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Partial tetrasomy 9 in an infant with clinical and radiological evidence of multiple joint dislocations

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Abstract. We report on an infant with partial tetrasomy of chromosome 9 due to the presence in her peripheral lymphocytes and in 55% of skin fibroblasts of an isochromosome 9 comprised of the p arm and of a portion of the q arm extending to band q21.1. The phenotype is comparable to that of other cases with a similar chromosome aberration, with multiple joint dislocations as a prominent manifestation.

Key words: Partial tetrasomy 9 – Chromosome aberration – Multiple congenital anomalies/mental retardation syndrome – Multiple joint dislocations – Arthrogryposis

Introduction

Partial tetrasomy of chromosome 9 is a rare condition described for the first time in 1973 by Ghymers and co-workers [8]. A total of 14 published cases were reviewed recently by Shapiro et al. [14]. An additional case was subsequently reported by Cavalcanti et al. [3]. The clinical manifestations are those of a multiple congenital anomalies/mental retardation (MCA/MR) syndrome, somewhat reminiscent of the trisomy 9p syndrome [12]. As expected, there is greater severity and variability than in the latter syndrome due to the larger amount of additional chromosome material present, which occasionally includes portions of the q arm. In fact, one can distinguish cases of pure tetrasomy 9p [4–7, 9, 10, 13], from cases that also involve the heterochromatic region of the q arm [2, 3, 8, 11], and cases in which the tetrasomy extends to a variable portion of the euchromatin of the q arm [1, 14–16].

We report on a case that falls into the latter category, that of a female infant with partial tetrasomy 9 in mosaic and with clinical manifestations that are compatible with this cytogenetic condition. Among these, multiple joint dislocations are prominent, both clinically and radiologically.

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Abbreviations: MCA/MR = multiple congenital anomalies/mental retardation; OFC = occipito-frontal head circumference

Case report

The patient, a female, was born at term by normal vaginal delivery after an uneventful pregnancy from healthy, non-consanguineous parents. The father was 29 and the mother 27 years old at the time of the patient's birth. The mother had had two first-trimester spontaneous abortions. Birth weight was 2100 g (< 3rd centile), length 41 cm (< 3rd centile), occipito-frontal head circumference (OFC) 31.5 cm (< 2nd centile), and the anterior fontanelle measured 5 × 4 cm. At 11 weeks the patient's weight was 2950 g, length 47 cm, OFC 34.4 cm, all measures below the 3rd centile. The anterior fontanelle was still widely open, measuring 5 × 3 cm; the posterior fontanelle was closed. The skull was scaphocephalic with bitemporal constriction, hypoplasia of the supraorbital ridges and prominent forehead. Facial characteristics were horizontal palpebral fissures with apparent hypertelorism; prominent root of the nose with bulbous tip and antiverted nostrils; cup-shaped, elongated and folded auricles; severe micrognathia and narrow palate. The arms were maintained flexed and adducted to the trunk and the fingers were also flexed. On the right hand the second and fifth fingers overlapped the third and fourth; there was ulnar deviation of the distal phalanx of the second and third fingers and radial deviation of the fourth and fifth. On the left, the third finger was overlapped by the second and fourth and there was radial deviation of the distal phalanx of the third, fourth and fifth fingers. The fifth finger had a single flexion crease and virtual absence of the finger nail bilaterally. Both hands had ulnar deviation and a single transverse palmar crease (Fig. 1).

Dermatoglyphycs were on the right: t′, hypothenar L^r, abd, L^rAAAA; and on the left: t′, a, AAL^{u}L^{u}A.

The knees were hyperextended and the feet were in calcaneovalgus with peroneal deviation of the toes. There was clinodactyly of the second toe, which overlapped the third bilaterally (Fig. 2). Dermatoglyphycs were an open field on the right hallucal area and L^t on the left.

Genitalia were female with hypoplasia of the labia majora and minora.

There was a skin tag over the tip of the sternum and a presacral pit.

