Clinical and Cytogenetic Aspects of the 21 Deletion Syndrome

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SUMMARY

The clinical, cytogenetic and dermatoglyphic findings in a patient with a ring chromosome 21 are presented. This anomaly acts as a deletion of chromosomal material and results in specific congenital defects.

A comparison is made with 24 cases of deletions involving chromosome 21 described in the literature. Six of these have been studied by means of recently developed chromosome banding techniques.

Cases presumably arise through somatic non-disjunction or chromosome breakage. When the chromosomes of both parents are normal the recurrence risk is negligible.

In 1964 Lejeune et al.[14] first described an infant with a mosaic chromosome pattern (45,XY, G-/46-minute) representing partial monosomy for a G chromosome. The possibility that this 'minute' represented a ring structure was considered. The phenotype was described as 'le contretype' of Down syndrome owing to the presence of antimongoloid slants of the palpebral fissures, a prominent nasal bridge and hypertonia. Lejeune proposed that 'antimongolism' is caused by the deletion of the same chromosome as the one which causes mongolism.

G group chromosome deletions have also been described in patients whose anomalies differed distinctly from the phenotype described above. Reisman et al.[18] and later Weleber et al.[25] suggested that two distinct syndromes existed which are caused by abnormalities in 2 pairs of G group chromosomes. These were later referred to as G deletion syndrome I and II respectively.

Advances in cytogenetic techniques have enabled investigators to identify each chromosome in the human karyotype, and two clinical syndromes can now be attributed to deletions involving G group chromosomes 21 and 22 respectively.

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Phenotypic findings of the 21 deletion syndrome usually include mental and motor retardation of variable severity. Antimongoloid slant of the palpebral fissures, a prominent nose bridge, hypertonia, abnormally large ears, micrognathia and skeletal anomalies are usually present. The 22 deletion syndrome is clinically a much less clearly defined entity. Findings include mental retardation, hypotonia, epicanthal folds, syndactyly of the second and third toes and minor skeletal abnormalities.[5] Six cases of the 21 deletion syndrome have subsequently been reported where Lejeune's hypothesis has been confirmed by means of either fluorescent staining studies or Giemsa bands.[8,10,13,16,20,24] We wish to report another infant with the 21 deletion syndrome who has been studied with fluorescent staining and Giemsa banding techniques.

CASE REPORT

A male infant weighing 2 160 g was admitted to the neonatal ward after an uncomplicated premature home delivery at 36 weeks' gestation. The mother was 27 and the father 31 years old at the time of his birth. The mother has 2 normal children from a previous marriage. She was first seen at an antenatal clinic at 18 weeks' gestation, when she presented with pyelonephritis. As this proved to be very resistant, she received 100 mg nitrofurantoin per day throughout the remainder of the pregnancy.

The infant appeared healthy but was premature and showed numerous congenital defects. His ears were abnormally large and floppy, especially the right ear (Fig. 1). Almost no scalp hair was visible and the skin was very dry and pale. The eyes were sunken and the palpebral fissures slanted downwards laterally. The fundi appeared pale, but were within normal limits. There were no epicanthal folds. The nose bridge was prominent, and the infant had a fish-like mouth with micrognathia. A high arched palate was noted. The neck was short and merged with the arms without clear shoulder tips. Clinodactyly of the 5th finger and a simian crease were present in the left palm. The nails were dystrophic.

