Monosomy for a G Autosome

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Infants with complete or partial deletion of a G group autosome and of similar appearance have been described by Lejeune *et al.* (1964), Reisman *et al.* (1966), and Thorburn and Johnson (1966). The infant with many congenital abnormalities reported by Lejeune *et al.* (1964) had a karyotype with autosomal mosaicism, involving a chromosome of the G group. One cell line was monosomic with 45 chromosomes. The other contained 45 chromosomes plus a 'minute', which was probably a ring chromosome. The infant's phenotype was such as to suggest the name 'le contre type' trisomy 21.

Reisman and collaborators (1966) described a similar infant whose karyotype showed partial deletion of chromosome '21' and they called the condition 'Antimongolism'.

Thorburn and Johnson (1966) reported a further case of apparent monosomy of a G autosome. R. C. Hindle (personal communication, 1967) has followed an infant of similar phenotype with a deleted acrocentric of the G group.

German and Bearn (1962) and Al-Aish *et al.* (1967) have described older children with anomalies of the G group. The karyotype of German and Bearn's case showed that a member of the pair believed to be No. 21 was very small, and was probably a ring chromosome (Penrose and Smith, 1966). The child described by Al-Aish *et al.* (1967) was monosomic for a small acrocentric autosome.

This paper describes a male infant in whom physical and cytogenetic findings are similar to the first four cases.

Case Report

The infant was the first child of a 24-year-old mother. The father was aged 40 and had 2 normal children by a previous marriage. There is no family history of malformations and the parents are not related by blood. Pregnancy was complicated by abdominal pain and vomiting, severe enough for the mother to be admitted

to hospital during the first month. The symptoms abated and pregnancy then proceeded normally up to term.

The infant was delivered by forceps at an estimated 41 weeks' gestation. He weighed 2069 g. at birth, and congenital abnormalities were noted on delivery.

The early neonatal course was complicated by mild respiratory distress and symptomatic hypoglycaemia.

Physical examination showed a short (40.6 cm.) hypertonic infant (Fig. 1-3). The head was scaphocephalic and in circumference measured 32.4 cm. The palpebral fissures slanted downwards and outwards. There were corneal opacities in both eyes and a cataract in the left eye. The right pupil was small but reacted normally to light. The ears were round, of normal size but low set. The nasal bridge was prominent and the palate high-arched with a posterior cleft. The patient had micrognathos and a low hair line posteriorly, with a large skin fold at the nape of the neck. The hands were tightly clenched, with the index fingers overriding the middle fingers. The nipples were widely separated, and there was a systolic murmur, maximal at the apex.

The infant had hypospadias and the skin of the scrotum presented a whorled appearance on each side. Both testes were palpable in the inguinal canal. There was a large right inguinal hernia. Both feet were oedematous at birth and were 'rocker-bottom' in type.

The infant showed generalized hypertonia but the tendon reflexes were normal. The arms and legs were flexed. He had a high-pitched cry.

At 10 weeks of age the baby's length was 47 cm., his head circumference 34.3 cm., head length 126 mm., breadth 82 mm., with a cephalic index of 66. He weighed 2409 g. The infant began to vomit soon after birth and this persisted until his death from bronchopneumonia at 16 weeks. He sucked normally but only gained weight slowly, and at death weighed 3845 g.

Investigations. The following were within normal limits. Hb, white cell count—total and differential, reticulocyte count, ESR, Hb electrophoresis, prothrombin time, cephalin/kaolin time, total and differential serum proteins. Urea and electrolytes, calcium and phosphorus. Red cell glucose-6-phosphate dehydrogenase, galactose-1-phosphate uridyl transferase (screening test), serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, lactate dehydrogenase, α -hydroxybutyric dehydrogenase, creatine phosphokinase.

FIG. 1-3.—*The Propositus.* FIG. 4.—*Karyotype, showing monosomy G.*

FIG. 5.—Karyotype, showing G chromosome, replaced by a small darkly staining chromosome, probably a ring.

Urinalysis. Urinary 5-hydroxyindoleacetic acid. Chest x-ray and skeletal survey. Whole blood 5-hydroxytryptamine: at 4 weeks = 172 ng./ml. (normal range at 4 weeks = 162 ± 64 ng./ml.); at 7 weeks = 123 ng./ml. (normal range at 7 weeks = 110 ± 62 ng./ml.).

