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

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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, with extension of the knees. She was born after termination of pregnancy. Her weight was 72 g (<10th centile) and head circumference 12.7 cm (50th centile for 17 weeks). Macroscopic examination confirmed the antenatal findings of fetal hypokinesia (fig 2). She had normal external and internal genitalia. Histologically, both kidneys showed microcystic dysplasia. Chromosomal studies on amniotic fluid cells and skin fibroblasts were normal in the four sibs. Extensive neuropathological studies were also normal. Brain examination was grossly and microscopically normal. Spinal cord examination was normal, with a normal number of anterior horn cells and normal corticospinal tract. Both lower and upper limb muscles were sampled (biceps, quadriceps, intercostal muscles, diaphragm) and were normal. Enzyme histochemistry showed a normal distribution of the different fibre types without stapling of fat or glycogen. There was a normal oxidative activity and there were no ragged red fibres nor abnormal inclusions. Immunocytochemistry with antibodies against dystrophin (dys1, dys2, dys3) was normal. Colouring with antibodies against dystrophin associated glycoproteins 35, 43, and 50 kDa was normal as was immunohistochemistry with antibodies against merosin. The clinical data and pathological findings of the four sibs are summarised in table 1.

**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 disproportionately 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 cleft hand in one male, proximal syndactyly of the toes (right II-III; left II-III/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 acrorenal 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.

| Table 1: Clinical data and pathological findings in the four siblings |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Sex** | **Male** | **Male** | **Female** | **Female** |
| Gestational age (wk) | 35 | 21 | 30 | 19 |
| Weight (g) | 970 | 105 | 740 | 72 |
| Head circumference (cm) | 32 | 16.2 | 29 | 12.7 |
| FADS | Polyhydramnios | Normal amount of amniotic fluid | Polyhydramnios | Normal amount of amniotic fluid |
| Bilateral talipes | Fixed anteflexion of hips | Bilateral talipes | Pulmonary hypoplasia | Fixed anteflexion of hips |
| Robin sequence | Bilateral talipes | Pulmonary hypoplasia | Microretrognathia |
| Pulmonary hypoplasia | Robin sequence |
| Limbs | Right foot: proximal syndactyly toes II-III | Bilateral ectrodactyly of hands with superdigit type I |
| | Left foot: proximal syndactyly toes II-III/IV-V |
| Genital | | Rokitansky sequence | Micropenis |
| | | | |
| Kidneys | | | | Renal hypoplasia |
| | | | | Cortical/medullary dysplasia |
| Adrenal | | | | Adrenal hypoplasia |
| Intestines | Intestinal non-fixation | Intestinal non-fixation |
| Karyotype (T banding) | 46, XY | 46,XX | 46,XY | 46,XX |

**Figure 2** Postmortem view of the fourth sib, a female, at 19 weeks with asymmetrical IUGR and hypokinesia.
The renal lesions vary from mild (duplicated collecting system) to renal hypoplasia and unilateral renal agenesis. Hypertelorism, hypoplasias, 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 \( \geq 30 \) weeks, Pierre-Robin sequence in two sibs, and talipes equinovarus. Extensive neuropathological 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. In the present affected sibs, the intrauterine growth retardation was severe and of early onset, visualised by ultrasound from 14 weeks’ gestation. In addition the IUGR was asymmetrical with a disproportionately large head in all four affected sibs. The growth retardation seemed to be primordial, rather than a consequence of the fetal hypokinesia. The fetal hypokinesia was prominent in the lower limbs with fixed anteflexion of the hips. Pterygia, as seen in lethal multiple pterygium syndrome, an early onset, and severe FADS with IUGR and early lethality were absent.

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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J Med Genet 2003 40: e1
doi: 10.1136/jmg.40.1.e1

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