The cardiovascular and respiratory systems were normal. The nipples were widely spaced. Abdominal palpation yielded no abnormalities or herniae. Both testes were incompletely descended. Examination of the external genitalia revealed empty labioscrotal folds and a small penis in chordee. Perineal hypospadias was present (Fig. 2). Examination of the joints revealed no abnormalities. The child had rocker-bottom feet with bilateral plantar creases. No skin lesions were seen. The central nervous system appeared intact, although the infant was slightly hypertonic. He had numerous episodes of gastro-enteritis
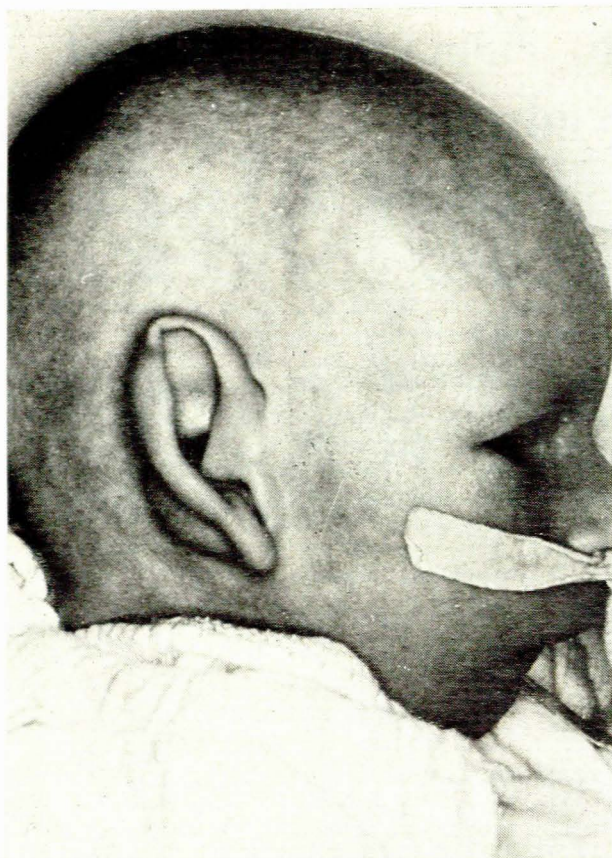
Fig. 1. Abnormally large ears, prominent nasal bridge, absence of scalp hair and micrognathia.
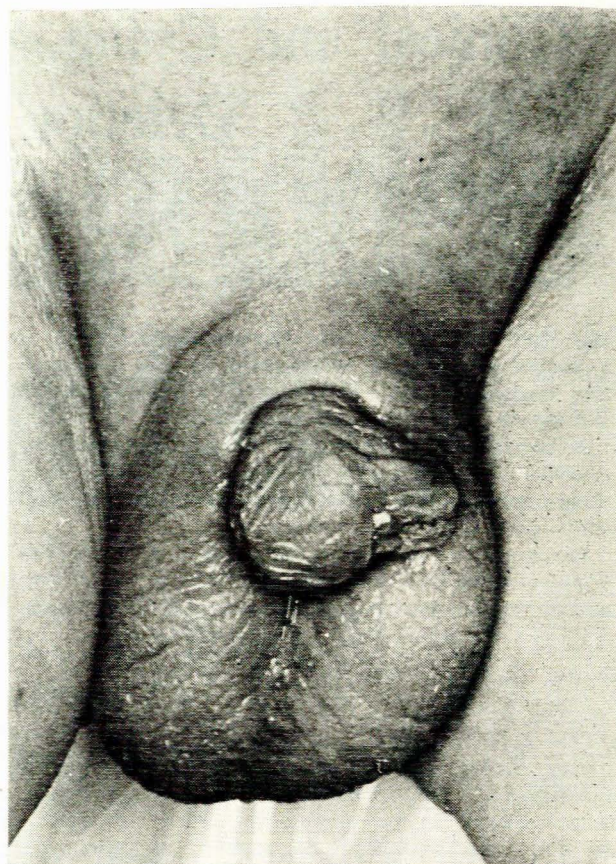

Fig. 2. Empty labioscrotal folds, small penis in chordee and perineal hypospadias.

and from the age of 4 months, convulsions occurred on several occasions. Easy bruising was a constant problem.

Examination at 7 months indicated retarded development: the patient fulfilled the criteria of development of a normal 3-month-old child. His weight (4,6 kg), length (55 cm) and head circumference (37 cm) were significantly below the 3rd percentile. Electrocardiography showed a normal pattern. Ophthalmological examination indicated a 7° divergent strabismus on the left side and slight endpoint nystagmus on the right side with dextrodeviation. No other abnormalities were noted.