The following abnormalities were found: thrombocytopenia (range 117,000–199,000); elongation of the pyloric canal on barium meal; and a low serum IgG at 3½ months.

Cytogenetic findings (Fig. 4, 5, and 6 and Table I). Chromosome studies on lymphocyte and fibroblast cultures revealed 2 cell lines, one with 45 chromosomes with a G group autosome missing (G-), and the other with 46 including a small chromosome of varying appearance (Gq- or Gr). In 25% of these cells this was clearly identified as a ring chromosome. In the others it varied from an amorphous fragment to a small seemingly metacentric chromosome about half the size of a G autosome. The buccal smear was chromatin-negative and the karyotypes of both parents were normal.

Blood grouping (Table II). This gave little relevant information. The baby was heterozygous at several loci. Thus, the Rh and MNSs were not on the deleted segment. The Ss results were not quite straightforward as the s reactivity was very low, and therefore no comment is possible on this locus.

TABLE I
Cytogenetic Studies on Propositus

	Cells with 45 Chromosomes	Cells with 46 Chromosomes	Cells with 47 Chromosomes
Blood culture (1) (3-day)	24	42	
Blood culture (2) (2-day)	10	23	
Blood culture (2) (3-day)	42	58	1 (2 rings)
Blood culture (3) (3-day)	19	66	
Skin culture	10	40	1 (2 rings)

TABLE II
Blood Groups of Propositus and Parents
(Dr. T. E. Cleghorn)

Father	A, B, R, R ₂ , P ₂ , F _y (a+), MNs
Mother	O, R, r, P ₁ , F _y (a-), NSs
Proband	B, R, R ₂ , P ₂ , F _y (a-), MNS (weak reactivity for s)
All three were Lu(a-b+); K-k+Kp(a-b+); Le(a-); Jk(a+); Xg(a+); Do(a+)

FIG. 6.—Partial karyotypes of 6 cells (G group). This shows 3 chromosome fragments, 2 monosomic cells, and 1 ring chromosome.

FIG. 7.—Dermatoglyphic patterns (Professor L. S. Penrose).

TABLE III
Dermatoglyphic Data (Professor L. S. Penrose)

Feature	Mongolism	Control Normals	German's Case	Lejeune's Case	Hindle's Case	Our Case
Finger-tip patterns	20% whorls 75% ulnar loops 3% radial loops 2% arches	26% whorls 64% ulnar loops 6% radial loops 4% arches	10 arches	—	6 arches (4 fingers not deciphered)	7 ulnar loops 1 index radial loop 2 whorls
Palmar interdigital triradii	C missing in ? 1% of palms	C missing in about 5% of palms	C missing on both sides, b very distally placed	C missing on both sides, other triradii distally placed	Left C missing but replaced by unusual ulnar palmar loop	C missing on both sides; unusual palmar ulnar loop
Palmar axial triradii	t 8% t' 8% t'' 84%	t 63% t' 28% t'' 9%	t both sides	t' both sides	t' both sides	t both sides
Patterns—hallucal area of sole	1% whorls 46% distal loops 3% tibial loops 3% fibular loops 47% tibial arches	33% whorls 51% distal loops 10% tibial loop 5% fibular loop 1% tibial arch	Fibular loop on both sides	Distal loop on left	Whorls on both sides	Fibular loop on both sides

Tests of genetically determined serum proteins and red cell enzyme systems were also uninformative.

Necropsy (Dr. J. Guthrie). The stomach was considerably dilated and the pylorus thickened due to increase in the muscle coat. The lungs were congested and showed patchy basal collapse. All other organs were macroscopically normal.

Dermatoglyphic data. See Table III and Fig. 7.

Examination of brain (Dr. L. Crome). The brain was markedly dolichocephalic. The meninges were congested but transparent. The pattern of gyri was normal. The optic nerves and chiasma were small and the other cranial nerves were normal. The main blood vessels at the base were normal. On the medial surface there was unevenness and interdigitating of the gyri. There was early myelination in the centrum semiovale. The basal ganglia were normal. Weight of whole brain, 410 g.

