VARIABILITY OF r(22) CHROMOSOME PHENOTYPICAL EXPRESSION

B. DALLAPICCOLA, V. BRINCHI, P. CURATOLO
Departments of Medical Genetics and of Child Neuropsychiatry, University of Rome, Italy

Two unrelated patients with multiple congenital malformations and severe mental retardation were found to be carrier of a non-mosaic ring 22 chromosome abnormality. These observations further confirm the phenotypical variability of r(22) expression, which makes unreliable the attempts to delineate a clinical profile of the syndrome

"G_2 deletion syndrome" includes a wide spectrum of chromosomal aneuploidies, like monosomy, monosomy-mosaicism, partial deletion of the long arm of chromosome 22, or mosaicism for such a deletion, translocation or ring 22 chromosome. Thus, it is possible to speculate about the existence of different clinical pictures associated with these non-homogeneous chromosome imbalances.

The best investigated aberration in this group is r(22), which has been identified by banding techniques in less than 20 patients. In the last major review, Rethoré et al. (1976) have pointed out the presence of scanty clinical symptoms characterizing the syndrome. Two additional patients investigated by us confirm the unfeasibility of the diagnosis on phenotype alone, and further confirm the phenotypical variability of the disorder.

CASE REPORTS

Case 1

C.A., a female girl, was born on April 19, 1976, as the only child of healthy, nonconsanguineous parents. The mother was 24 years old and the father 25. Pregnancy was complicated by threatened abortion during the first trimester. Delivery was normal ten days beyond term. The birth weight was 3500 g. No consistent clinical dysmorphisms were recorded at birth.

Because of psychomotor retardation, the patient was referred for evaluation to the Department of Paediatric Neurology and Psychiatry, University of Rome, at the age of 11 months. When first examined (Fig. 1), she was 74 cm tall (10th percentile), and weighted 11.5 kg (90th percentile); head circumference was 46 cm (50th percentile). She had a round face, wide forehead, well designed and furnished eyebrows, horizontal palpebral fissures with bilateral convergent strabismus, flat nasal bridge, with rounded nose tip, normal philtrum, large mouth, high arched palate and protruding tongue. Ears were normal, with two furrows on the right lobule. The neck was short; the back and the pubis were downy. Deep olecranic dimples were present.

Neurological examination showed marked, generalized hypotonia and hyperextensible joints. Deep tendon reflexes were present. At the age of 13 months, the motor age corresponded to 6 months and the mental age to 4 months.

Dermatoglyphic analysis showed 6 whorls, 2 ulnar loops and 2 radial loops, the latter on the 2nd right and 3rd left fingertips. Palmar axial triradii were bilaterally displaced in t″ position and associated with loop and S patterns in hypothenar areas.

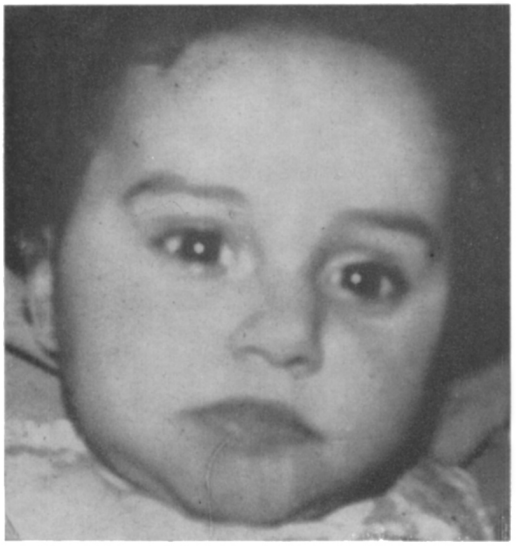
No consistent skeletal dysmorphisms were detected by systematic roentgenological investigations. At the age of 12 months the radiological age corresponded to 30 months. A pneumoencephalogram showed the presence of an intraseptal cyst.

The EEG was diffusely slow for the age, with irregular multifocal spikes during wake and sleep recordings.

The electrocardiogram and fundus oculi were normal. Routine laboratory investigations, thyroid function evaluations by RIA, and urinalysis for screening of inborn errors of metabolism were normal. Immunodiffusion assays revealed normal levels of IgG and IgM and low IgA values (28 mg%/ml).

