pericentric inversion and an unbalanced crossover segregation product from the inversion. However, the structurally abnormal chromosome involved is No. 4 and not a D chromosome.

Summary

A non-satellited, slightly submetacentric chromosome replacing one of the members of the 13–15 group was found in the apparently healthy father, paternal uncle, and sister; their karyotypes were otherwise normal. The aberrant chromosome is interpreted as being a result of pericentric inversion. One of the D chromosomes of the propositus was abnormally large and is assumed to represent duplication of a part of the long arm as a result of single crossover during meiosis in the father.

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References


A 45,XX,21– Child: Attempt at a Cytological and Clinical Interpretation of the Karyotype

Of the chromosomal diseases occurring in man, G-group abnormalities are among the most frequent and important. G-trisomy or Down’s syndrome was the first chromosomal error described in man (Lejeune, Gautier, and Turpin, 1959). Other abnormalities of the G group are translocations, deletions of the short and long arms (Gp– and Gq–), rings (Gr), and mixoploidy comprising monosomic cell lines.

The present paper is a report on an infant with minor somatic anomalies and signs of mental retardation. A chromosome No. 21 is missing in all the cells studied from the blood, bone marrow, and skin. Three other cases of apparent G-monosomy have been described in the literature (Thorburn and Johnson, 1966; Al-Aish et al, 1967; Hall, Fredga, and Svennisen, 1967).

Autoradiographic and fluorescence studies gave unequivocal results with regard to the G group chromosome involved, the missing chromosome being No. 21.

Case Report

Family History. The child is the younger of two sibs born to nonconsanguineous parents. The father and mother were aged 25 and 22, respectively, at her birth. The parents and the brother are phenotypically normal and healthy. The mother had been taking an oral contraceptive at the time of conception.

The grandmother of the patient has two brothers who have emigrated to Canada. One of these is said to have a mongoloid child, the other also has a retarded child.

Case History. As a newborn baby the propositus was referred for cytological examination. Her birth weight was low and she showed a peculiar facies with small mandible, high palate, flexion deformity of the fingers, and a short trunk.

She was born at term after an uneventful pregnancy and normal delivery; birth weight was 2350 g and length 45 cm. After birth the child was slightly blue and her temperature fell below normal. She was given oxygen for the first few days and made a good recovery.

The child was found to have congenital dislocation of the hips and some signs of arthrogryphosis. She was transferred to Aurora Hospital at the age of 3 days.

Physical examination. The child was small and pale, with signs of general dysplasia. Some moderately

Received 1 June 1971.
deviating traits were seen (Fig. 1): a small mandible, ears rather low-set but of normal size and shape, a high palate, long fingers with a flexion deformity, slight ulnar deviation of the metacarpals, and stiffness in all her joints, especially the elbows, shoulders, and hips.

The nasal bridge was flattened and the palpebral fissures had a slight downward and outward slant. Muscle tone was normal. Examination of the heart revealed no abnormality.

The hip joint dislocation was not curable with an abduction pillow, as it usually is in newborn babies. Reduction in anaesthesia was necessary, followed by treatment with plaster of Paris for 6 months.

The child was seen several times during her first year of life. She was found to develop well, although at the lower limit of normal growth (Fig. 2).

Radiological examination of the bones and joints at the age of 10 months revealed dysplasia and slow maturation of the shoulder joints. The scapulae were located high and turned slightly outwards.

Her limbs were long, slender, and thin; the thorax had an unusual form; and the pelvis was narrow. The rigidity of the joints had diminished. The dislocation of the hip was cured. There was scoliosis of the spinal column to the right in the thoracolumbar region, and the skull was asymmetric. The mandible had grown and the x-ray showed a normal condition. The eyes were normal.

The child appeared friendly and smiled readily. Her psychomotor development was still slightly retarded. At the age of 13 months she was not yet able to sit well. She was unable to stand up, but if supported she could stand upright, though not very well, for a moment; she did not crawl nor did she try to walk.
Case Reports

Laboratory investigations. Electroencephalograms repeated twice indicated normal development.
Radiology of the kidney was normal. Urinalysis was unremarkable.
Investigation of the blood showed anaemia, which has required repeated iron medication. No pathological blood cells were seen.
On serum electrophoresis there was decreased albumin (3.45 g/100 ml) and gammaglobulin according to the age of the child. Nothing out of the ordinary was seen on autoimmuno- or immunoelectrophoresis.

Dermatoglyphs. The digital pattern is in no way abnormal.

Blood groups (Table I) of the proposita and her parents show no deviation from the expected inheritance pattern.

Chromosome Studies. The chromosomes of the proposita and her parents were studied from blood cultures. She showed only 3 chromosomes in group G (Fig. 3). The chromosomes of the mother and father were normal; 46,XX and 46,XY respectively. In addition, bone marrow and skin culture cells from the patient were studied (Table I). Among a total of 447 cells studied, no cell showed a normal karyotype.

Autoradiography clearly revealed two G group chromosomes with early label and one G group chromosome with a late label. The missing chromosome was one of the late labelling G group chromosomes or No. 21.