Discussion

Table IV summarizes the findings in the three previously described cases, to which we have added R. C. Hindle's case and our own.

A comparison of the clinical features in these cases suggests that they constitute a syndrome. The most constant abnormalities are in the facies, and in the presence of generalized muscular hypertonia and of persistent vomiting. The infants were all retarded in motor and sensory development and 4 out of 5 cases were of low birthweight for gestational age.

The facies in each case had palpebral fissures that sloped downwards and outwards (antimongoloid), a prominent nasal bridge, and micrognathos.

Examination of the central nervous system showed normal tendon reflexes but marked muscular hypertonia. Vomiting also began soon after birth in 4 cases and this persisted until pyloroplasty in 2 cases and until death in our case. The dermatoglyphic findings in 3 of the infants showed an absence of the C triradius on one or both palms (Table III).

R. C. Hindle (personal communication, 1968) has followed the only surviving infant at regular intervals, and he was last seen at 20 months. He continued to vomit until 5 months of age when this gradually improved. At 7½ months he developed fits which were controlled by phenobarbitone. Investigations at that time were normal, and phenobarbitone was withheld without the fits recurring.

At 13½ months the palpebral fissures were horizontal and the child was no longer hypertonic. His over-all motor and sensory development were at the 7-month level. At 15 months his fits re-

curred and an air encephalogram showed generalized cerebral hypoplasia, with symmetrical dilatation of the lateral, third, and fourth ventricles. The cerebellum was very small and there was an increase in the size of the cortico-subarachnoid channels in the frontal region.

The case described by German and Bearn is now aged 16 years. Recent autoradiographic studies (J. L. German, personal communication, 1967) have shown that the ring chromosome is a late replicating chromosome, presumably of the G group.

This syndrome does not appear to show a parental age effect, nor were there any abnormalities in parental karyotype in 4 instances examined.

Until recently, complete autosomal monosomy has been considered to be incompatible with life. However, Al-Aish *et al.* (1967) have now described a case of complete autosomal monosomy G in a mentally retarded 4½-year-old girl.

Autosomal monosomy is also a rare finding in the fetus. Kelly *et al.* (1965) described fetal monosomy, probably of the A group, and recently R. K. Dhadi (personal communication, 1967) showed 9% of the fibroblasts in a 12 week spontaneous abortion to be monosomic for a chromosome of the G group.

The monosomic line in our case may have arisen by loss of a ring chromosome. The latter may have formed during parental gametogenesis by a double break in the affected chromosome, the two ends of this chromosome then joining to form a ring. The zygote therefore might have had 46 chromosomes including a ring, and the monosomic line could have arisen by subsequent loss of the ring. By repeated sampling of peripheral blood cultures at 2 and 3 days, it has been possible to show loss of the ring *in vitro*. A culture terminated at 2 days had 30% monosomic cells and at 3 days 42%. Serial cultures taken at intervals have failed to show cell selection *in vivo* in the relatively short time of follow-up.

As deletion mapping of chromosomes is a method of establishing the position of gene loci, we investigated blood groups and biochemical factors that have been associated with the G autosomes.

The level of leucocyte alkaline phosphatase was normal in 3 of the above cases and raised in one.

It has also been suggested that the loci for ABO blood groups might be on G 21 (Shaw and Gershowitz, 1962). Our findings were non-contributory. The excretion of 5-hydroxyindoleacetic acid was noted to be low in 15 mongol children, by Jérôme, Lejeune, and Turpin (1960). In his case of this syndrome Lejeune reported an increased ratio of urinary 5-hydroxyindoleacetic acid to

