Early onset asymmetrical intrauterine growth retardation with fetal hypokinesia and variable expression of acral and genitourinary malformations: a new lethal MCA syndrome

I Witters, P Moerman, F A Van Assche, J-P Fryns

We report four sibs, two males and two females, with severe and early onset asymmetrical intrauterine growth retardation (IUGR) with a disproportionally large head and a fetal akinesia deformation sequence. Neuromuscular studies were normal in the four sibs. Variable acral malformations (bilateral cleft hand in one male, proximal syndactyly of the toes (right II-III; left II-III/IV-V) in the other male) and genitourinary malformations (Rokitansky sequence in one female, renal hypoplasia/dysplasia in one male and one female, cryptorchidism in the males) were present.

The spectrum of malformations seen in these four sibs dominated by severe asymmetrical IUGR with fetal hypokinesia and early lethality provides evidence for the existence of a new MCA syndrome with apparent autosomal recessive inheritance.

CASE REPORTS

The parents of the four sibs described in this report are non-consanguineous, healthy Europeans. Two other pregnancies had ended with a first trimester miscarriage. They also have two healthy daughters.

The first sib was a male newborn, who died a few minutes after birth at 35 weeks gestation. The pregnancy was complicated by polyhydramnios. The boy presented with severe asymmetrical growth retardation (weight 970 g (<10th centile), head circumference 32 cm (50th centile)) and features of FADS (Pierre-Robin sequence, pulmonary hypoplasia, fixed anteflexion of the hips, and bilateral talipes). Additionally, he had cutaneous syndactyly of several toes on both feet (left foot: toes II-III and IV-V; right foot: toes II-III), cryptorchidism, and intestinal non-fixation.

The second sib was a small macerated 21 week old female fetus with severe asymmetrical IUGR (weight 105 g (<10th centile), head circumference 16.2 cm (50th centile for 19 weeks)) with features of FADS (Pierre-Robin sequence, fixed anteflexion of the hips, bilateral talipes). Additionally, she had a Rokitansky sequence with absence of Fallopian tubes, uterus, cervix, and the upper part of the vagina.

The third affected sib, a male, born at 30 weeks, also had severe and asymmetrical IUGR (weight 740 g (<10th centile), head circumference 29 cm (50th centile)) and features of FADS (polyhydramnios, pulmonary hypoplasia, fixed anteflexion of the hips, bilateral talipes). The marked macrocephaly contrasted with the small triangular shaped midface with low set ears, broad nasal bridge, upward slanting palpebral fissures, cylindrical nose, short columella, small mouth with thin lips, and micrognathia (fig 1A). The palate was normal. A lobster claw deformity was present on both hands. On the left hand the third finger was missing. X rays showed five metacarpals. Metacarpals III and IV supported a single digit with an enlarged proximal phalanx (superdigit III-IV). The right hand showed an apparently completely absent fourth
on x rays, however, metacarpals III and IV supported an enlarged single digit (“superdigit III-IV”) (fig 1B). He had a micropenis and cryptorchidism. At necropsy, internal malformations included renal hypoplasia (left kidney 0.9 g, right kidney 0.6 g), low lumbar ectopia of the right kidney, a bilateral rotation anomaly, adrenal hypoplasia, and intestinal non-fixation. Histologically, there was microcystic renal dysplasia.

The fourth affected sib was a 19 week old female fetus. She presented again with early onset asymmetrical IUGR visualised at 14 weeks by ultrasound. There were signs of fetal hypokinesia with microretrognathia and fixed anteflexion of the hips, a bilateral rotation anomaly, and intestinal non-fixation. Histologically, there was microcystic renal dysplasia.

DISCUSSION
We present a family with four sibs, two males and two females, affected by a distinct MCA syndrome.

This syndrome is dominated by early onset and severe intrauterine growth retardation with a disproportionally large head, a fetal akinesia deformation sequence with marked involvement of the lower limbs (fixed anteflexion of the hips), and early lethality. Variable expression of additional acral malformations (bilateral clefthand in one male, proximal syndactyly of the toes (right II-III; left II-III/IV-V) in the other male) and genitourinary malformations (Rokitansky sequence in one female, renal hypoplasia/dysplasia in one male and one female, cryptorchidism in both males) were present.

Because the third sib, a male, had bilateral ectrodactyly of his hands and renal hypoplasia/dysplasia with ectopia, the diagnosis of acrocerebral syndrome was considered. This condition, first described by Dieker and Opitz, is acknowledged as a distinct clinical entity including the following acral defects: ectrodactyly, oligodactyly mostly involving the middle digits, sometimes part of a split hand/split foot, skin syndactyly of toes I-II, brachy- and clinodactyly.

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<tr>
<th>Table 1</th>
<th>Clinical data and pathological findings in the four siblings</th>
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<tr>
<td></td>
<td>Sex</td>
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<tr>
<td>Gestational age (wk)</td>
<td>35</td>
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<tr>
<td>Weight (g)</td>
<td>970</td>
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<td>Head circumference (cm)</td>
<td>32</td>
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<tr>
<td>FADS</td>
<td>Polyhydramnios</td>
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<td>Bilateral talipes</td>
<td>Fixed anteflexion of hips</td>
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<tr>
<td>Robin sequence (microretrognathia-cleft palate)</td>
<td>Bilateral talipes</td>
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<tr>
<td>Limbs</td>
<td>Right foot: proximal syndactyly toes II-III</td>
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<td></td>
<td>Left foot: proximal syndactyly toes III/IV-V</td>
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<tr>
<td>Genital</td>
<td>(Cryptorchidism) (Hypospadias)</td>
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<td></td>
<td>(Cryptorchidism) (Hypospadias)</td>
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<tr>
<td>Kidneys</td>
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<tr>
<td>Adrenal</td>
<td>–</td>
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<tr>
<td>Intestines</td>
<td>Intestinal non-fixation</td>
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<tr>
<td>Karyotype (T banding)</td>
<td>46, XY</td>
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</table>
The renal lesions vary from mild (duplicated collecting system) to renal hypoplasia and unilateral renal agenesis. Hypertelorism, hypospadias, and cryptorchidism may occur. Although the third sib presented with acral and renal defects, the present MCA syndrome is distinctly different from the acrorenal syndrome. It is dominated by severe and early onset asymmetrical intrauterine growth retardation and early lethality, features not observed in the acrorenal syndrome.

All four sibs presented with fetal hypokinesia with marked involvement of the lower limbs and a fixed anteflexion of the hips. Additional features of FADS were polyhydramnios and pulmonary hypoplasia in the two sibs born at ≥30 weeks. Pierre-Robin sequence in two sibs, and talipes equinovarus. Extensive fetopathological studies (central nervous system, spinal cord, muscles) were normal in the four sibs.

Intrauterine growth retardation is a common feature in patients with FADS, which is known to be no more than a non-specific symptom complex resulting from early intrauterine limitation of movement of any cause.1114

In conclusion, the MCA syndrome in the present four sibs is thus characterised by (1) severe, early onset asymmetrical intrauterine growth retardation, (2) fetal hypokinesia, (3) variable acral malformations, and (4) variable genitourinary malformations. Inheritance is most likely autosomal recessive, although an autosomal dominant lethal mutation owing to germline mosaicism in one of the parents cannot be formally excluded.

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REFERENCES