Parental consanguinity and the Majewski syndrome

SUMMARY We report a female infant with the Majewski syndrome, one of a group of conditions characterised by short ribs, polydactyly, dwarfism, and early neonatal death. This syndrome seems to be extremely rare, with only five well documented cases reported and, including this case, nine recorded in all. The Majewski syndrome is considered to be recessively inherited, and this report adds further support to this hypothesis, as the infant was born to consanguineous parents.

In 1971, Majewski *et al*¹ first described four unrelated infants with short ribs, small thoraces, polysyndactyly, cleft lip, abnormal genitalia, and death in the early neonatal period. In addition the infants showed major abnormalities of the internal organs. Subsequent case reports suggested the possibility of two other types of short rib-polydactyly (SRP) syndrome considered distinctive on clinical, radiological, and necropsy findings.

In the Majewski syndrome, labelled SRP type 2, there is a median cleft of the lip or palate or both, the epiglottis is rudimentary, and *x*-rays show short tibiae with rounded ends. In the Saldino-Noonan syndrome (SRP type 1),² the extremities are more markedly shortened and the common abnormalities of the internal organs include major cardiac malformations, atresia of the bowel, and renal dysplasia. On *x*-ray, the metaphyseal ends of the long bones are grossly irregular. In the Naumoff variety (SRP type 3), there are intermediate *x*-ray changes in the long bones and recently chondrocytic inclusions in epiphyseal cartilages have been reported in this condition.³ Milder examples of similar syndromes compatible with survival include the Ellis-van Creveld syndrome and asphyxiating thoracic dysplasia of Jeune.

Case report

After 38 completed weeks of gestation a 36-year-old gravida 7, para 4+2 Pakistani woman delivered a stillborn female infant by normal vertex delivery. The birthweight was 2140 g, length was 44 cm, and

head circumference was 35.5 cm. The marriage was consanguineous; the parents were first cousins, their mothers being sisters.

In her first pregnancy in Pakistan, she had an apparently normal, but stillborn, female infant. She subsequently had three healthy male infants, then developed severe asthma which resulted in termination of her fifth pregnancy at 10 weeks' gestation. The sixth pregnancy ended in a miscarriage at 10 weeks.

In this pregnancy, she took beclomethasone by inhaler throughout for her asthma, but booked late at the antenatal clinic. At 28 weeks hydramnios was detected clinically, and at 34 weeks an abdominal *x*-ray showed a single fetus with unusually short ribs. At 38 weeks she was admitted for assessment, but had a sudden antepartum haemorrhage after which no fetal heart beat was heard and the infant was delivered stillborn. The placenta weighed 425 g.

On examination the infant was grossly abnormal (fig 1) with short limbs, polysyndactyly, a median cleft of the upper lip and palate, a short neck, and a distended abdomen. There was no oedema. The

FIG 1 Proband showing shortened limbs with polysyndactyly of the hands and feet, abnormal facies with cleft lip and nasal groove, and small thorax

face was round, the eyes wide-spaced, the nasal bridge flat, and there was a vertical groove from the base to the tip of the nose. The ears were low set and slanted backwards, and the outer helices were thickened and folded. The hands and feet were short, with eight fingers on both hands, seven toes on the right foot, and six on the left foot. There was duplication of the thumbs, with complete syndactyly of the sixth, seventh, and eighth fingers. There was syndactyly of the first, second, third, and fourth toes of the right foot and of the first and second and third and fourth toes of the left foot. A soft swelling was present in the right labia majora.

On post mortem examination there was a complete palatine cleft, with hypertrophy of the lower labial frenulum. The gingiva were hypoplastic, and the natal teeth were exposed on the lower alveolar margin. The epiglottis was rudimentary with an underdeveloped larynx and the lungs were hypoplastic. The heart and great vessels were normal, with a patent foramen ovale and ductus arteriosus. The left renal pelvis and left ureter were slightly dilated, but there was no evidence of urinary tract obstruction. The genitalia were of normal female type and the right labial swelling was the result of an underlying hydrocele of the canal of Nuck. The brain was macroscopically normal.

There was gross hepatomegaly with moderate splenomegaly, but there was no ascites or evidence of portal vein thrombosis. There was malrotation of the bowel (fig 2) with shortened small and large intestines. The duodenum appeared normal. The jejunum (11 cm) and ileum (15 cm) together measured 26 cm, and the large intestine 20 cm. There was evidence of meconium peritonitis but no perforation was apparent.