Radiographic examination indicated a normal chronological bone age, normal hip joints and 13 pairs of ribs. A barium meal showed the oesophagus, stomach, proximal intestine and diaphragms to be normal. Intravenous pyelography revealed a normal functioning kidney on the left side, but no right renal structures, and a subsequent renal radio-isotope scan showed a normal left kidney, with no activity on the right side.

On electromyographic examination small motor units suggestive of myopathy were found. A search was made for biochemical signs of renal rickets which may be associated with a myopathy, but serum phosphorus, calcium and alkaline phosphatase were normal. The creatinine clearance and tubular reabsorption of phosphate were within normal limits. An audiological evaluation revealed air-conducted responses indicating a hearing loss of average grade. The EEG background showed episodes of spike waves suggestive of an epileptic pattern.

The child was admitted to an institution for mentally retarded patients. When he was next seen, at the age of 10 months, he had severe gastro-enteritis. He had fallen further behind in his development and was severely anaemic. His condition deteriorated rapidly and he died after 2 days in the ward.

A postmortem examination revealed bilateral cryptorchidism, a haemorrhagic enteropathy in the terminal ileum and caecum, a hypoplastic right kidney (Fig. 3), hyperaemia and oedema of the lungs, and fatty changes in the liver. The gums were grossly hypertrophied.

Relevant laboratory findings were as follows: platelet counts were 80 - 100 000/mm³; the prothrombin time was 44 sec (normal 25 - 40); prothrombin activity was 90% (Owren) (normal 70 - 120); the prothrombin index 88% (Quick) (normal 80 - 120); coagulable fibrinogen was 35 mg/100 ml (normal 150 - 300); and fibrin degradation products were less than 10 μg/ml (normal <10). The leucocyte count was 14 000, with neutrophils predominating (68%) and leucocyte alkaline phosphatase was very low at 6 units (normal 4 - 76 units). The total serum protein
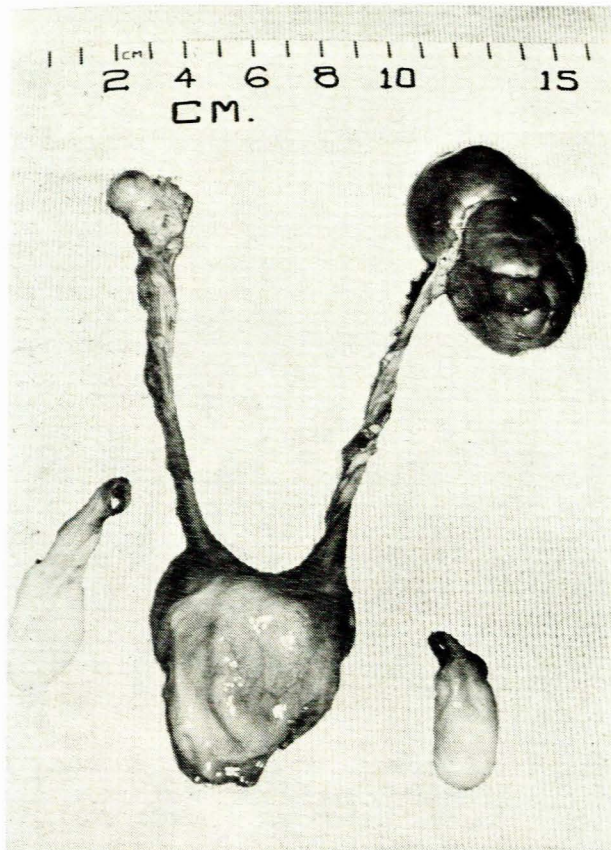
Fig. 3. Hypoplastic right kidney found at postmortem examination.

Fig. 4. Fluorescence staining shows a structurally variable chromosome replacing one of the chromosome 21 pair.

level fluctuated between 4 and 5 g/100 ml, with an especially low albumin fraction of 2,34 g/100 ml. Immunodiffusion showed both γA and γM to be normal and γG to be in the low normal range; the total γ-globulin level was 0,66 g/100 ml.