Chromosome analysis. Chromosome investigations were carried out on short term peripheral blood cultures. The modal number was 46, but a G-group chromosome was consistently replaced by a small-sized ring chromosome. G and R banding, by in vitro incorporation of 5-BduR, showed that the ring

CODEN: AGMGAK 26 287 (1977) — ISSN: 0001-5660
Acta Genet. Med. Gemellol., 26: 287-290



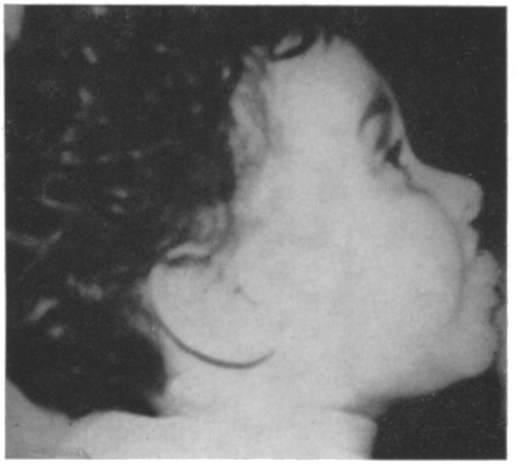


Fig. 1. Case 1.

was derived from a no. 22 chromosome, and occasionally was dicentric. Two ring chromosomes were coexisting in the same cell in 3 out of 100 examined metaphases (Fig. 2).
The chromosome analyses of parents were normal.

Case 2

M.A., a female baby, was born on February 2, 1970, as the third child in a sibship of four. The first child died of "asphyxia" two hours after delivery; the other two sons are alive and normal. The four children were delivered by CS.
The mother was 30 years old and the father 33 at the time of patient's conception. Pregnancy was uncomplicated and delivery occurred in the VIII month. The birth weight was 2200 g. Cleft palate, umbilical hernia and bilateral club foot were recorded at birth.
At the age of 3.8 years, she was hospitalized because of severe mental and growth retardation and hypotonia. Physical findings included palpebral teleangiectasias, diffuse venous dilatations, resulting in a cutaneous arabesque, particularly evident on the neck, the upper thorax and the legs, hip dislocations, long slendering hands.
When first seen by us at the age of 5.7 years (Fig. 3), the patient was 93 cm tall (<3rd percentile) and weighted 11.6 kg (<3rd percentile). Head circumference was 44 cm (—2 SD). The occiput was flat and the glabella prominent. Eyebrows were bushy with synophrys; eyes were widely spaced with bilateral epicanthal folds and horizontal slant of palpe-

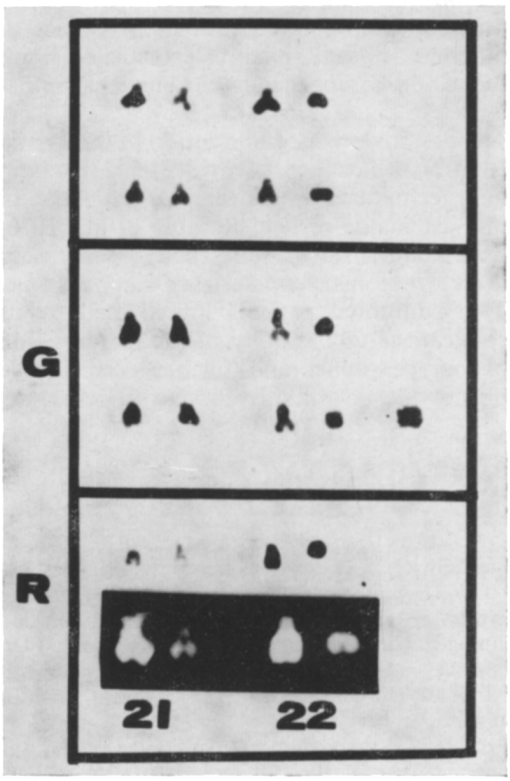


Fig. 2. The G-group chromosomes from selected metaphase plates of case 1 (Giemsa standard staining, G-bands and R-bands).

https://doi.org/10.1017/S0001566000009788 Published online by Cambridge University Press

