ELECTRONIC LETTER

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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We report four sibs, two males and two females, with severe and early onset asymmetrical intrauterine growth retardation (IUGR) with a disproportionately 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 antelexion 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 antelexion 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 antelexion 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

Key points

- We present four sibs with a MCA syndrome characterised by severe, early onset asymmetrical growth retardation, fetal hypokinesia, variable acral malformations, and variable genitourinary malformations.

Figure 1 (A) The third affected sib, a male, with macrocephaly, a small, triangular shaped midface with low set ears, broad nasal bridge, cylindrical nose, small mouth, and micrognathia. A lobster claw deformity was present on both hands. (B) The right hand of the third sib, with absent fourth ray and metacarpals III and IV supported by a single digit.

Table 1 Clinical data and pathological findings in the four siblings

	Sex			
	Male	Female	Male	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 Robin sequence (microretrognathia-cleft palate) Pulmonary hypoplasia	Fixed ante flexion of hips Bilateral talipes Robin sequence	Bilateral talipes Pulmonary hypoplasia	Fixed ante flexion of hips Microretrognathia
Limbs	Right foot: proximal syndactyly toes II-III Left foot: proximal syndactyly toes II-III/IV-V	–	Bilateral ectrodactyly of hands – with superdigit type I	–
Genital	(Cryptorchidism) (Hypospadias)	Rokitansky sequence	Micropenis (Cryptorchidism) (Hypospadias)	–
Kidneys	–	–	Renal hypoplasia Cortical/medullary dysplasia	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.

ray. 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 ante flexion 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 fibro-

blasts 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 ante flexion 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/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 acrorenal syndrome was considered. This condition, first described by Dieker and Opitz¹ 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.

The renal lesions vary from mild (duplicated collecting system) to renal hypoplasia and unilateral renal agenesis. Hyertelorism, hypospadias, and cryptorchidism may occur.²⁻¹²

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 antelexion 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 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.¹³⁻¹⁴

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 disproportionally 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 antelexion of the hips. Pterygia, as seen in lethal multiple pterygium syndrome, an early onset, and severe FADS with IUGR and early lethality were absent.¹⁵⁻¹⁷

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

- 1 **Dieker H**, Opitz JM. Associated acral and renal malformations. *Birth Defects* 1969;**5**:68-77.
- 2 **Gehler J**, Grosse R. Fehlbildungs-Retardierungs-Syndrom mit Spaltfussen, Iriskolobom, Nierenagenesis und Ventrikel-septum Defekt. *Klin Padiatr* 1972;**184**:387-392.
- 3 **Curran AS**, Curran JP. Associated acral and renal malformations: a new syndrome? *Pediatrics* 1972;**49**:716-725.
- 4 **Elfenbein IB**, Baluarte HJ, Gruskin AB. Renal hypoplasia with oligomeganephronia: light, electron, fluorescent microscopic and quantitative studies. *Arch Pathol* 1974;**97**:143-9.
- 5 **Salmon MA**, Wakefield MA. The acro-renal syndrome of Curran. *Dev Med Child Neurol* 1977;**19**:521-4.
- 6 **Miltenyi M**, Balogh L, Schmidt K, Detre Z, Hernady T, Czeizel A. A new variant of the acrorenal syndrome associated with bilateral oligomeganephronic hypoplasia. *Eur J Pediatr* 1984;**142**:40-3.
- 7 **Massafra C**, Bartolozzi M, Bartolozzi P, Scillone L. Rokitansky-Kuster-Hauser syndrome with ectrodactyly. *Acta Obstet Gynecol Scand* 1988;**67**:557-60.
- 8 **Zeier M**, Tariverdian G, Waldherr R, Andrassy K, Ritz E. Acrorenal syndrome in an adult - presentation with proteinuria, hypertension, and glomerular lesions. *Am J Kidney Dis* 1989;**14**:221-4.
- 9 **Miltenyi M**, Czeizel AE, Balogh L, Detre Z. Autosomal recessive acrorenal syndrome. *Am J Med Genet* 1992;**43**:789-90.
- 10 **Houlston R**, MacDermot K. Acrorenal syndrome: further observations. *Clin Dysmorphol* 1992;**1**:23-8.
- 11 **Evans JA**, Vitez M, Czeizel A. Patterns of acrorenal malformation associations. *Am J Med Genet* 1992;**44**:413-19.
- 12 **Akl K**. Acrorenal syndrome in a child with renal failure. *Am J Med Genet* 1994;**49**:447.
- 13 **Hall JG**. Analysis of Pena Shokeir phenotype. *Am J Med Genet* 1986;**25**:99-117.
- 14 **Moerman P**, Fryns JP. The fetal akinesia deformation sequence. A fetopathological approach. *Genet Couns* 1990;**1**:25-33.
- 15 **Meyer-Cohen J**, Dillon A, Pai GS, Conradi S. Lethal multiple pterygium syndrome in four male fetuses in a family: evidence for an X-linked recessive subtype? *Am J Med Genet* 1999;**82**:97-9.
- 16 **Froster UG**, Stallmach T, Wisser J, Hebisch G, Robbiani MB, Huch R, Huch A. Lethal multiple pterygium syndrome: suggestion for a consistent pathological workup and review of reported cases. *Am J Med Genet* 1997;**68**:82-5.
- 17 **de Die-Smulders CE**, Schrander-Stumpel CT, Fryns JP. The lethal multiple pterygium syndrome: a nosological approach. *Genet Couns* 1990;**1**:13-23.