Cytogenetic Findings

Standard laboratory methods were used for culturing whole blood from the patient and his parents, and skin from the patient. The skin fibroblast cultures were slow-multiplying and chromosome preparations were made at the 4th passage after 6 weeks in culture. Chromosome preparations for fluorescence studies and Giemsa bands were treated according to methods of Caspersson et al.[5] and Chaudhuri et al.[7] respectively, slightly modified to suit our laboratory conditions.

In the blood cultures a structurally variable chromosome replacing a G group chromosome was observed (Fig. 4). A ring chromosome was assumed because of variability of size and shape characteristic of this aberration.[15] In the G group fluorescence preparations revealed a normal Y chromosome with its brilliantly fluorescing distal long-arm region, a normal chromosome 21 with a bright band, and 2 normal chromosomes 22 with dull fluorescence, all
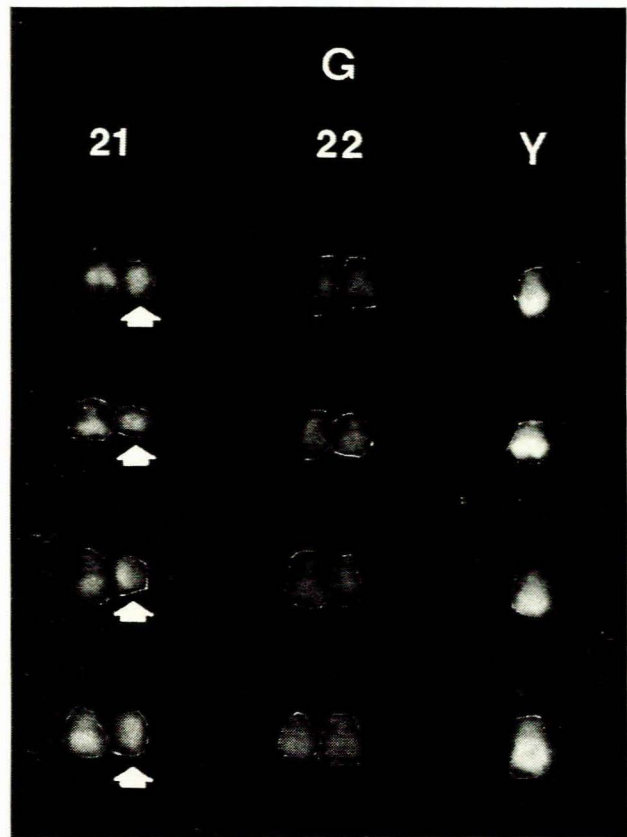
in the long arms. The abnormal chromosome, in spite of its size and shape, possessed a fluorescing region of more or less equal intensity to that of the 21q21 band, i.e. the bright band on chromosome 21.[4] This was observed in most metaphases. Giemsa-band preparations were more variable but helpful. No further abnormalities were identified in the karyotype, shown in Fig. 5. The karyotype is therefore 46,XY,r(21) (p11 - q22) if the one breakpoint is below q21 and the other at the same position as in Robertsonian translocations, p11. Chromosome counts, showing the presence of the ring chromosome in blood lymphocytes, are given in Table I.

In the fibroblasts, however, mosaicism could be identified. Two lines, one similar to the blood analysis and the other with 45 chromosomes without the ring chromosome were present (45,XY,-21/46,XY,r(21)). Fluorescence and Giemsa-band preparations confirmed that chromosome 21 was absent. Chromosome counts in fibroblasts are given in Table I, and according to the counts the monosomic line constitutes 25% of the total.

The chromosome complement of the parents was normal.

Dermatoglyphs

In Table II the patterns present on the fingers of the patient and his parents are given. Whereas an oroscope

Fig. 5. The full karyotype. The abnormal chromosome 21 is indicated by the arrow.

