Unusual traits associated with Robinow syndrome

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Abstract

We report on some members of two unrelated families showing the characteristic features of Robinow syndrome. In a consanguineous Kuwaiti family, the index case with Robinow syndrome showed some unusual features including severe IUGR, laxity of ligaments, hyperextensible joints, redundant skin folds, severe normocytic anaemia, repeated infection, increased percentage of total T cells and CD4 positive population, reduced percentage of CD8 positive cells, and EMG abnormality. In a Pakistani family with a high degree of multigenerational consanguinity, a single case with the Robinow phenotype also had congenital heart disease, mainly involving the right side of the heart, with pulmonary stenosis, tricuspid atresia, ASD, VSD, double outlet right ventricle, and right atrial isomerism. This report suggests that the disease profile of Robinow syndrome may be extended to accommodate the unusual traits mentioned above. The association of the Robinow phenotype with congenital heart disease in case 2 of this report is consistent with the previously reported finding that congenital heart disease, particularly involving the right side of the heart, may be a prominent component of Robinow syndrome in a subset of patients. 

Keywords: Robinow syndrome; congenital heart disease; joint laxity

The Robinow (fetal face) syndrome (MIM 180700, 268310) is a malformation syndrome with characteristic dysmorphic features and with as yet no known biochemical or cytogenetic markers. Features suggesting the diagnosis include the presence of micropenis with normal scrotum and testicles in males, hypoplastic labia minora and clitoris in females, characteristic facies with frontal bossing, hypertelorism, small nose with anteverted nostrils, large, downturned mouth, pseudoexophthalmia owing to hypoplasia of the lower lids, costovertebral anomalies, and meso/acromelia. Other features of the syndrome include mental retardation, short stature, delayed dental maturation, cleft lip/palate, crowded teeth, gingival hyperplasia, midline indentation of the lower lip, ankyloglossia, bilobed tongue tip, distal ulnar and proximal radial hypoplasia, brachymetacarpalism, brachy/clinodactyly, broad/split distal phalanx of the thumb, bifid/duplicated thumb or big toe, and congenital heart disease. Two genetic forms of Robinow syndrome have been identified, autosomal dominant and autosomal recessive.

We describe here two unrelated families with some of their members showing the Robinow phenotype. In one family a single case was associated with congenital heart disease, mainly involving the right side of the heart. In the other family the index case had some unusual features including IUGR, severe normocytic anaemia, laxity of ligaments, hyperextensible joints, redundant skin folds, repeated infection, microcephaly, absent proximal flexion crease of the little fingers, and EMG abnormality. Several sibs/cousins of this case showed some features of the Robinow phenotype.
Case reports

CASE 1

A female child was born at term by caesarian section because of fetal distress and IUGR. The Kuwaiti parents of Bedouin background were first cousins once removed. The pregnancy was complicated by poor fetal movements and hydramnios. Birth weight was 1900 g (<3rd centile), length 42 cm (<3rd centile), head circumference (OFC) 33.5 cm. The baby was resuscitated at birth by tracheal/gastric suction of meconium and was put in an incubator because of poor sucking and mild respiratory distress. Examination at 9 months of age showed that the baby was pale and had delayed psychomotor development. She was markedly hypotonic with severe head lag, laxity of ligaments, redundant skin folds (fig 1), and absent deep reflexes. She had repeated chest infections with fever and hypernatraemic gastroenteritis. Her weight was 4000 g (<3rd centile) and OFC 40 cm (<2SD). She was found to have frontal bossing, blue sclerae, epicanthic folds, depressed nasal bridge, small nose, anteverted nostrils, downturned, large mouth, mild midline indentation of the lower lip, delayed eruption of teeth, high arched palate, micrognathia, and low set, posteriorly angulated ears (fig 2). There was rhizomelic, small hands, brachydactyly, broad thumbs, clinodactyly of the 5th fingers (figs 3 and 4), hyperextensible hand joints (fig 5) with subluxation (fig 4), zygodactyly, abnormal dermatoglyphics with left simian crease and bilateral absence of the proximal flexion creases of the little fingers (fig 3), hypoplastic nipples, right congenital hip dislocation (fig 6), bilateral talipes equinovarus, and large big toes (fig 4).

The baby had slightly hypoplastic clitoris and labia minora.

