic conditions (Patau, Therman, Inhorn, Smith, and Ruess, 1961; Patau, Therman, Smith, Inhorn, and Picken, 1961; Zellweger, Mikamo, and Abbo, 1962; Gustavson, Hagberg, Finley, and Finley, 1962; Dent, Edwards, and Delhanty, 1963). The present case probably represents such an incomplete trisomy, where there appears to be an extra chromosome that does not fit readily into any of the accepted groups and in which the clinical picture is not entirely typical of any of the recognized trisomy syndromes. As the recording of detailed cytological and clinical data in such cases may be of value in the elucidation of possible specific effects of different chromosome regions, the following case is presented.

Case Report

This was the first child of intelligent parents: the father, a machine operator aged 30 years at the birth of the infant, has since died of a coronary thrombosis, and the mother, aged 22 years, is apparently healthy. Pregnancy was uneventful but went 18 days beyond the expected date of delivery before being terminated on July 10, 1963, by an artificial rupture of the membranes after a medical induction had failed. Forceps extraction of the head was carried out because of foetal distress during the second stage.

The male infant (weight 3,180 g.) breathed almost immediately. He had an imperforate anus and was transferred to the Department of Child Health, Welsh National School of Medicine, at 6 hours. He had a somewhat long and narrow head, with a biparietal diameter of 9.2 cm. and an anterior posterior of 13.5 cm. but a normal circumference (38 cm.). The fontanelles were normal in size and tension. The eyes were small but showed no colobomata and the palpebral fissure sloped downwards and outwards (Fig. 1). There was well-marked micrognathos and the ears, both low set,

the right more severely, were thick and had irregular accessory auricles 0.5 cm. in length (Fig. 2). The cardiovascular and respiratory systems appeared normal and the abdomen was full but not distended. Penis was small and was situated partially within the scrotum (Fig. 3) in which only the left testis could be palpated. The prominent median raphe was present where the anus should have been. A bulge was noted in this region when the child was crying and an anal reflex was thought to be present. The limbs showed no abnormalities but both hands showed transverse palmar creases.

On the day following delivery (July 11) he passed meconium per urethra and appeared 'cerebral' with occasional fits. A transverse colostomy was established which appeared to be working well. On July 17 the fits were still occurring and he was vomiting bile-stained mucus. Ten days later there was a sudden rise of both pulse and respiration rates and a basal systolic murmur could be heard and he was found to have bronchopneumonia. A large tumour was felt in the left subcostal region. His condition steadily deteriorated with a progressive upset of the electrolytes and he died on July 30, aged 20 days.

At necropsy carried out 8 hours after death, apart from oedema of the orbits, some hypertrophy of the breasts, and the colostomy, the external features were those already described. The lungs showed circumscribed areas of consolidation in the right lower lobe, found on microscopy to be due to infarction with pneumonia. The heart was anatomically normal, though there was a moderate amount of right-sided dilatation and slight ventricular hypertrophy. The ductus arteriosus was closed. The uvula was bifid but the soft palate was otherwise complete (Fig. 4).

The distal loop of the large intestine was progressively dilated and ended blindly about 2 cm. from the anal skin, a well-marked recto-urethral fistula being present. The right kidney and ureter were absent. The left kidney, grossly enlarged (weight 73 g.), was infarcted together with its associated suprarenal gland. The left renal vein and most of the inferior vena cava were distended with antemortem thrombus. The right suprarenal gland, though congested, was normal. The right testis was situated in the scrotum, the left in the inguinal canal. Both showed the typical infantile

FIG. 1. Appearance of the patient at necropsy, with the palpebral fissures sloping downwards and outwards.

FIG. 2. Side view of the head at necropsy showing the micrognathos and the abnormal ear with its accessory auricle.

FIG. 3. Excised external genitalia showing the small penis which is partially situated within the scrotum. The prominent median raphe is also shown.

FIG. 4. Dissection of the pharynx, with the oesophagus opened up to reveal the bifid uvula above with soft palate otherwise complete. The normal epiglottis and opening into the larynx is in the centre of the photograph.

seminiferous tubules but there were pus cells in the epididymis.

The brain was normal in size (weight 440 g.) but showed slight cerebral oedema with convolutional flattening. The olfactory tracts and trigones were absent and there was some irregularity of the convolutions of the rhinencephalon (Fig. 5) but no histological abnormality was noted. The olfactory bulbs

were vestigial, being composed of undifferentiated nerve cells and were connected to the brain by a minute blood vessel only. The cribriform plate was small.

The only family history of congenital malformation is that a brother of the propositus' mother had one normal infant and one with an imperforate anus and accessory auricles (Fig. 6). This child is now apparently well after a successful operation.