TABLE I. DISTRIBUTION OF CHROMOSOME COUNTS

	45 + r	45 − r	46 + r	Total
Blood lymphocytes	5*	1	31	37
Skin fibroblasts	2*	7	19	28

* Random loss.

TABLE II. FINGER PATTERNS

		I	II	III	IV	V
Patient	R	U	A	A	U	U
	L	U	A	A	A	U
Mother	R	U	U	A	U	U
	L	U	U	A	U	U
Father	R	U	U	U	U	U
	L	U	U	U	U	U

was used for the documentation of the results in the patient, prints of fingers and palms were obtained from the parents.

The palms of the patient showed normal t-triradii and on the left hand an associated radial loop was seen in the hypothenar region. On both palms the c-triradii were missing and the d-triradii were laterally displaced.

The hypothenar regions of the mother have an ulnar loop in the right hand and in the left hand a radial loop similar to that of the child. Neither of the parents possesses peculiarities of the digital palmar triradii.

DISCUSSION

The theory of opposite phenotypes for monosomy and trisomy of the same chromosome was first postulated by Bridges in 1916. Lejeune et al.[14] saw a parallel in human genetics and proposed that the same chromosome which causes mongolism when present in triplicate causes antimongolism when deleted.

It was not until the discovery that chromosomes have bands and that by this means each chromosome can be individually identified[6] that the hypothesis of Lejeune et al. could be further elucidated. Results from autoradiography[3] were not sufficient evidence. The value of the various banding techniques is therefore well illustrated in the context of these syndromes, and our case lends further support to the specific relationship between this cytogenetic abnormality and particular clinical features.

Clinical Analysis

In Table III the clinical findings of our patient are compared with 24 other cases described in the literature. The clinical findings are tabulated in decreasing order of frequency and some of the more important aspects will be discussed.

TABLE III. COMPARATIVE CLINICAL FINDINGS IN CASES OF CHROMOSOME 21 LONG-ARM DELETION

Phenotypic features	Number of cases	%	Our case
Mental and physical retardation ...	24	100	+
Abnormal ears	21	87	+
Antimongoloid slant	18	75	+
Micrognathia	18	75	+
Prominent nasal bridge	17	70	+
Skeletal anomalies	14	58	+
Genito-urinary abnormalities ...	12	50	+
Hypertonia	11	46	+
Repeated infections	11	46	+
Microcephaly	11	46	+
Low birthweight	10	41	+
Cardiovascular abnormalities ...	10	41	−
High arched palate	9	37	+
Cleft palate	8	33	−
Thrombocytopenia/prolonged bleeding time	7	29	+
EEG abnormal/history of convulsions	7	29	+
Anomalies of pupils and lenses ...	7	29	−
Pyloric stenosis	5	21	−
Inguinal hernia	5	21	−
13 pairs of ribs	4	16	+
Renal hypoplasia/agenesis	3	12	+

It is interesting to note that all 24 patients with this syndrome were mentally and physically retarded. Fourteen (58%) had skeletal anomalies, although only 4 (16%) had 13 pairs of ribs. Genito-urinary abnormalities were found in 12 patients (50%) and 3 of these had unilateral renal agenesis or hypoplasia. Ten of the 24 patients (41%) suffered from various cardiovascular problems, of which 3 were ventricular septal defects. Thrombocytopenia or a prolonged bleeding time was seen in 7 patients (29%). The same figure applies to EEG abnormalities or a history of convulsions. The possibility of pyloric stenosis or deviation from normal on a barium meal must be sought, since 5 patients (21%) had this abnormality.

Deletion Mapping

The investigation of chromosomal deletions creates the opportunity for assigning genes and linkage groups to specific chromosomes by the discovery of recessive traits in the hemizygote. Attempts at deletion mapping have yielded no results in our case. Blood typing was uninformative, since it was possible to ascribe an intelligible genotype to every one of 17 blood group systems. Antiviral immunity, reported to be situated on the long arms of chromosome 21,[21] could have been partially lost. The patient here described suffered from repeated episodes of gastro-enteritis. Eleven (46%) of the 24 patients who have been described suffered from repeated infections or had diminished γ-globulin levels. Leucocyte alkaline phosphatase, reported to be raised in trisomy 21,[2,23] was very low in our patient. It seems important to do a complete immunological survey in future patients.

