Syndrome Associated with a Deficiency of Part of the Long Arm of Chromosome No. 18*

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In 1964 de Grouchy, Royer, Salmon, and Lamy described a deaf and mentally retarded microcephalic girl in whom the long arm of one No. 18 chromosome was about half its usual length. Since then two other microcephalic children, a boy and a girl, have been found to have this chromosome aberration (Lejeune, Berger, Lafourcade, and Réthoré, 1966). Lejeune suggested on the basis of their findings that a recognizable syndrome was emerging in association with this deficiency.

This paper presents the clinical features and results of the genetic investigations of two further cases, both boys, in whom the tetrad of microcephaly, minute penis, cryptorchidism, and talipes equinovarus was present.

Case Reports

Case 1. This boy, birthweight 2.63 kg., was the only child of a 20-year-old mother and a 23-year-old father. There was no history of miscarriage, and the pregnancy was uneventful. At delivery the cord was tight around the neck and the baby was slow to breathe. Cryptorchidism and bilateral talipes equinovarus deformities were noted, and the skull bones were unusually soft. Subsequent progress was slow and he failed to gain his milestones. Feeding was laborious.

He was investigated when he was 16 months old. Microcephaly (head circumference 40.5 cm.; chest circumference 40 cm.) and mental retardation were marked. He was small, length 71.7 cm.; weight 7.27 kg. The facies were not striking but he did have a left internal strabismus, epicanthic folds, and a carp mouth (Fig. 1). The ears, their drums, the palate, and the five erupted teeth were normal.

The heart was normal to auscultation and all peripheral pulses were palpable. There were deep skin dimples over the acromial processes. The penis only protruded for 0.5 cm. above the fatty ridge that lay over the pubis. The scrotum was flat (2 cm. × 2 cm.) and was devoid of testes.

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Syndrome Related to a Chromosomal Deficiency

Chromosomal analysis. In the 30 lymphocyte and 15 skin fibroblast cells examined, a chromosome, probably the 18th, was replaced by a small metacentric chromosome whose short arms were identical to those of the No. 18 chromosome but whose long arms were only equal to about half the length of the long arms of the 18 chromosome (Fig. 3). These findings were confirmed in a further 50 skin fibroblasts by Dr. Joy Delhanty (Galton Laboratory). The lymphocyte cultures from both parents showed normal chromosomes.

Dermatoglyphics (Professor L. S. Penrose) (Fig. 4). There was nothing peculiar on the palms but 6 whorls on the fingers was well above the average number (which is about 2). This difference is on the other side of the average from what one would expect in trisomy 18 where whorls have a frequency of about 1%.

The patterns on the hallucal areas were peculiar: the triradius was unusually far out on the tibial side. I have seen two cases of trisomy 18 with somewhat similar hallucal patterns.

X-ray skeletal survey (Dr. R. Astley). A left cervical rib extended to the angle of the first rib. A much smaller right cervical rib was also present. The lower femoral and upper tibial epiphyses were relatively large.

There was a small exostosis on the medial side of the right tibia at its upper end. Ossification was consistent with age.

FIG. 2.—Case 1. The feet were still oedematous several months after successful treatment of the talipes equinovarus. The second toes override the third.

Fig. 3.—Case 1. Karyotype: the deficient chromosome is arrowed.
proteins; non-fasting blood substances, H. Professor electrophoresis of (see Steinberg)

