Normal psychomotor development in a child with mosaic trisomy and pericentric inversion of chromosome 9

SUMMARY A female infant with trisomy 9 in 58% of her cells is reported. Multiple congenital malformations were present, but she had normal psychomotor development. A pericentric inversion involving a portion of the centromeric heterochromatin of chromosome 9 was identified in the patient and her mother. This variant chromosome 9 was present in duplicate in the trisomic line. Since similar variants of 9qh have been found repeatedly in this syndrome, we feel that this association may be a non-random one.

Nine cases of mosaic trisomy 9 and three cases of complete trisomy 9 have been reported to date. An additional case of mosaic trisomy 9, sharing many features in common with previously reported cases, is presented. We regard this case to be of interest since the baby had normal psychomotor development.

Case report

The proband, a female infant (fig 1), was delivered spontaneously after a 40 week uneventful gestation to a 25-year-old primigravida mother and a 26-year-old father. The parents were healthy and unrelated and the family history was unremarkable. Birth-weight was 3270 g, length 51 cm, and head circumference 34 cm (50th centile). The head was asymmetrically dolichocephalic, the left occipital and the left parietal bones being prominent. The nose was bulbous and the nostrils faced forward. The palate was high and retrognathia with asymmetry of the mandible were observed. The neck was short and webbed. The left upper four ribs were prominent anteriorly, deforming the chest. The sternum was short and the nipples were laterally displaced. No heart murmurs were audible. The right kidney was found at pyelography to be hydronephrotic, and the left one was found in the pelvis. Hypoplasia of the labia majora was evident. Movements of the shoulders and the elbows were restricted, the thumbs were flexed, and there was marked limitation of hip abduction. The knees could not be fully extended. The hands were clenched. The third and fourth fingers were overlapped by the second and fifth fingers bilaterally. Club feet were present and the heels were prominent. Both big toes were hammer shaped and the left third toe overlapped the second. Deep secondary palmar skin creases and a left simian line were observed. Skin dimples were present in the sacral region as well as over the elbows, acromion, and posterior iliac spines.

Radiological findings included 13 thoracic segments, incomplete vertebral arches from D12 to L5, and a Y vertebra at L3, with resulting scoliosis. The iliac bones were smaller than usual.

The postnatal course was complicated by a haemorrhagic disease necessitating a blood transfusion. Because of a presumed sepsis, gentamicin and ampicillin were administered. Repeated episodes of apnoea were observed during the first 2 months of life. A urinary tract infection was successfully treated with trimethoprim-sulphamethoxazole at 11 months of age. Orthopaedic aids and exercises helped to relieve the tight joints. Developmental milestones were achieved on time.

Developmental screening (DDST) at 26 and 52 weeks of age was within normal limits for age. The Gesell Developmental Test (1963 modified Yale Standards) was administered at 24 months of age. The overall DQ was 126. Relative weakness in fine motor skills was due to residual hand deformity with difficulty in pincer grasp.

Cytogenetic studies

Peripheral blood lymphocytes of the child and both of her parents were studied. Skin fibroblasts and marrow cells of the proband, from two different sites across the midline, were examined. Trypsin G banding was used for chromosomal analysis. C banding was used for evaluation of heterochromatic polymorphisms.

FIG 1 The proband at 6 months.

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TABLE Results of chromosome studies

<table>
<thead>
<tr>
<th>Sample</th>
<th>Age</th>
<th>Side</th>
<th>46,XX</th>
<th>47,XX, +9</th>
<th>Total</th>
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<tbody>
<tr>
<td>Blood</td>
<td>5 days</td>
<td></td>
<td>41</td>
<td>59</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td></td>
<td>44</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td>Bone</td>
<td>1 month</td>
<td>R</td>
<td>7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>marrow</td>
<td></td>
<td>L</td>
<td>9</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Skin</td>
<td>3 months</td>
<td>R + L</td>
<td>8</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>109</td>
<td>151</td>
<td>260</td>
</tr>
</tbody>
</table>

![image of C banded partial karyotype]

FIG 2 C banded partial karyotype. Upper row, mother's pair of No 9 chromosomes. Middle row, patient's normal line. Lower row, patient's trisomic line.

Trisomy 9 was found in 58% of the cells, without significant variations in different tissues and sites of sampling. The results are summarised in the table.

Both parents had a normal karyotype. The mother was heterozygous for a partial pericentric inversion in 9qh, resulting in the presence of almost half of the constitutive heterochromatin in the short arm of chromosome 9 (p11q12). This marker chromosome was present twice in the trisomic line of the proband (fig 2).

Discussion

Cases of phenotypically normal autosomal mosaic trisomies are well documented. The present case, however, is not phenotypically normal, having many of the characteristic facial and somatic features of trisomy 9 syndrome. Normal psychomotor development has not been reported in this condition.