In 1970 Say et al.[19] reported a patient with a Chédiak-Higashi syndrome, a rare autosomal recessive disease, with an associated mosaic chromosome pattern 45,XY,G-/46,XY,Gr. This syndrome is characterised by photophobia, partial albinism, increased susceptibility to infections, hepatosplenomegaly and anomalous giant granules in leucocytes. These have been shown by electron microscopy to be varieties of lysosomal structures. The absence of hepatosplenomegaly, the normal skin histology and electron microscopic studies of peripheral blood leucocytes excluded this condition in our patient. A specific karyotype for the Chédiak-Higashi syndrome has not subsequently been confirmed.

Cytogenetic and Dermatoglyphic Aspects

Autosomal monosomy is widely held to be lethal, and it is not known whether reported cases of G monosomy might have represented low-grade mosaic patterns. The first patient with a complete monosomy was the case reported by Al Aish et al.[1] This patient had a G monosomy in blood, bone marrow and skin. Subsequently, 2 other cases with supposed monosomy were described by Thorburn et al.[22] and Hall et al.[11] It is impossible to distinguish clinically between these 3 monosomic cases and others carrying a partially deleted chromosome 21.

The spectrum of cytogenetic abnormalities of the 24 cases listed in Table III is wide, but in effect it represents a loss of G chromosome material to a greater or lesser extent, whether by mosaicism or by partial deletion. Although only 6 cases have been studied by means of banding patterns, the chromosome responsible should be assumed to be No. 21, because of supporting clinical evidence.[8,10,12,16,20,24]

The majority of the 24 patients, i.e. 18, had structurally altered chromosomes; of the rest, 4 cases were monosomes and 2 were monosomy/normal mosaics. The structural abnormality causing deleted material was in the form of a ring in 12 cases, 4 of them monosomy/r(21) mosaics, denoting instability of the ring. One case[19] was reported to have 3 lines: a normal line as well as monosomy and r(21) lines. Those cases where the chromosome abnormality was denoted fragment, centric fragment or minute — 5 in all — could represent ring chromosomes, especially when mosaicism was present. In the case described by Lejeune et al.[14] ring structure was suggested by the authors. The morphological similarity of these cases to reported cases of rings is notable. In the case described by Engel et al.[9] there was also a deletion of the short arm of a B group chromosome. Of interest is the case described by Kelch et al.[12] who reported a short-arm deletion of G chromosome material. This is in agreement with the professed mode of ring formation which includes deletion of short-arm material, and indicates that not only the distal long-arm material is responsible for the clinical picture. It is known, however, that normal individuals can have short-arm deletions.[17]

Sixteen of the 24 patients reported in Table III have been studied dermatoglyphically. Of these, 7 showed either missing c-triradii or abnormality of distribution of digital palmar triradii. A preponderance of arches was found in only 2 cases. Although both these findings occurred in our patient, in the absence of data from dermatoglyphic analysis, only the first should be regarded as typical of the well-known association of a chromosomal defect with characteristic dermatoglyphs.

CONCLUSION

Although the advent of banding techniques did not add anything to the phenotypic picture, it opened new possibilities in gene mapping and brought us nearer to the understanding of the aetiology of the condition. Furthermore, we are now able to classify cases correctly, which will help us to estimate the relative prevalence of the two G deletion syndromes.

Follow-up studies indicate the grave prognosis of this disorder and strengthen the indications for termination of pregnancy if the disorder is diagnosed antenatally. This possibility will remain largely hypothetical, however, since most cases reported are of a sporadic nature.

When an affected child is born, it is nevertheless important to study the chromosomes of the parents, and if they are normal — as in most cases — it must be pointed out that the recurrence risk is the same as that for any abnormality for any other pregnancy, viz. 2 - 3%.

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