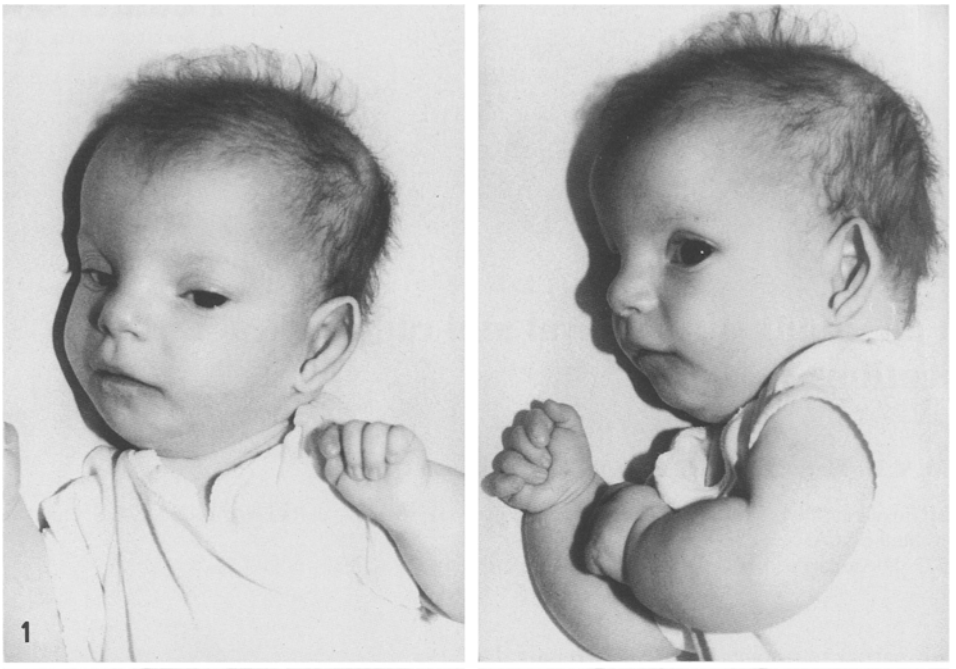


Fig. 1. Front and lateral view of the patient. Note micrognathia, malformed ears, adducted arms and flexed position of the fingers.

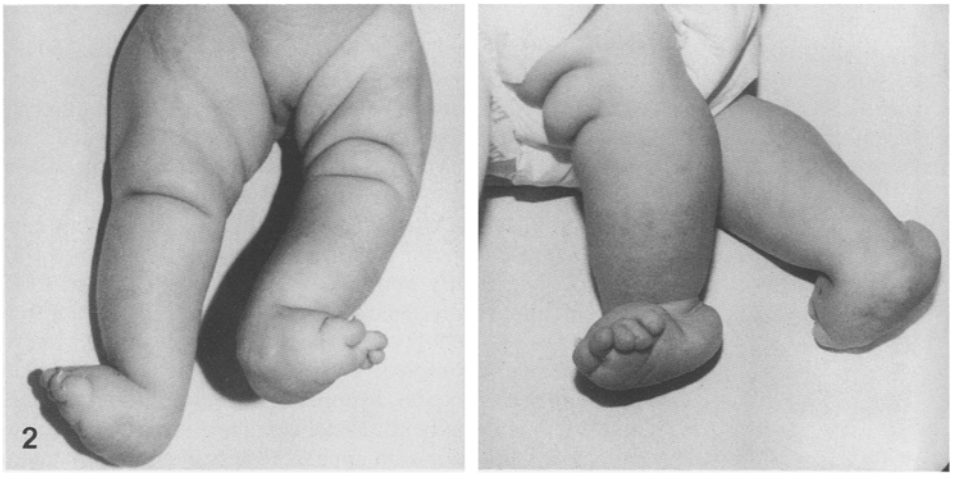


Fig. 2. Lower limbs of the patient. Note genu recurvatum and calcaneovalgus foot

There was a 3–4/6 systolic murmur due to a ventricular septal defect, ascertained by echocardiography.

The infant was hypotonic and her motor development was severely delayed.

Radiographs showed multiple joint dislocations. The femora were laterally and cranially displaced and the knee joints over-extended. Other findings were apparent sclerosis of the skull and severe micrognathia, a spatula-like shape of the first metacarpal, absent ossification centres of the os pubis and a larger than normal Y cartilage of the pelvis. There were 11 ribs bilaterally (Fig. 3).