Case A Mother. Case MNSs + Father. Ai

Case markers (Dr. R. R. Race Blood Other investigations. A. Ai

FIG. 4.—Case Lua Lutheran; Dr. E. B. Robson; Dr. A. Dermatoglyphs

TABLE

Results of Blood Typing. Red Cell Enzymes and

<table>
<thead>
<tr>
<th>ABO</th>
<th>MNS</th>
<th>P1</th>
<th>Rh</th>
<th>Lu^a</th>
<th>Kk</th>
<th>Le^aLe^b</th>
<th>FyaFyb</th>
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<tbody>
<tr>
<td>Case 1 Father ...</td>
<td>A1</td>
<td>MNSs</td>
<td>-</td>
<td>R^a</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Mother ...</td>
<td>A1</td>
<td>MNSs</td>
<td>+</td>
<td>R^bR^2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Case 2 Father ...</td>
<td>A1</td>
<td>NNSs</td>
<td>+</td>
<td>R^a</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mother ...</td>
<td>A1</td>
<td>MNSs</td>
<td>+</td>
<td>R^b</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Case 2 ...</td>
<td>A1</td>
<td>MNSs</td>
<td>+</td>
<td>R^a</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Rh = rhesus; Lu^a = Lutheran; Kk = Kell; Le^a Le^b = Lewis; FyaFyb = Duffy; Jk^a Jk^b = Kidd; Do^a = Dombrock; Hp = haptoglobins; Tf

Blood markers (Dr. R. R. Race and Dr. Ruth Sanger; Professor H. Harris and Dr. E. B. Robson; Dr. A. C. Steinberg) (see Table 1).

Other investigations were normal. They included electrophoresis of haemoglobins, serum lipids, and serum proteins; non-fasting blood sugar; urine screening for reducing substances, keto acids, protein total nitrogen, and porphobilinogen; urinary amino acid chromatogram, and EEG.

Case 2. This boy, birthweight 2.6 kg., was the only child of a 25-year-old mother and a 30-year-old father. There was no history of a previous miscarriage. His mother, a secretary, had worked for some years, up to and including part of the pregnancy, in hospital x-ray departments. She had some vaginal blood loss during the third month, but apart from this, pregnancy was uneventful and ended in the 38th week. Both feet were in the equinovarus position and he was cryptorchid. The penis was minute.

At 17 months of age he was referred for further investigation. He then weighed 8.26 kg., was 70 cm. long, with a head circumference of 43 cm., and a chest circumference of 43.5 cm. Gross mental retardation and growth retardation now accompanied the major genital and foot deformities.

Head and neck. The head was small and was accompanied by plagiocephaly. The facies were compounded of rather deep-set eyes with short, narrow, and upward slanting palpebral fissures, a prominent upper lip, and a carp mouth (Fig. 5). Eight normal teeth had erupted. The outer ears, the drums, the palate, and the chin were normal.

Trunk. A pulmonary systolic murmur which had been present a few weeks after birth had disappeared. The peripheral pulses were palpable. The penis was buried in an inverted horseshoe of fat and only projected for 0.5 cm. above the surface. The testes were impalpable. The scrotum which was hypoplastic measured 1.3 cm. across by 3 cm. in length (Fig. 6).

Limbs. There were two antecubital skin creases in each elbow. The hands appeared to be unusually small, with tapering fingers but with normal nails.

The deformity of the feet had been corrected by manipulations and serial plasters. The second toe on each foot was implanted a little more dorsally than expected, and the feet were small and oedematosus (Fig. 7). The child tended to lie with the hips partially flexed and fully abducted.
I

Serum Groups. No Anomalous Results Found

<table>
<thead>
<tr>
<th>Jka/Jkb</th>
<th>Xga</th>
<th>Doa</th>
<th>Gm+</th>
<th>Inv</th>
<th>Hp</th>
<th>Tf</th>
<th>PGM</th>
<th>AK</th>
<th>6-PGD</th>
<th>Ac. Ph.</th>
</tr>
</thead>
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<td>+</td>
<td>+</td>
<td>1, 2, 3, 5, 13, 14</td>
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<td>1-1</td>
<td>C</td>
<td>1</td>
<td>1</td>
<td>A</td>
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<td>1</td>
<td>2-2</td>
<td>C</td>
<td>2-1</td>
<td>1</td>
<td>A</td>
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<tr>
<td>+ +</td>
<td>-</td>
<td>+</td>
<td>3, 5, 13, 14</td>
<td>-</td>
<td>2</td>
<td>1-1</td>
<td>C</td>
<td>2-1</td>
<td>1</td>
<td>A</td>
</tr>
</tbody>
</table>

transferrins; PGM = phosphoglucomutase; AK = adenylate kinase; 6-PGD = 6-phosphogluconatedehydrogenase; Ac. Ph. = acid phosphatase.