Cardiovascular examination was normal. Chest examination showed bilateral expiratory wheeze and crepitations. The abdomen was lax with no organomegaly. Follow up at 14 months showed normal liver and thyroid function tests, unremarkable abdominal ultrasonography, normal brain CT scan, normal sweat chloride test, and urinary hydroxyproline was not raised. Complete blood count showed severe normocytic normochromic anaemia (haemoglobin 825 g/l, MCV 82 fl, MCH 23 pg, serum iron 10 mμol, normal range 6-27, transferrin saturation 23%). Hb electrophoresis was normal with no evidence of sickling (Hb A 98.2%, A2 1.8%). Total blood and platelet counts were normal and so was immunoglobulin profile while immunophenotyping showed an increased percentage of total T cells (74.2%, NR for age 1-6 years=62-69%) with increased percentage of CD4 positive population of 47.5% (NR=30-40) and reduced CD8 positive percentage of 21.4 (%) (NR=25-32%). Total B cell percentage was 21.2 (%) (NR=21-28%). Bone marrow biopsy showed a normal picture of haematopoiesis and the karyotype was of a normal female constitution (46,XX). Skeletal survey at the age of 14 months showed that the skeleton appeared small for age. The lumbar vertebrae appeared slightly higher (fig 6) with the presence of congenital right hip luxation, a possible neoacetalabulum formation above the steep right acetabular roof, and an unossified right femoral head. No ossification centres were seen in the carpus on either side, and there was marked bilateral brachymeso-

Figure 2 (A) Photograph of case 1 aged 14 months showing the characteristic facial features. (B) Lateral view of the face of case 1.

Table 1 Phenotypic variables of the sibs/cousins of case 1

<table>
<thead>
<tr>
<th>Subjects</th>
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<td>Anteverted nostrils</td>
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<td>Long phalum</td>
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<td>Simian crease</td>
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<td>Absent digital flexion crease</td>
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<td>Crowded teeth</td>
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<td>Talipes equinovarus</td>
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<td>Failure to thrive</td>
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FC=first cousin, + or − denotes presence or absence of a trait, G=good, L=low.
*Height <3rd centile for age and sex.
†Weight <3rd centile for age and sex.
‡OFC <−2SD.
first cousins. Apgar scores were 7, 8, and 9 at one, five, and 10 minutes, respectively. Birth weight was 2275 g, length 48 cm, and OFC 34 cm. She was found to have a large anterior fontanelle, hypertelorism, upward slanting palpebral fissures, blue sclerae, depressed nasal bridge, antverted nostrils, downturned mouth, accentuated Cupid’s bow, midline lower lip indentation, low set, prominent ears, bilateral talipes equinovarus, and normal female genitalia (fig 8). At the age of 4 months, OFC was 39.5 cm, length 55 cm (<3rd centile), upper segment 33 cm, upper arm 10 cm, forearm 10 cm, and hand 6 cm on both sides. She was noted from birth to have cyanosis while feeding and a soft systolic murmur was heard parasternally. Echocardiography showed pulmonary stenosis, tricuspid atresia, ASD, VSD, double outlet right ventricle, and right atrial isomerism. Skeletal survey was unremarkable and brain CT scan was normal. She had a normal female karyotype (46,XX).

Discussion

The index cases in the above report showed some highly diagnostic features of Robinow syndrome including the characteristic facial features with a bulging forehead, hypertelorism, short, upturned nose, broad, downturned mouth, midline indentation of the lower lip, the presence of pre/postnatal short stature, delayed skeletal maturation, and bilateral talipes equinovarus. This was accompanied in case 1 by some other important traits that have been found to be significantly associated with Robinow syndrome including short limbs with mesosacromelic involvement, the presence of mild vertebral anomalies, hypoplastic clitoris and labia minora, brachydactyly, brachymetacarpalism, clinodactyly, abnormal dermatoglyphics with a simian crease and absence of the proximal flexion crease of the little fingers, large thumbs and big toes with broadening of the terminal phalanges of the thumbs, and right hip dislocation. In case 2, on the other hand, the Robinow phenotype was complicated by congenital heart disease (CHD), particularly involving the right side of the heart.

Some unusual features have been previously reported in association with Robinow syndrome, including oligophrenia, sensorineural hearing loss, hepatosplenomegaly, and calyctasia and cystic kidney disease. In case 1 of the present report, several new unusual traits were identified that have not been reported before with Robinow syndrome. These include the presence of skin redundancy, laxity of ligaments, and hyperextensibility/subluxation of hand joints. Such manifestations overlap with the congenital recessive form of cutis laxa (MIM 219200), although the facial manifestations which are characteristic of the congenital recessive form of cutis laxa (for example, doli-choephaly, triangular face, antimongoloid slant, deep set eyes, mandibular prognathism, long pointed chin, and drooping cheeks) are not present in our patient. Moreover, our patient showed many of the characteristic diagnostic traits of Robinow profile as mentioned above.