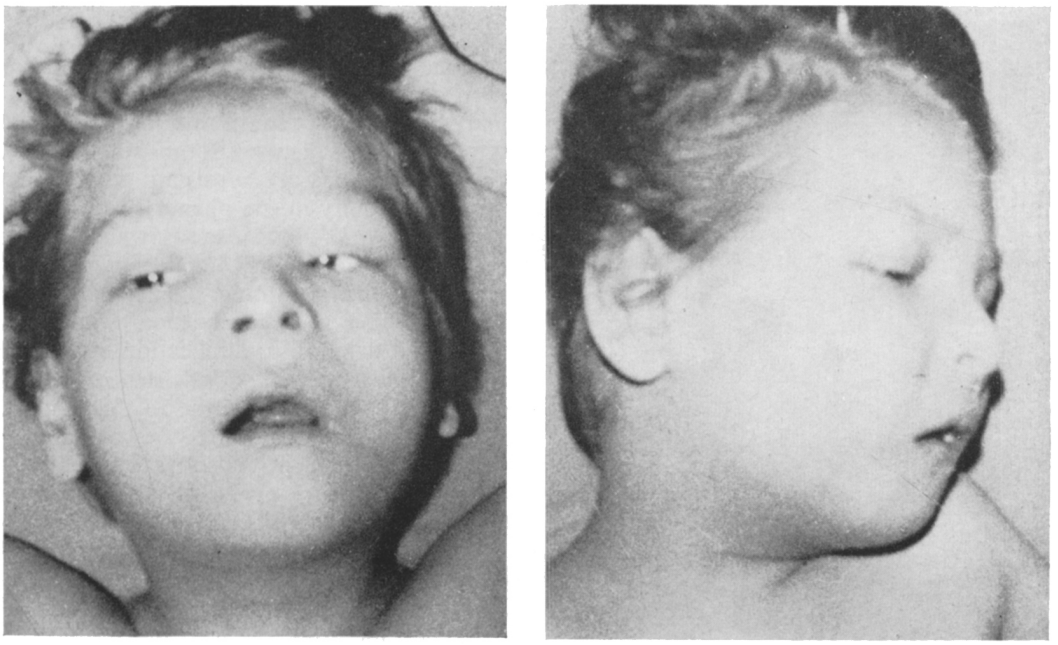


Fig. 3. Case 2.

bral fissures; there was bilateral convergent strabismus. Nose bridge was large and flat; the nose tip large and pointed, with narrow ovalar nostrils. The philtrum was long and flattened. There was a marked micrognathia; the teeth were carious, with irregular placements. Ears were low-set and malformed, with folded helix, prominent anthelix, and thick lobule. Abdomen showed a large umbilical hernia. External genitalia were female, with hypertrophic clitoris and protruding vaginal ostium.

There was a bilateral club foot, more pronounced at right. Partial syndactyly was present between toes II-III. The skin was thin and crossed by diffuse venous network.

Neurological examination showed marked generalized hypotonia, severe mental and motor retardation. At the age of 7 years, the patient was unable to hold her head up and her speech was restricted to a few monosyllables. Deep tendon reflexes were present.

Dermatoglyphic analysis revealed bilateral simian line, 9 arches and 1 loop on fingertips. The total ridge count was 2. Palmar axial triradii were bilaterally displaced in position t′.

Radiological investigations of the skeleton showed hip dislocations, hypoplastic iliac wings, squared vertebral bodies, schisis of S_1, marked hypoplasia of long bones. At the age of 7 years, the radiological age corresponded to 4 years.

The EEG was diffusely slow, with an electrocortical depression, more evident at right.

Fundus oculi was grossly normal.

Routine laboratory investigations and urinalysis for screening of inborn errors of metabolism were unremarkable.

Chromosome analysis. Cytogenetic preparations were obtained from peripheral blood leucocytes and showed 46 chromosomes, with the constant absence of a G-group chromosome, which was replaced by a ring. G-banding studies identified the abnormal chromosome as a r(22) (Fig. 4). The ring structure appeared to be stable. Only in 1 out of 100 examined cells the ring was dicentric and in no metaphase its duplication was observed.

The parents had normal karyotypes.