CNS. At 17 months he could just sit with rounded back on his mother’s lap. He had gained head control some two to three months earlier. Sight and hearing appeared normal. The fundi and the muscular tone were considered to be within normal limits.

Nuclear sexing. The nuclei of the buccal mucosal cells and polymorphonuclear neutrophils were chromatin negative.

Chromosomal analysis. A small metacentric chromosome replaced a No. 18 chromosome in the 95 cells examined from two lymphocyte cultures (Fig. 8). This chromosome was very similar to that seen in the cells of Case 1 and was also thought to represent a No. 18 chromosome deficient of about half its long arms.

Fig. 5.—Case 2. The facies: microcephaly was not apparent but the head circumference 43 cm. was below the 10th centile for his size.

Fig. 6.—Case 2. Hypoplastic external genitalia.

Fig. 7.—Case 2. This infant’s feet closely resemble those of Case 1.
The lymphocyte cultures from both parents showed normal chromosomes.

Dermatoglyphics (Professor L. S. Penrose) (Fig. 9). There were probably 6 whorls on his digits (there was some uncertainty about the whorls on both 5th digits). There were quite unusual patterns, on both sides, in the digital areas III, which suggested some zygodactyly of the fourth and fifth digits. On the left hand there was also probably some zygodactyly of digits II and III. The feet had patterns not unlike those of Case 1. However, there was in addition, slight zygodactyly of digits II and III.

X-ray skeletal survey (Dr. R. Astley). There were developmental anomalies of the cervical and upper thoracic spine with spina bifida and hemivertebrae (Fig. 10). Several other bodies were incompletely cleft in the sagittal plane.

The ribs were slender and irregular in calibre. Small cervical ribs were seen. The right 12th rib was considerably smaller than the left. The femora were slender with coxa valga. Bone-age was consistent with chronological age.

Blood markers (Dr. R. R. Race and Dr. R. Sanger; Professor H. Harris and Dr. E. B. Robson; Dr. A. G. Steinberg) (see Table I). As in Case 1 no chromosome marker was found.

Other investigations were normal: they included electrophoresis of haemoglobins, serum lipids, and serum proteins; non-fasting blood sugar; urine screening for reducing substances, keto acids, protein, total nitrogen, and porphobilinogen, urinary amino acid chromatogram, and EEG.

Discussion

These two boys have many features in common. They were both of low birthweight, and growth has been slow. Even when body size is taken into account they are both microcephalic and are severely mentally retarded. Carp mouth, minute penis, cryptorchidism, bilateral talipes equinovarus, and irregularity of toe insertion complete the list of similarities.

The genital hypoplasia and cryptorchidism occurred in the absence of a sex chromosome anomaly. This was not surprising since minor anomalies of external genital development occur in association with autosomal aberrations, particularly in the trisomic syndromes. They are known to include faulty testicular descent, encroachment of the scrotum on the penis, and clitoral enlargement. Severe defects are rare. Hypospadias with cryptorchidism in association with a deficient chromosome
21 or 22 appears to be the most severe intersexual state so far related to autosomal imbalance. The form of genital defect seen in these two boys is sometimes also associated with microcephaly, growth retardation, and an XXXXY sex chromosome constitution. Whereas such a defect might be the end result of either genic imbalance or faulty testicular development in the XXXXY syndrome, its occurrence with an autosomal aberration suggests (in the absence of testicular histology) that genetic imbalance may be the more important of the two factors.