FIG 2 *Malrotation of a shortened small intestine and meconium peritonitis*

FIG 3 *Post mortem x-rays showing short ribs, shortened limbs, and absence of the fibulae*

Abnormal histological findings included glomerular cysts of the kidneys, pancreatic duct ectasia with no evidence of fibrosis, and abnormal endochondral bone formation. There were no PAS positive chondrocytic inclusion bodies seen. There was marked cholestasis with canalicular bile plugging and persistent myelopoeisis in the portal tracts, features presumed to be causally related to the hepatomegaly. Meconium peritonitis was histologically confirmed. Brain histology was normal.

Post mortem x-rays of the whole baby (fig 3) showed significant shortening of all ribs and short long bones, in particular the tibiae and to a lesser degree the femur, humerus, radius, and ulna. The bone ends of the tibia and femur were smooth and rounded. The fibulae were absent. Ossification centres were present in both femoral heads, in the talus, and in the calcaneus. The pelvis and spine were normal.

Chromosomal analysis of cultured fibroblasts showed a normal female karyotype.

Discussion

The abnormalities found in this infant closely resemble those of the first case in Majewski's original report and the diagnosis would seem to be in little doubt. However, as more cases of the SRP syndromes are reported, it is apparent that there is considerable overlap in both the clinical and radiological findings in each type.

TABLE Constant, common, and occasional features in reported cases of Majewski and Saldino-Noonan short rib polydactyly syndrome

Majewski syndrome	Saldino-Noonan syndrome
<i>Constant</i>	<i>Constant</i>
Short extremities	Very short extremities
Narrow thorax	Narrow thorax
Polydactyly, pre- and postaxial	Polydactyly, postaxial
Cleft lip and/or palate	
Early neonatal death	Early neonatal death
Hypoplastic lungs	Hypoplastic lungs
Rudimentary epiglottis	
Short ribs	Short ribs
Short tibiae, rounded ends	Short tibiae, irregular metaphyseal margins
Advanced skeletal ossification	Advanced skeletal ossification
<i>Common</i>	<i>Common</i>
Low set ears	
Flat nasal bridge	
Telecanthus	
Abnormal genitalia	Abnormal genitalia
Renal cystic disease	Renal dysplasia/cystic disease
Polyhydramnios	Cardiac malformation (major)
<i>Occasional</i>	<i>Occasional</i>
Short small intestine	Short small intestine
Malrotation of bowel	Malrotation of bowel
Cardiac malformation (major)	Imperforate anus
CNS malformation	
Dysplastic pancreas	Dysplastic pancreas
	Flat nasal bridge
	Low set ears
	Oligohydramnios

Constant = present in all reported cases.

Common = present in more than half of reported cases.

Occasional = present in less than half of reported cases.

Abnormalities previously reported in type 1 and type 2 SRP are summarised in the table. The clinical features have been considered sufficiently distinct to allow for clear differentiation of the two conditions. However, several of the findings in our patient have been reported in cases of both SRP 1 and SRP 3 syndromes. These include intestinal abnormalities, mainly short small intestine and malrotation, renal cystic disease, abnormalities of the external genitalia, abnormalities of the epiglottis, and pre- and postaxial polydactyly.⁴ Clinical overlap is apparent also between type 1 and type 3. Both oligohydramnios and polyhydramnios have been described in these SRP syndromes and would not appear to be a useful distinguishing feature. Radiological findings in the limited number of patients reported to date appear to suggest definite differentiating features between the various syndromes but further confirmation of these differences is required.

It would appear that detailed information from successive reports gives less support for 'splitting' the SRP syndromes and 'lumping' may still be more appropriate.⁵ Earlier suggestions that these syndromes could be separated were based on findings in a limited number of patients, several with little necropsy information. Perhaps the recent reports of

chondrocytic inclusion bodies in SRP type 3 might, if confirmed in other patients, be grounds for suggesting that this is a different condition. However, until the basic biochemical mechanism has been identified or there is further detailed clinical and radiological information available, it would seem premature to invoke genetic heterogeneity and we may have to consider variable expression as just as likely an explanation for the differences.

Previous reports have suggested autosomal recessive inheritance for all three SRP syndromes. In reports of the Majewski type, consanguinity was present in the case of Chen *et al*⁶ and two affected sibs were reported by Motegi *et al*.⁷ The consanguinity in this family lends further support to the concept of recessive inheritance. This implies a high recurrence risk, but the condition should lend itself to prenatal diagnosis. This has recently been successfully applied by Richardson *et al*⁸ in the Saldino-Noonan syndrome.

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