DISCUSSION

According to current knowledge the G-group deletion syndromes may be separated in two distinct clinical entities, the G_1 or "antimongolism", and the G_2 deletion syndromes, which have been related to partial monosomies of chromosomes 21 and 22, respectively (Warren and Rimoin 1970, Warren et al. 1973).

https://doi.org/10.1017/S0001566000009788 Published online by Cambridge University Press

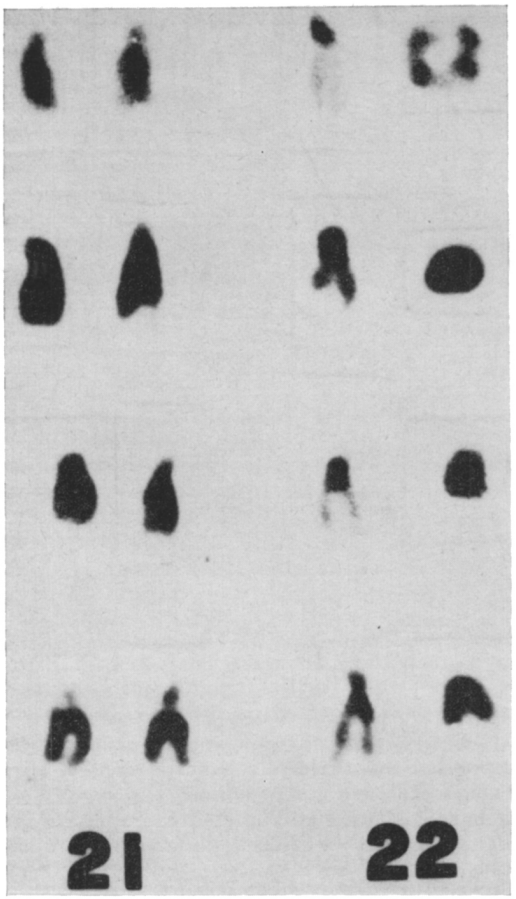


Fig. 4. The G-group chromosomes from selected metaphase plates of case 2 (G-bands).

The evidence accumulated in recent literature does not contrast with the idea of the existence of a clinically recognizable G_1 deletion syndrome, whose symptoms are grossly superimposable to the ones firstly described by Lejeune et al. (1964). However, also in the "antimongolism" itself a wide phenotypic variability may be expected, so that phenotype-karyotype correlations can hardly be established without knowing the origin of the ring.

The first reported cases of r(22) had suggested that a series of dysmorphisms was invariably present in the patients, resulting in a distinct clinical entity. However, in the last major review of the syndrome it has been concluded that the "doe's eye" anomaly is the only consistent morphological symptom of the disease (Rethoré et al. 1976). Our observations are consistent with an extreme variability in the phenotypical expression of ring 22 chromosome, which makes unreliable the attempts to delineate a clinical profile of the syndrome. This variability may be either the consequence of different amount of deletion or duplication within the ring, or the result of mosaicisms of several cell lines in different tissues. In this respect, improved cytogenetic techniques or analysis on prometaphase chromosomes, and comparative studies on various tissues could be adequate to subclassify the different cytogenetic types of G_2 deletion syndromes. Furthermore, little is known about the chromosome 22 gene map, and some features of the syndrome might derive from the expression of recessive alleles due to partial monosomy resulting from the ring formation. Finally, comparison of clinical symptoms would take into account individuals of similar age.

The possibility to establish r(22) as a distinct clinical entity may be succes ful only when the patients will be cathegorized in more homogeneous groups.

REFERENCES

Lejeune J., Berger R., Rethoré M.O., Archambault L., Jerome H., Thieffry S., Aicardi J., Broyer M., Lafourcade J., Cruveiller L., Turpin R. 1964. Monosomie partielle pour un petit acrocentrique. C.R. Acad. Sci. (Paris), 259: 4187-4190.

Rethoré M.O., Noel B., Couturier J., Prieur M., Lafourcade J., Lejeune J. 1976. Le syndrome r(22). A propos de 4 nouvelles observations. Ann. Génét., 19: 111-117.

Warren R.J., Rimoin D.L. 1970. The G deletion syndromes. J. Pediatr., 77: 658-663.

Warren R.J., Rimoin D.L., Summitt R.L. 1973. Identification by fluorescent microscopy of the abnormal chromosomes associated with the G-deletion syndromes. Am. J. Hum. Genet., 25: 77-81.

Prof. B. Dallapiccola, Cattedra di Genetica Medica, Ospedale Spallanzani, Via Portuense 292, 00149 Roma, Italy.