Figure 3 (A) Left hand of case 1 showing abnormal dermatoglyphics with a single palmar crease, absent proximal flexion crease of the little finger, and large thumb. (B) Feet of case 1 showing large big toes.

phalangism of the 5th fingers with clinodactyly, and mild brachymesophalangism of the 2nd and 4th digits (fig 4). There was bilateral broadening of the terminal phalanges of the thumb (fig 4). EMG showed denervation activity in the left tibialis anterior and left rectus femoris muscles. Nerve conduction studies were inconclusive. A PCR based molecular test for Werdnig-Hoffmann disease was negative with no deletion of exons 7 or 8 of the SMN gene or exons 5 or 13 of the NAIP gene.

Two of the proband’s five sibs (fig 7) and five of her first cousins showed some of the facial dysmorphic features and dermatoglyphic abnormalities of Robinow syndrome. Most of them had low school performance, although none was considered to be mentally retarded. The phenotypic variables of the proband’s sibs/cousins, with particular emphasis on craniofacial/dermatoglyphic traits, are documented in table 1. Neither of the parents of the index case nor cousins showed any similar profile.

CASE 2

A Pakistani girl was delivered normally after an uneventful 37 week pregnancy. She was the only child of her double first cousin young parents and her grandparents on both sides were
Unusual traits associated with Robinow syndrome

Figure 4 (A) Radiograph of the right hand of case 1 at 14 months showing large thumb shadow, a broad terminal phalanx of the thumb, unossified carpal bones, and interphalangeal joint subluxation. (B) Radiograph of the feet of case 1 showing large big toes.

Figure 5 (A) Hyperextensible thumb joints in case 1. (B) Hyperextensible finger joints in case 1.

Figure 6 Radiograph of the spine of case 1 (lateral view) showing slightly higher lumbar vertebrae.

Other unusual features of case 1 in the present report include repeated infections, increased total T cell population with increased percentage of CD4 positive fraction relative to the CD8 positive population, severe normocytic normochromic anaemia, and EMG abnormality. Microcephaly, which was also detected in case 1 and in some of her phenotypically similar cousins (table 1), is probably a rare finding in Robinow syndrome although it has been reported before. As stated above, the absence of proximal flexion creases of the little fingers as well as the presence of a single palmar crease were elicited in case 1 and some of her phenotypically similar relatives. These traits have been emphasised as the major dermatoglyphic changes associated with the Robinow phenotype, although other dermatoglyphic changes have also been reported. Several sibs/cousins of case 1 showed some features of Robinow syndrome (table 1). The most consistent traits of Robinow syndrome exhibited in this family were the presence of frontal bossing, hypertelorism, downturned, large mouth, and low set and abnormal ears. On the other hand, none of the phenotypically similar sibs/cousins in this family showed any of the unusual traits described in the index case, namely the severe hypotonia, the laxity of ligaments, the hyperextensible hand joints, the
redundant skin folds, the severe anaemia, or the repeated infections. In light of the parental consanguinity of the affected members of this family, an autosomal recessive mode of inheritance of Robinow syndrome seems likely.

Congenital heart disease, which was found in case 2, has been previously described in some cases of Robinow syndrome. Webber et al\textsuperscript{1} described an affected case with pulmonary atresia and VSD. They reviewed previously reported cases with CHD associated with Robinow syndrome and suggested that CHD, especially right ventricular outflow obstruction, may be a component of the syndrome in some cases. Atalay et al\textsuperscript{2} described another infant with Robinow syndrome who also had tricuspid and pulmonary valve atresia, ASD, and PDA. In the present report, echocardiographic study of case 2 showed pulmonary stenosis, tricuspid atresia, ASD, VSD, double outlet right ventricle, and right atrial isomerism. Thus, the present report confirms the notion that CHD, with predominantly right sided heart involvement, is probably a prominent component of Robinow syndrome in a subgroup of patients. Because of the high degree of parental and grandparental consanguinity of case 2, an autosomal recessive mode of inheritance is suggested.

In conclusion, this report highlights some unusual traits associated with Robinow phenotype in one patient: redundant skin, hyperextensible joints, repeated infection, abnormal percentage of T cell subpopulations, severe normocytic anaemia, and EMG abnormality. The report re-emphasises CHD, particularly with right sided heart involvement, as a prominent component of Robinow syndrome in a subset of patients.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Subject 2 in table 1, a sib of case 1 with some facial manifestations of the Robinow phenotype.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Photographs of case 2.}
\end{figure}

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