Chromosome 18q22.2→qter deletion and a congenital anomaly syndrome with multiple vertebral segmentation defects

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Abstract
Multiple vertebral segmentation defects occur in a group of conditions variably associated with anomalies of other organ systems. This report describes a female child in whom a deletion of chromosome 18 (18q22.2→qter) is associated with congenital anomalies including multiple vertebral segmentation defects resembling sporadic spondylocostal dysplasia. The child also has unilateral renal agenesis and unilateral fibular aplasia. The association of severe multiple vertebral segmentation defects with 18q in this patient suggests the possibility that a gene important for somite formation or vertebral differentiation maps to this segment of chromosome 18.

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Since first described by DeGrouchy in 1969, the syndrome of 18q- has been recognised as a clinically well defined disorder. Over 100 people with this syndrome have been described, with major phenotypic features being midfacial hypoplasia, somewhat dysplastic auricles with stenosis or atresia of the external auditory canal, “carp shaped” mouth, eye abnormalities, and tapering fingers, as well as abnormalities of the genitourinary tract and foot. In addition, affected subjects are almost all severely mentally retarded. While skeletal anomalies have occasionally been reported in patients with an 18q- deletion, we describe a child with 46,XX,del(18)(q22.2) karyotype who has multiple vertebral segmentation defects resembling the sporadic form of spondylocostal dysplasia. This condition has not previously been associated with chromosome 18q deletions but has sometimes been associated with anomalies of other organs. Renal anomalies and fibular hemimelic leg and foot anomalies were also noted in the subject of this report.

Case report
The proband was the female product of an uncomplicated vaginal delivery at term to healthy, non-consanguineous parents following an uncomplicated gestation. Apgar scores were 7 and 8 at one and five minutes respectively. Birth weight was 3180 g (50th centile), length 44.5 cm (<5th centile), and occipitofrontal circumference 35 cm (45th centile). The neonatal course was complicated by mild respiratory distress necessitating oxygen supplementation without intubation or mechanical ventilation. No neonatal hypoglycaemia was detected and maternal testing for gestational diabetes showed euglycaemia.

Multiple congenital anomalies were noted at birth including asymmetry of the left hemithorax with widely spaced nipples, scoliosis, a skin covered thoracolumbar myelomeningocele, left talipes equinovarus, and severe right paraxial fibular hemimelia. The lateral ray of the right foot was absent with preservation only of the hallux. The calvarium was square with mild frontal bossing and deep orbits. A glabellar capillary haemangioma was noted. The auricles had overlapping helices and the external acoustic canal was considerably narrowed. The nose was small with a somewhat bulbous tip. The neck was very short. Fingers were spindle shaped. The abdomen was somewhat distended and her anus was anteriorly displaced.

Further characterisation of the anomalies in this child were achieved by multiple imaging procedures. A chest radiograph (fig 1) showed multiple rib anomalies including absence, bifurcation, and posterior fusion of ribs in the right hemithorax. Spinal x rays showed the large neural arch defect extending from T11 to L3 as well as multiple malsegmentation anomalies of the thoracic vertebrae, including butterfly and hemivertebrae (fig 1). The fibular hemimelia was documented by plain radiographs of the leg (fig 2) and talipes equinovarus was present in the left foot. Magnetic resonance images of the brain and spine confirmed the vertebral anomalies and showed a cervical syrinx. In addition, the thoracolumbar lipomyelomeningocele associated with a dysplastic spinal cord was visualised. There was immature cerebral myelination as well as mild cerebral atrophy. Ultrasound of the abdomen and pelvis showed absence of the right kidney and normal function of the left kidney was confirmed by renal scintigraphy using TC™. A two dimensional echocardiogram showed patency of the foramen ovale and trivial tricuspid insufficiency. There was no family history of any congenital malformation. Physical examination of the parents failed to show any significant abnormality, including of the spine and thorax.

By 1 year of age the infant smiled spontaneously but manifested significant psychomotor developmental delay. She reached for objects, transferred them, and brought them to her
to understand simple commands and is able to recognise body parts and colours.