The infant did not make any progress and died at 6 months of congestive heart failure. Autopsy could not be performed.

Cytogenetic findings

A cytogenetic study was performed on peripheral lymphocytes and skin fibroblasts by standard methods with G (GTG), R (RBG), C (CBG) and G-11 banding. In all lymphocyte metaphases examined (100) there was an extra chromosome of the C group that was identified as an isodicentric chromosome 9, comprising the p arm and a portion of the q arm, up to band q21.1. One of the two centromeres was inactive (Fig. 4). In fibroblasts this chromosome was present in 55% of the 82 metaphases examined, the other 45% being normal. The chromosome constitution of the patient can thus be described as 46,XX/47,XX,+dic(9)(pter→ cen→ q21.1: :q21.1 → cen→ pter), resulting in tetrasomy for the entire p arm of chromosome 9 and for a portion of the q arm, extending beyond the heterochromatic region, to band q21.1. The chromosomes of the parents were normal.

Discussion

This is the fifth case described in the literature of partial tetrasomy of chromosome 9, in which the tetrasomic material includes a euchromatic portion of the long arm. Of the four previous cases [1, 14–16] one was unusual in showing characteristics of the Marfan syndrome [15]. The other three [1, 14, 16] were reviewed recently by Shapiro et al. [14] and shown to have a number of manifestations also present in our patient, i.e.: delayed physical and motor development; microcephaly;

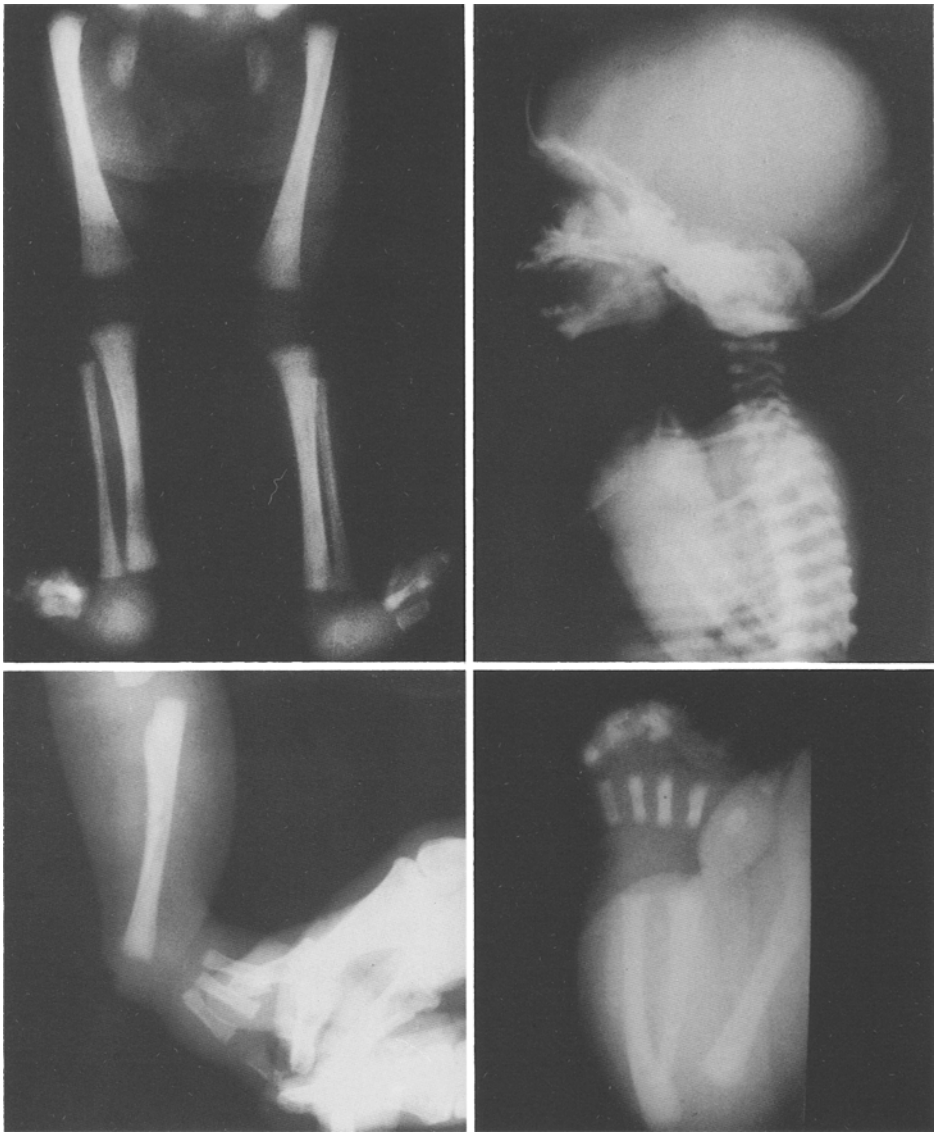
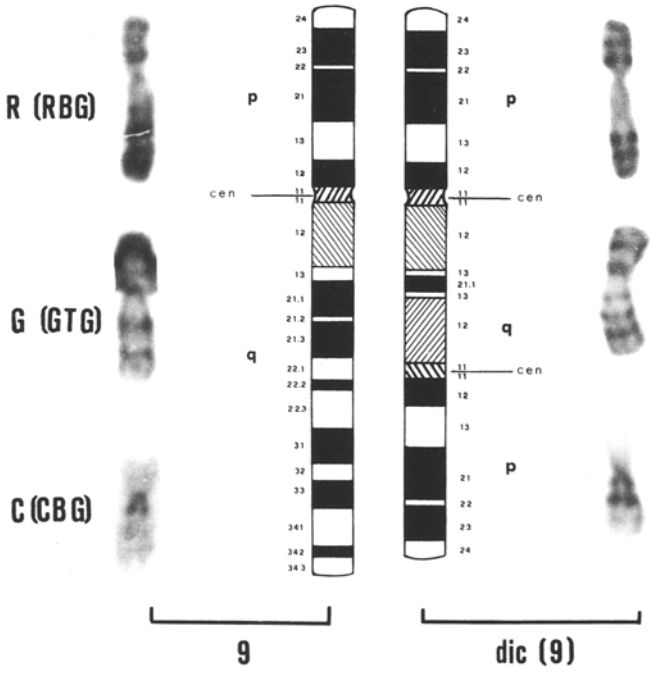