Staining with 0.5% quinacrine hydrochloride (Sigma) was performed by a technique described by Caspersson et al (1970). Photographs were obtained with a Leitz Orthoplan microscope fitted with an Opak vertical illuminator. The light source was an HBO 200 W mercury vapour lamp with 1.5 mm BG 12 excitor filter and a 530 barrier filter. The G group chromosomes show a distinctly different fluorescence pattern (Caspersson et al, 1970). The chromosome trisomic in Down's syndrome (conventionally referred to as No. 21) has recently been shown to be the G group chromosome with a distinctive fluorescent band (O'Riordan et al, 1971). The preparations consistently showed the presence of the two No. 22 chromosomes with rather weak fluorescence of the long arms and a brightly fluorescent body usually visible close to the centromere. Only one No. 21 chromosome with stronger fluorescence of the long arms was seen (Fig. 4).

TABLE I

<table>
<thead>
<tr>
<th>ABO</th>
<th>MNS</th>
<th>P1</th>
<th>Rh</th>
<th>K</th>
<th>Lea</th>
<th>Fya</th>
<th>Fyb</th>
<th>Jka</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposita</td>
<td>A1</td>
<td>MNs</td>
<td>+</td>
<td>R, R2</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Mother</td>
<td>O</td>
<td>MNS</td>
<td>+</td>
<td>R, R2</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Father</td>
<td>A1B</td>
<td>MNS</td>
<td>+</td>
<td>R1, R2</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

TABLE II

<table>
<thead>
<tr>
<th>Sample</th>
<th>No. of Chromosomes per Cell</th>
<th>No. of Cells Counted</th>
<th>No. of Cells Karyotyped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>≤ 44 45 46 47 Polyploid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>— 6 — — —</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Skin</td>
<td>6 30 — — —</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>Blood I</td>
<td>14 190 2* — —</td>
<td>207</td>
<td>6</td>
</tr>
<tr>
<td>Blood II</td>
<td>6 184 — — 8</td>
<td>198</td>
<td>29</td>
</tr>
<tr>
<td>Mother</td>
<td>— 1 29 — —</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Father</td>
<td>— 1 30 — —</td>
<td>32</td>
<td>10</td>
</tr>
</tbody>
</table>

* One of these cells had an extra fragment, the other had a supernumerary C group chromosome.
The results obtained by the fluorescence technique are consistent with the autoradiographic findings.

Discussion

Retardation of mental and physical development associated with different malformations is frequently found to be of chromosomal origin. In the present case chromosomal material has obviously been lost, since the number of centromeres is only 45, and a piece the size of a G group chromosome is missing. As to the interpretation of the cytological and clinical findings we wish to discuss this case from two different points of view.

Translocation. A reciprocal translocation between No. 21 and a chromosome of unknown identity could be the initial event, followed by loss of the smaller translocation chromosome containing material of both of the chromosomes involved. Loss of chromosomal material usually results in more generalized and major malformations than in the present case (Taylor, 1969).

A translocation comprising parts of unequal lengths would make the loss of a rather small translocation chromosome more understandable. On the other hand, an uneven translocation would noticeably increase the length of the other chromosome involved in the translocation. In spite of a careful examination, we have not been able cytologically to detect addition of chromosomal material to any member of the complement.

Monosomy. The possibility of the existence of true G-monosomy has been emphasized in the 3 cases described previously (Thorburn and Johnson, 1966; Al-Aish et al, 1967; Hall et al, 1967). Two of these patients died young, and the third was a mentally retarded child with a number of unusual, but not very disabling features.

Autosomal monosomy in man has generally been considered incompatible with life.
Meiotic non-disjunction, resulting in 21-trisomy, may theoretically be expected to cause monosomy with the same frequency as trisomy. This, however, is not the case. G-monosomy does not occur in the large series of cytologically investigated abortions (Carr, 1967; Arakaki and Waxman, 1970) either.

Whether the absence of G-monosomy is due to gametic selection or to early fetal death, remains unknown. Assuming the gametic selection to be true, the rare occurrence of G-monosomy would be accounted for only if the selection, although close to 100%, were not complete.

In the human complement, No. 21 is the only chromosome compatible with life and development in the trisomic state. Furthermore, deficiencies of the chromosomes in group G are of three categories: deletions associated with congenital abnormalities (Weleber, Hecht, and Giblett, 1968; Ricci, Dallapiccola, and Preto, 1970; Warren and Rimoin, 1970), monosomy for one cell line likewise associated with a variation of abnormalities (Lejeune et al., 1964; Reisman et al., 1966; Bauchinger, Schmid, and Röttinger, 1968; Challacombe and Taylor, 1969; Endo et al., 1969; Zdansky et al., 1969), and, finally, deletions without any clinical signs (Migeon, 1965; Neu, Leao, and Gardner, 1966). In the various cases with abnormalities the clinical picture shows considerable variation. The patient of Lejeune et al. showed several signs such as eyes that slanted outward and downward, micrognathia, prominent nose bridge, which they described as the reverse of those found in 21-trisomy. Some of these stigmata have been seen in the other patients with G-monosomy or with monosomic cell lines. The present case showed micrognathia, which later disappeared, and a slight antimongoloid slant of the eyes.