**Materials and methods**

**Karyotypic analysis**

Chromosomal analysis was performed using standard G banding of chromosomes obtained from phytohaemagglutinin stimulated lymphocytes. The breakpoint of the deletion was determined at the 550-600 band stage by analysis through the microscope.

**Microsatellite analysis of parental origin of the deletion**

The parental origin of the deleted chromosome 18 was determined using polymorphic dinucleotide repeat elements D18S61 and D18S554. For this study, DNA was extracted from whole blood of the proband and parents using the protocol of Miller et al. Aliquots of genomic DNA (100 ng) from each sample were amplified individually in two PCR assays, one each for D18S61 and D18S554, as described by Gyapay et al. Results were visualised by autoradiography and allele lengths were referenced to a DNA sequence ladder.

**Results**

Karyotype analysis of the proband showed 46,XX,del(18)(q22.2) (fig 3). Parental karyotypes were normal. Analysis of the parental ori-
gin of the deleted chromosome 18 using microsatellite markers described above showed that the deleted chromosome was of paternal origin.

**Discussion**

Although this child has several of the features described in patients with deletion of the same terminal segment of chromosome 18q, the strikingly abnormal vertebral formation is not a phenotypic feature of 18q− patients. In 1938, Jarcho and Levin described two sibs with short trunk dwarfism resulting from generalised vertebral and rib malformations. Since that time, over 100 cases have been described which fit broadly into the categories of spondylocostal or spondylothoracic dysplasia. Several classification systems have been proposed and although some overlap of characteristic features occurs, the groupings proposed in 1996 by Mortier et al. from reviewing ~140 cases are logical. These provide a reasonable clinical and radiological framework which will probably suffice until aetiologies are defined at the molecular level. While no data have emerged to provide insights concerning the identity or map locus of genes responsible for spondylocostal dysplasias, alterations in certain murine hox genes suggest a very important role for these genes in vertebral and rib formation.

The ribs of patients with the autosomal recessive Jarcho-Levin syndrome have a crowded origin from malformed thoracic vertebrae and fan out like the legs of a crab. In these children, associated congenital abnormalities of other organs are rare and death, usually from respiratory compromise, is frequent by 2 years of age. In those cases classified as spondylyothoracic dysostosis, an autosomal recessive mode of inheritance has been postulated albeit with considerable intrafamilial variability of expressivity. Again, congenital anomalies outside the axial skeleton are not common and affected subjects generally either die as neonates from respiratory failure or live to adulthood without restriction of lung capacity. Spondylocostal dysostosis is an autosomal dominant condition in which the severity of multiple vertebral segmentation defects is usually milder than the above conditions. Clearly there is considerable phenotypic overlap between these three conditions and our patient is difficult to categorise neatly into one descriptive grouping. The frequency and type of extraskletal manifestations in the Jarcho-Levin syndrome, spondylocostal dysplasia, and spondylothoracic dysplasia have been studied; patients with Jarcho-Levin syndrome generally do not have extrasketal manifestations and they are rare in patients with autosomal recessive spondylothoracic dysplasia and autosomal dominant spondylocostal dysplasia. The exception to this generalisation is perhaps those with lethal autosomal recessive spondylothoracic dysplasia. Non-skeletal anomalies are most frequent in patients with multiple vertebral segmentation defects categorised as sporadic by the absence of affected relatives or consanguinity. The proband most closely resembles patients in this group, sporadically arising and associated with extrasketal anomalies.

Comparison between the non-skeletal features of 18q− syndrome and spondylothoracic/spondylocostal dysplasias shows overlap. However, vertebral and rib anomalies of the types seen in patients with multiple vertebral segmentation defects have not been common in 18q− patients. In reporting data from seven patients with 18q− deletions (18q21.3→qter), Kline et al. determined that the severity of the phenotype generally correlated with the size of the deletion.