FIG. 5. Inferior view of the anterior portion of the cerebral hemispheres to show the absence of the olfactory tracts and trigones.

FIG. 6. Pedigree of family.

Chromosome Studies. Chromosome studies were carried out on cells obtained from a culture of skin taken at necropsy. 45 cells were counted and in 40 of these the chromosome number was 47 (Fig. 7). The extra chromosome in each cell was abnormal: in size, it was approximately equal to or slightly shorter than a 21-22 chromosome, but it appeared to be slightly more metacentric. In some cells, satellites were visible on its short arms (Fig. 8) and it tended to associate with other satellited chromosomes.

Blood specimens were taken for chromosome studies from 6 other members of the family (II. 2, 3, 5, and 6, and III. 3 and 4). In specimens taken from III.4 and III.3 on two occasions, cells suitable for examination were few (Table I), but those seen were examined in detail, and in none was the abnormal chromosome seen.

TABLE I
CYTOGENETIC RESULTS ON PART OF THE FAMILY

Case No.	Tissue	Number of Cells With Chromosome Number of				
		43	44	45	46	47
III.5	Skin				3	40
II.2	Blood				9	
II.3	Blood				8	
II.5	Blood			1	10	
II.6	Blood				6	
III.3	Blood 1			2	3	
	Blood 2			3	5	
III.4	Blood 1	7 Culture failed	5		5	
	Blood 2		3		1

FIG. 7. Karyotype of III.5.

FIG. 8. Part of karyotype from 5 cells of III.5.

FIG. 9. Diagram to show possible origin of the aberrant chromosome.

Discussion

It is not possible to identify the extra chromosome material conclusively, but its probable origin, since it is satellited, is from an extra 21-22 or 13-15. Deletion of a small fragment of the long

TABLE II

COMPARISON OF THE FEATURES OF THE CASE WITH THOSE OF THE 13-15 AND 17-18 TRISOMIES

Abnormalities of 13-15 Trisomy	Abnormalities of Case	Abnormalities of 17-18 Trisomy
<i>Mental retardation</i>	?	<i>Mental retardation</i>
<i>Apnoeic spells</i>	+	<i>Failure to thrive</i>
<i>Deafness</i>	?	<i>Gross osseous retardation</i>
<i>Motor seizures</i>	+	<i>Hypertonicity</i>
<i>Arrhinencephaly</i>	+	<i>Prominent occiput</i>
<i>Sloping forehead</i>	±	<i>Micrognathia</i>
<i>Eye abnormalities</i>	+	<i>Short sternum</i>
<i>Abnormal ears</i>	+	<i>Abnormal ears</i>
<i>Cleft palate or lip</i>	+	<i>Small pelvis</i>
<i>Capillary haemangiomas</i>		<i>Eventration of diaphragm</i>
<i>Abnormal dermal pattern</i>		<i>Heterotopic pancreas</i>
<i>Horizontal palmar crease</i>	+	<i>Meckel's diverticulum</i>
<i>Abnormal fingers</i>		<i>Abnormal fingers</i>
<i>Abnormal feet</i>		<i>Abnormal feet</i>
<i>Congenital heart disease</i>		<i>Congenital heart disease</i>
<i>Renal malformations</i>	+	<i>Renal malformations</i>
<i>Accessory spleen</i>		<i>Hernias</i>
<i>Large gall-bladder</i>		
<i>Abnormal rotation of colon</i>		
<i>Cryptorchism</i>		
<i>Abnormal scrotum</i>	+	

Features in italics are common to the majority of cases in both trisomies

arms of a 21-22 would produce a chromosome similar to the one described, though perhaps the aberrant chromosome is too long for this. A pericentric inversion would account for the more metacentric appearance of the chromosome. Gross deletion of the long arm of a 13-15, with loss of the acentric fragment, would also account for the abnormal chromosome (Fig. 9).

From a clinical point the three well-recognized autosomal trisomies have to be considered in this case. No specific syndrome has so far been associated with trisomy 22, though a number of cases have been reported (Hayward and Bower, 1960; Turner and Jennings, 1961; Dunn, Ford, Auersperg, and Miller, 1961; Bieseke, Schmid, and Lawlis, 1962) with trisomy of the 21-22 group, having none of the features of mongolism. The present case appears to have no significant similarities with these cases.

No clinical or pathological features of mongolism were present, which seemed to eliminate incomplete trisomy 21. However, it may not be impossible that that part of the chromosome, which when present in the trisomic state is responsible for the expression of mongolism, was the part that was deleted in this case (Ellis, Marshall, and Penrose, 1962).