TABLE IV
Summary of Findings in 5 Reported Cases

	Lejeune <i>et al.</i>	Thorburn and Johnson	Reisman <i>et al.</i>	Hindle	Our Case
Sex	Male	Female	Male	Male	Male
Age	Died 7½ mth.	Died 1 yr.	Died 8 mth.	Age 20 mth.	Died 16 wk.
Birthweight (g.)	2100	—	2009	2150	2069
Parental Age (yr.)	Fa 28 Mo 27	Fa 30 (approx) Mo 18	Fa 23 Mo 18	Mo 43	Fa 40 Mo 24
CNS	Retarded development; hypertonia	Retarded development; hypertonia of lower limbs	Retarded development; hypertonia	Retarded development; hypertonia	Retarded development; hypertonia
Eyes	Slope down and outwards; blepharochalasis	Slope down and outwards	Slope down and outwards; bilateral cataracts	Slope down and outwards	Slope down and outwards; bilateral corneal opacities; left-sided cataract
Ears	Large external ears with large conchae; wide external auditory canal	Large low-set ears	Large, low-set ears; absent helix of left ear	Low-set ears; misshapen helix of left ear	Rounded low-set ears
Nose	Prominent nasal bridge	—	Prominent nasal bridge	Prominent nasal bridge	Prominent nasal bridge
Mandible	Micrognathos	Receding chin	Micrognathos	Micrognathos	Micrognathos
CVS	Systolic murmur	—	Systolic murmur	Normal	Systolic murmur
GI	Pyloric stenosis	Pylorus normal at necropsy	Pyloric stenosis	Frequent regurgitation; barium meal suggestive of achalasia of cardia; pyloric canal normal	Frequent vomiting; pyloric stenosis at necropsy
GU	Hypospadias; inguinal herniae	Normal	Hypospadias, cryptorchism ? agenesis of kidney	Cryptorchism; poorly developed scrotum	Hypospadias, cryptorchism; right inguinal hernia
Skeleton	13th rib present; increased acetabular and iliac index; growth retarded; Length: 53 cm. at 7 mth.; head circ. 31 cm. at 7 mth.	Skeletal survey normal	Sacral hemivertebrae; normal acetabular and iliac angles; retarded growth Length: (at 4 dy.) 40.6 cm.; head circ. 29.4 cm.	Retarded growth; spine and iliac angles normal; Length: 51 cm.; head circ. 35.8 cm. (at 19 wk.); 6 lumbar vertebrae; 13 ribs on both sides	Retarded growth Length: 46.9 cm.; Head circ.: 34.3 cm. (at 10 wk.); skeletal survey normal
Hands	Koilonychia	Thumbs held flexed	Nails dystrophic	Normal	Hands tightly clenched; thumbs low set; nails normal
Blood	Thrombocytopenia; eosinophilia; leucocyte alkaline phosphatase raised	—	Thrombocytopenia; leucocyte alkaline phosphatase normal	Platelets normal; eosinophilia for 5 wk. when 3 mth. old; leucocyte alkaline phosphatase normal	Thrombocytopenia; leucocyte alkaline phosphatase normal
Karyotype	Mosaic: 1 cell line with 45 chromosomes; 1 cell line with 46 chromosomes including ring	Monosomy G	45 chromosomes + a centric fragment	45 chromosomes + a fragment	Mosaic: 1 cell line with 45 chromosomes; 1 cell line with 46 chromosomes including ring

CNS, central nervous system; CVS, cardiovascular system; GU, genito-urinary system; GI, gastro-intestinal system.

kynurenine, but in our case the excretion of 5-hydroxyindoleacetic acid was normal.

The presence of hypertonia is of interest in these cases in contrast to the hypotonia of Down's syndrome.

Administration of 5-hydroxytryptophane to patients with Down's syndrome, who have been shown to have low levels of whole blood 5-hydroxytryptamine (Rosner *et al.*, 1965), increases muscle

tone (Bazelon *et al.*, 1967). Overdosage with this substance produces opisthotonos, motor restlessness, vomiting, diarrhoea, hypertension, and cutaneous flushing.

As several of these signs appeared in our case, we estimated whole blood 5-hydroxytryptamine levels. These were within the normal range for age, but may be relatively high as the platelet count was consistently low. In the above cases vomiting

caused by pyloric stenosis occurred in 3 out of 4 male babies. This has also been reported with high frequency in subjects with ovarian dysgenesis and abnormal sex chromosomes (Benson and King, 1964).

Summary

An infant with autosomal mosaicism of the G group is reported. One cell line contained 45 chromosomes with a G group autosome missing. The other contained 46, including a small chromosome of varying appearance.

Comparison of the congenital abnormalities in this case with four other cases of similar karyotype suggests that they represent a syndrome.

Features common to each case were the characteristic facies, generalized muscular hypertonia, and persistent vomiting. There was also a high incidence of pyloric stenosis.

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