This patient, with multiple vertebral segmentation defects, absent kidney, myelomeningocele, and lower extremity malformations, is the first patient with multiple vertebral segmentation defects for whom a cytogenetic abnormality has been described. It is of interest to note that the constellation of non-skeletal anomalies in this child have been reported in other patients with multiple vertebral segmentation defects. The particular occurrence of associated anomalies has been loosely correlated with the site of vertebral involvement.

The current patient’s unusual lower extremity deformity deserves mention. This abnormality may best be described as a unilateral congenital aplasia of the entire fibula. While the fibula is the most common long bone to be congenitally absent, this anomaly, of uncertain aetiology, is generally associated with other abnormalities of the extremity involved, including tibial bowing and femoral shortening. Neither of these features is evident in our patient. Absence of single or multiple rays of the foot is also characteristic of congenital fibular aplasia with this patient illustrating the severe end of that spectrum. The presence of only a single hallux in our patient, however, may explain the lack of tibial bowing. Since the deformational forces are postulated to result from abnormal muscle and tendon attachment in the affected limb, the severity of our patient’s foot abnormality may actually have precluded deformation of the remaining long bones.

While lower extremity abnormalities are described in patients with 18q− syndrome and some cases of spondylocostal/spondylothoracic dysostosis, they are generally much less severe than those seen in this patient. This lower
extremity deformity, as well as spondylocostral dysplasia, may be coincidental to the patient’s 18q- karyotype. However, this would imply that multiple rare independent events occurred simultaneously during embryonic development to account for the unusual phenotype of this patient. Rather, the finding of the cytogenetic anomaly in this patient may provide a hint that an important gene in somite formation or vertebral differentiation maps to chromosome 18q22.2→qter. From this cytogenetic observation, several explanations might be advanced. Firstly, the chromosomal deletion may point towards a dominantly inherited gene on 18q involved in vertebral formation. Studies of breakpoints in 18q21.1→18q22.2 in a series of 18q- patients have suggested that the variability in phenotype may be the result of a contiguous gene syndrome. Although the additional malformations could result from involvement of such contiguous genes on chromosome 18, one might expect that other 18q- patients would have manifest multiple vertebral segmentation defects. In view of this, autosomal dominant inheritance seems unlikely. Secondly, the chromosome 18 deletion in this patient may be exposing a mutant gene on the other cytogenetically normal chromosome 18. In this scenario, both alleles at the putative locus would be involved, one deleted from the 18q-chromosome and one mutated on the other chromosome. It is interesting to note that associated malformations have not been common in autosomal recessive forms of spondylocostral dysplasia or Jarcho-Levin syndrome, although one Jarcho-Levin syndrome patient is reported with myelomeningocele and one with an anal abnormality. These anomalies were seen in the subject of this report. A third possibility is that the deletion has exposed an abnormally imprinted chromosome. In one study of a subset of 15 patients from a group of 26 patients with deletions ranging from 18q21.1→qter to 18q22.3→qter, no correlation between parental origin of the deleted chromosome and the phenotype was evident. Perhaps in view of that finding, one might have expected other 18q- patients to have manifested multiple vertebral segmentation defects if a parent of origin effect was operative. No genes have been mapped to the deleted region which can be postulated as candidate genes.

Some of the complex of malformations seen in this child are observed in other congenital conditions. Vertebral anomalies are frequent in both VATER/VACTERL associations and ouluariculovertebral (Goldenhar) syndrome. However, many of the patients’ other anomalies extend beyond the scope of the phenotypic features typically associated with these conditions. Similarly, without evidence of gestational diabetes, it is difficult to attribute the vertebral anomalies to altered glucose homeostasis in the embryonic life of this infant.

The clinical and cytogenetic observations in this case suggest that careful focus of attention upon distal chromosome 18q using high resolution cytogenetics and molecular techniques is warranted in patients presenting with an apparently sporadically arising form of spondylocostral dysostosis. Further characterisation of expressed sequences in the 18q22→qter region may permit identification of a specific gene in that region involved in somite formation or vertebral differentiation.