The deficient chromosome was considered to be a No. 18 chromosome rather than a 17 from the length of its short arms. This conformed with De Grouchy's interpretation of the same syndrome. But examination of the deficient chromosome could not reveal whether the distal half or an interstitial segment of the long arm had been lost. Whichever was the case it seems from a comparison of the clinical features that the same segment had been lost from the chromosomes of both boys. The length of the deficient chromosomes of two of the three cases examined by De Grouchy et al. (1964) and

Lejeune et al. (1966) appeared identical to those seen here, but the clinical resemblances, partly by reason of sex and possibly as the result of variation, were not quite so close.

Two of the children they described were girls and the other was a cryptorchid boy. One of the girls was Eurasian. Gross mental retardation and microcephaly were present in all. Certain other features: skin nodules in the nasal folds, tapering fingers, skin dimples over the acromial processes, widely separated nipples, irregular implantation of the toes, and pale optic discs were common to at least two of the five cases taken together. One child
TABLE II

The Loci For These Systems Cannot Lie on the Missing Segment, Since the Presence of Two Alleles Can Be Inferred from the Phenotype

<table>
<thead>
<tr>
<th>Case 1</th>
<th>MNSs</th>
<th>Kidd</th>
<th>Hp</th>
<th>Ac. Ph.</th>
<th>Case 2</th>
<th>MNSs</th>
<th>Rhesus</th>
<th>Kell</th>
<th>Hp</th>
<th>Ac. Ph.</th>
<th>PGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>MNSs</td>
<td>a - b +</td>
<td>1.1</td>
<td>CB</td>
<td>Father</td>
<td>MNSs</td>
<td>Rtr</td>
<td>K -</td>
<td>2.1</td>
<td>CB</td>
<td>2.1</td>
</tr>
<tr>
<td>Mother</td>
<td>MNSs</td>
<td>a + b +</td>
<td>2.1</td>
<td>BA</td>
<td>Mother</td>
<td>MNSs</td>
<td>tr</td>
<td>K + k +</td>
<td>2.2</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Child</td>
<td>MNSs</td>
<td>a + b +</td>
<td>2.1</td>
<td>CA</td>
<td>Child</td>
<td>MNSs</td>
<td>tr</td>
<td>K + k +</td>
<td>2.1</td>
<td>CB</td>
<td>2.1</td>
</tr>
</tbody>
</table>

had a cleft palate and corneal opacities and another atresia of the middle ears.

Certain of the infants’ blood groups, red cell enzymes, enzymes, serum fractions, and haemoglobin were compared with those of their parents. Since there was no inconsistency in the mode of their inheritance, a genetic marker could not be ascribed to the deficient segment. On the other hand, the MNSs, Kidd, haptoglobins, and acid phosphatase systems in Case 1, and the MNSs, Rh, Kell, haptoglobins, acid phosphatase, and phosphoglucomutase systems in Case 2 could not, by their segregation patterns, lie on this section of the 18 chromosome (Table II).

Urine screening for abnormal metabolites, and the scrutiny of the haemoglobins, serum lipids, and proteins did not yield any evidence that an abnormal recessive gene had been uncovered on the hemizygous segment of the long arm of chromosome 18.

Summary

Two unrelated boys with generalized and similar congenital malformations associated with a deficiency of about half of the long arm of a presumptive 18 chromosome are described. A marker on this segment of the chromosome was not found.

I am deeply indebted to Dr. J. H. Edwards for all the advice and encouragement he gave me during the preparation of this paper and to Professor J. Lejeune and his colleagues for a preview of their paper. My thanks are also due to Dr. G. Aldridge and Dr. D. C. Thursby-Pelham who referred the cases, and to Dr. R. Astley, Dr. Joy Delhanty, Professor C. E. Dent, Professor H. Harris, Dr. E. B. Robson, Professor L. S. Penrose, Dr. R. R. Race, Dr. Ruth Sanger, and Dr. A. G. Steinberg for carrying out their investigations. Thanks are also due to Miss Barbara Nunley for technical assistance.

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