Fig. 3. Radiological findings. Note dislocation of femora and hyperextension of knee joints, ample space at the wrist and elbow joints and spatula-like first metacarpal



unusual face with bulbous nose, malformed ears and micrognathia; congenital heart defect; hypoplastic genitalia; hypoplastic phalanges and nails; overlapping fingers; hip dislocation; genu recurvatum and foot deformity; arthrogryposis of lower limbs; early death. This phenotype overlaps to some extent with that of the trisomy 9p syndrome. However, it seems to be distinctive enough to deserve consideration as a separate entity.

Because of their severity, we would like to draw special attention to the muscolo-skeletal manifestations of this condition, i.e. multiple joint dislocations, especially marked in the lower limbs, arthrogryposis of hands and feet, severe retromicrognathia and radiological findings consistent with such clinical manifestations. Although these seem to be typical of cases that show partial tetrasomy of 9q euchromatin, they were also present in a case of tetrasomy 9p [9], raising once more the difficult question of genotype-phenotype correlation in chromosome syndromes.

As to the origin of the aberrant chromosome, four mechanisms have been proposed: (1) formation of the isochromo-

Fig. 4. Normal and isodicentric chromosome 9 and respective ideograms

some at meiosis I through rearrangement of two of the four chromatids of the bivalent chromosome 9, followed by non-disjunction of the isochromosome from the normal 9 [13]; (2) selective endoreduplication of a portion of chromosome 9 during meiosis I or post-zygotic mitosis [13]; (3) translocation between non-sister chromatids at meiosis, followed by non-disjunction [16]; (4) non-disjunction of chromosome 9 in a normal zygote, followed by simple deletion and formation of an isochromosome [4]. In the present case, we have no elements to decide in favour of one or other of these possibilities. The secondary constrictions of chromosome 9 in the proposita and her parents did not show any quantitative polymorphism that could help in determining the paternal or maternal origin of the rearranged chromosome.

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