The majority of chromosomal mosaics are the result of a postzygotic non-disjunction and therefore might be regarded as acquired trisomies. It is conceivable that if this error occurs after organogenesis is completed, the subject may be phenotypically normal. In fact, trisomy 9 mosaicism was found in skin fibroblasts of a phenotypically normal newborn infant who died of congenital leukaemia. The authors presumed that the aneuploidy developed at an early embryonic stage. The high proportion of trisomic cells in our case suggests an error occurring in early cleavage. The presumed error, however, might have occurred at a later stage of embryogenesis, mainly affecting cells destined to form the mesodermal layer and sparing the already formed ectodermal layer, and thus, possibly, not interfering with normal brain development. It is conceivable that had sampling of brain or other non-mesenchymal tissue been possible, a totally different chromosomal complement might have been found.

Chromosomal variants similar to the one observed in this case have been reported in two cases of mosaic trisomy 9, and in both cases the variant chromosome appeared twice in the trisomic line. It seems to us that the inversion involved at least one third of the constitutive heterochromatin in these cases. An enlarged 9qh was identified in the case of complete trisomy 9 reported by Seabright et al and in a prenatally diagnosed fetus with complete trisomy 9. In both cases the variant chromosome 9 was present only once. In five of the 12 reported cases only G banding was used and therefore additional cases with similar or smaller variants might have been missed.

The frequency of inv(9) (p11q12), as well as that of 9qh+, is not firmly established. In different unselected populations, where appropriate banding techniques were used, the frequency of inv(9) ranges from 1 to 5%. Nielsen et al reported the frequency of 9qh+ to be 0.1% in an unselected population of newborns, and 2.8% in relatives of chromosomally abnormal patients. However, since banding techniques were used only in the chromosomally abnormal groups, one may question the validity of these observations. Metaxotou et al using C banding in studying a selected population, found the frequency of 9qh+ to be 2%. Hence, the presence of inv(9) and 9qh+ in at least five of 13 patients is significant even if we use a value as high as 0.07 as the population frequency of these variants (p=0.0013, by the exact binomial distribution). Wang and Hamerton studied a group of 93 patients with Down syndrome and found inv(9) to be present in 12.9% of the cases, as compared to 3.3% in unselected normal controls. These authors hypothesised that these variants “predispose the carrier parent to non-disjunction”. Howard-Pebles and Stoddard recently reviewed the association between these chromosomal variants and chromosomal aberrations. They felt that this association was...
significant enough to make amniocentesis available to a normal carrier.

We share the feeling that the presence of these variants is significant, and may have an aetiological role in causing non-disjunction. However, it seems to us that carefully controlled studies are necessary before one can support a recommendation for amniocentesis in an otherwise normal carrier.

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11. Wang HS, Hamerton JL. C-band polymorphisms of chromosomes 1, 9, and 16 in four subgroups of mentally retarded patients and a normal control population. Hum Genet 1979; 51:269-75.


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Absence of constitutive heterochromatin in a partially identified supernumerary marker chromosome

SUMMARY A retarded child with multiple malformations was found to have a karyotype 47,XY,del(11)(11pter->q21::),+mar(11qter)->q21::?). The mitotically stable centric marker had no demonstrable C heterochromatin.

Phenotype-karyotype correlation and the role of C heterochromatin in phenotypic effects are discussed.

Supernumerary chromosomes of unknown origin are not uncommon in phenotypically abnormal subjects. When they occur in normal subjects, they are presumably composed of only genetically inert C heterochromatin. The supernumerary marker we describe here was found in a malformed child and is unique because of a complete deficiency of demonstrable heterochromatin along its length.

Case report

The proband was born to a healthy, young, non-consanguineous couple after an uncomplicated term gestation. He weighed 3.2 kg at birth and showed the following malformations: left sided complete cleft lip and palate, hypotelorism, sinus over right pinna, umbilical hernia with diastasis recti, anal stenosis, tapering fingers, and a distal axial triradius. During 18 months of observation, his growth and development were slow. His fontanelle, closed early, a ridge along the metopic suture became palpable, the skull showed bitemporal narrowing and trigonocephaly, esotropia became evident, the nose was short with a wide low bridge, and cafe-au-lait spots appeared over his face and chest (fig 1). No internal malformations were discovered. Radiographic appearance of the skeleton was not unusual except for trigonocephaly. Several laboratory studies, including lactate dehydrogenase levels in the serum and isozyme patterns, were normal.

CYTOGENETIC DATA

Cultured lymphocytes showed 47 chromosomes in each of 50 orcein stained cells. The extra chromosome was the size of a chromosome 16 and appeared metacentric to submetacentric in morpho-

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