In the first two classes of group G deficiencies, the symptoms could originate from recessive hemizygous genes as well as from the deletion.

It seems quite likely that No. 21 is largely composed of inert genetic material. The inertness of the chromosome would explain the fact that among the autosomes of comparable size, No. 21 is the only one occurring in trisomic state. Likewise 21-monosomy, once it has arisen, would most probably be expected to show relatively minor defects.

The human Y chromosome, too, is known to contain a very small number of genes. Similarly, the occurrence of a supernumerary Y chromosome is compatible with life and afflicts few features (Jacobs et al., 1965).

In conclusion, the clinical and cytological findings seems to be consistent with true 21-monosomy. With the present cytological technique, however, a hidden translocation cannot be ruled out.

Summary

The karyotype 45,XX,21— was found in a newborn baby with minor congenital malformations and a low birth weight. At the age of 18 months the child showed signs of slight retardation in her physical as well as mental development. Evidence suggestive of 21-monosomy is discussed. A hidden translocation, with loss of most of the chromosomal material from No. 21 would also account for the cytological as well as the clinical findings.

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The study was supported by grants from the Sigrid Jusélius Foundation, and the National Research Council for Biological Sciences. We wish to acknowledge the contributions of Miss Barbara von Schoultz, BSc, Mrs Veronica Süderlund, and Miss Pirkko Winter.

References
True Hermaphroditism: Cytogenetic Analysis, Surgical Repair, and Social Implications

True hermaphroditism is rarely encountered in man. Whenever this condition exists the contradiction between genotype and phenotype stimulates an extensive investigation of such an affected individual.

The chromosomal findings of true hermaphroditism were first reported by Hungerford et al (1959) who demonstrated a 46,XX chromosomal complement in the leucocytes of peripheral blood. An attempt to simplify the nomenclature and assign a specific term to this anomaly (gonadal intersexuality) was made by Russell (1954). Overzier (1964) reviewed the findings of 171 authenticated cases of true hermaphroditism reported in the literature and of these cases only 14 had the benefit of cytogenetic analysis. However, with the progress in cytogenetic techniques and the incorporation of gonadal biopsies more comprehensive analyses have been reported. From this it has become apparent a normal female 46,XX karyotype is the usual finding in true hermaphroditism with the exception of a limited few who demonstrate a 46,XY chromosomal complement or a variant due to mosaicism.

The diagnosis of true hermaphroditism requires the demonstration of both ovarian and testicular tissue in the same individual. These patients usually have varying degrees of ambisexual development. The testicular tissue is generally located in the scrotum or outside the abdomen, while the ovarian tissue is usually found in an intra-abdominal position.

Himman (1935) classified true hermaphroditism into four categories. (1) Bilateral with testis and ovary or ovotestis on each side and usually demonstrating a uterus and tubes. (2) Unilateral with ovotestis on one side and an ovary or testis on the other side (these appear to be the most frequent). (3) Lateral with testis on one side and an ovary on the other side. (4) Indeterminates with no conformity as to location or type of gonadal tissue.

Case Report

Clinical History and Details of Surgical Repair.

The patient was a well developed, well nourished, alert, cooperative 3-year-old Tunisian child with no visible anatomic abnormalities other than ambiguous genitalia. He was the 3rd sib of a normal healthy young mother aged 26 at the birth of the propositus. There was no history of hormonal therapy or other medication taken prenatally. The pregnancy was normal and delivery in a local Tunisian hospital was without incident with a sage-femme (midwife) in attendance. There was no history of consanguinity nor was there a history of any similar defect in the family. The child progressed normally, walked and talked at approximately one year. This child was being reared as a male despite the fact that the ambiguous genitalia were noted at birth.

Physical examination of the external genitalia revealed a small phallus which lacked a penile aperture. A slit-like mucosal lined aperture resembling a urogenital sinus was located on the ventral side at the base of the phallus. Urine was voided through this slit-like aperture and caused the child no discomfort. The scrotum was not fused and gave the appearance of labia. Palpable masses in both inguinal areas could be expressed downward into the labia like structures. A chordee was present.

Laboratory examinations were not remarkable; creatinine, urea, total protein, and electrolytes were all within normal range. Urinary excretion of 17-ketosteroids (2.8 mg/24 hr) was within normal limits for age of the patient. No tests for 17-hydroxycorticoids or gonadotropins were available. Retrograde cystography and voiding urography indicated a normal male-type urethra with no unusual bladder neck obstructions. There was no evidence of urethral reflux. Intravenous pyelograms showed bilateral reduplication of the renal...
A 45,XX,21--child: attempt at a cytological and clinical interpretation of the karyotype.
U Gripenberg, J Elfving and L Gripenberg

doi: 10.1136/jmg.9.1.110

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