Our patient shows some clinical and pathological features of the 13-15 and 17-18 trisomy syndromes. As shown in Table II, the only features of the 17-18 trisomy found in the present case are those common to both trisomies, with the possible exception of micrognathia. This, which is a constant feature of the 17-18 trisomy syndrome, has, however, been described in a number of undoubted cases of 13-15 trisomy (Lubs, Koenig, and Brandt, 1961; Rosenfield, Breibart, Isaacs, Klevit, and Mellman, 1962; Northcutt, 1962). It is of interest that one of the cases of Zellweger *et al.* (1962), which was regarded as a partial trisomy of one of the chromosomes of the 13-15 group, also had an imperforate anus and probably an absent right kidney and ureter, as did a maternal cousin with an imperforate anus.

It is concluded, therefore, that the abnormal chromosome represents a gross deletion of an additional 13-15 chromosome. Such an additional chromosome could have arisen as a result of non-disjunction and deletion. As the mother was young the usual increased tendency to non-disjunction of the satellited chromosomes with advanced maternal age does not apply. The most likely explanation of both deletion and non-disjunction is that they occurred during meiosis when the paired chromosomes were

naturally breaking and rejoining during crossing-over. Complex and unnatural twisting of arms could conceivably account for both events. That it is a phenomenon of gametogenesis and not of embryogenesis is supported by the apparent absence of mosaicism, though this has not been conclusively eliminated since only one tissue was examined.

Summary

A patient is described having some of the clinical manifestations of trisomy 13-15 with arrhinencephaly, microphthalmia, micrognathos, abnormal ears, and accessory auricles, a bifid uvula, renal malformations, and an abnormal scrotum, with, in addition, an imperforate anus. The chromosome constitution of the patient is unique and the interpretation of the abnormality as a possible incomplete trisomy of a 13-15 chromosome is discussed.

We wish to thank Mr T. J. Cooke, Mr N. J. Stark, and Mr J. O. Dew for technical assistance and the illustrations, and Dr A. Kertesz for bringing the case to our attention.

REFERENCES

- Bieseke, J. J., Schmid, W., and Lawlis, M. G. (1962). Mentally retarded schizoid twin girls with 47 chromosomes. *Lancet*, **1**, 403.
- Dent, T., Edwards, J. H., and Delhanty, J. D. A. (1963). A partial mongol. *ibid.*, **2**, 484.
- Dunn, H. G., Ford, D. K., Auersperg, N., and Müller, J. R. (1961). Benign congenital hypotonia with chromosomal anomaly. *Pediatrics*, **28**, 578.
- Ellis, J. R., Marshall, R., and Penrose, L. S. (1962). An aberrant small acrocentric chromosome. *Ann. hum. Genet.*, **26**, 77.
- Gustavson, K.-H., Hagberg, B., Finley, S. C., and Finley, W. H. (1962). An apparently identical extra autosome in two severely retarded sisters with multiple malformations. *Cytogenetics*, **1**, 32.
- Hayward, M. D., and Bower, B. D. (1960). Chromosomal trisomy associated with the Sturge-Weber syndrome. *Lancet*, **2**, 844.
- Lubs, H. A., Koenig, E. U., and Brandt, I. K. (1961). Trisomy 13-15: A clinical syndrome. *ibid.*, **2**, 1001.
- Northcutt, R. C. (1962). Multiple congenital anomalies in a negro infant with 13-15 trisomy. *Sth. med. J. (Bgham, Ala.)*, **55**, 385.
- Patau, K., Therman, E., Inhorn, S. L., Smith, D. W., and Ruess, A. L. (1961). Partial-trisomy syndromes. II. An insertion as cause of the OFD syndrome in mother and daughter. *Chromosoma (Berl.)*, **12**, 573.
- , —, Smith, D. W., Inhorn, S. L., and Picken, B. F. (1961). Partial-trisomy syndromes. I. Sturge-Weber's disease. *Amer. J. hum. Genet.*, **13**, 287.
- Rosenfield, R. L., Breitbart, S., Isaacs, H., Jr., Klevit, H. D., and Mellman, W. J. (1962). Trisomy of chromosomes 13-15 and 17-18: its association with infantile arteriosclerosis. *Amer. J. med. Sci.*, **244**, 763.
- Turner, B., and Jennings, A. N. (1961). Trisomy for chromosome 22. *Lancet*, **2**, 49.
- Zellweger, H., Mikamo, K., and Abbo, G. (1962). Two cases of multiple malformations with an autosomal chromosomal aberration — partial trisomy D? *Helv. paediat. Acta*, **17**, 290.