The lethal multiple congenital anomaly syndrome of polydactyly, sex reversal, renal hypoplasia, and unilobular lungs

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SUMMARY Three cases are reported of a lethal multiple congenital anomaly syndrome. The infants had moderate limb shortening, joint contractures, polydactyly, and the two with male karyotypes had female external genitalia. Internal anomalies included unilobular lungs, hypoplasia of the anterior portion of the tongue, and renal hypoplasia.

We report three unrelated infants with a lethal multiple congenital anomaly (MCA) syndrome who had moderately short limbs, polydactyly, and valgus deformity of the feet with syndactyly. All had female external genitalia but two had 46,XY karyotypes. All cases had micrognathia and microglossia and at necropsy unilobular lungs and renal hypoplasia were found. We consider that these infants have the lethal MCA syndrome recently described by Rutledge *et al*¹ and that the two sibs described by Kohler² as probably having the Smith-Lemli-Opitz syndrome³ also have this condition. Although documentation is sometimes incomplete, other reported cases⁴⁻⁸ are also likely to have been affected.

Case reports

CASE 1

This apparently female infant was born at 35 weeks' gestation, the first child of a healthy, unrelated, Caucasian 26 year old woman and 30 year old man. The mother had had a healthy baby and a termination of pregnancy in a previous relationship. In this pregnancy urinary and serum oestriols were low when measured between 32 and 35 weeks' gestation, but human placental lactogens were normal. The baby, which had female external genitalia, died of respiratory failure at the age of 1½ hours.

The baby weighed 2.325 g, length 45 cm, occipito-

frontal circumference (OFC) 30 cm. The limbs appeared to have moderate rhizomelic shortening (fig 1), there were bilateral transverse palmar

FIG 1 Case 1 postmortem. Note rhizomelic limb shortening and female external genitalia.

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creases, short thumbs, and postaxial hexadactyly of the hands (fig 2). There was limited abduction of the hips and marked calcaneovalgus deformity of the feet with complete soft tissue syndactyly of the second and third toes (fig 3). Bilateral cataracts were present, the chin was small, and the soft palate absent.

At necropsy the posterior two-thirds of the tongue was bulky and the anterior one-third shortened. The larynx appeared normal but the left lung was unilobular and the right lung bilobular.

There was a high interventricular septal defect of the heart and the left kidney was extremely hypo-

plastic (1 g); the right kidney weighed 10 g and appeared normal. Histological sections of the left kidney showed normal glomeruli.

There was a transparent, thin, flat sheet of tissue behind the bladder which was thought to represent the uterus. From this led normal looking tubes and the gonads which histologically were found to be testes.

The only other internal abnormalities found were excessive length and dilatation of the descending and sigmoid colon. Histologically, prominent nerve fibres were found in the submucosal and intermuscular layers but ganglion cells were not found.

FIG 2 Case 1. Note postaxial hexadactyly and proximal placement of thumbs.

FIG 3 Case 1. Note valgus deformity, syndactyly 2/3, and short halluces.

Histological sections of the pancreas showed increased size of islets.

Chromosome analysis of cultured blood lymphocytes and fibroblasts from a skin biopsy showed a normal male karyotype, 46,XY.

CASE 2

This phenotypically female Caucasian baby was born at 38 weeks' gestation and was the product of the tenth pregnancy of a 41 year old father and 38 year old mother, who were healthy and unrelated. Three previous pregnancies had resulted in normal infants, two girls and one boy. The other six pregnancies had resulted in miscarriages at 12 weeks.

The mother took no drugs during the pregnancy and felt well throughout. However, during the last four weeks urinary oestriol levels were measured on 12 separate occasions and were always either very low or unrecordable. Serum human placental lactogen levels were normal.

The baby, who lived only four hours, had a weight of 1890 g, length 41 cm, and OFC 30 cm. Ultrasonography shortly before death showed very small kidneys. She had an abnormal facies (figs 4 and 5) with a prominent capillary naevus on the forehead, anteverted nares, low set ears, cleft soft palate, small tongue with thick alveolar margins, and

FIG 5 Case 2. Note micrognathia and short neck.

marked micrognathia. Her neck was short with a loose fold of skin posteriorly. Her hands had small thumbs, proximally placed index fingers, and a left single palmar crease. Both feet showed severe calcaneovalgus with syndactyly of the second and third toes, complete on the right and partial on the left (fig 6). The right foot also showed postaxial polysyndactyly. Both hips were dislocated and there was reduced range of movement at the left knee. Both arms showed moderate mesomelic and rhizomelic shortening. The external genitalia were female.

At necropsy both lungs were unilobular. Seminal vesicles and undescended testes (confirmed histologically) were present. The brain, heart, and abdominal viscera including the adrenal glands were normal macroscopically. No histological studies were carried out on these organs. Blood lymphocyte and fibroblast cultures showed a normal male karyotype, 46,XY.

CASE 3

This female infant was born at 40 weeks' gestation to a healthy, unrelated 21 year old woman and 26 year old man. Previous pregnancies had resulted in spontaneous miscarriages at 10 and 12 weeks' gestation. Oligohydramnios and intrauterine growth retardation were noted in pregnancy. Delivery was by caesarian section for fetal distress and breech presentation. The infant, who died of respiratory failure at the age of 30 hours, weighed 2320 g and

FIG 4 Case 2. Note limb shortening, abnormal facies, and haemangioma.

FIG 6 Case 2. Note valgus deformity, syndactyly, and polydactyly.

had a crown-rump length of 29 cm, crown-heel length 41 cm, OFC 33 cm. There was rhizomelic and mesomelic shortening of all limbs (fig 7) with limited joint movements. The shoulders were internally rotated, there was a limited range of movements at elbows and wrists, and the hands were clenched with flexion deformity of the metacarpophalangeal joints. Bilateral transverse palmar creases were present and the thumbs were short and proximally placed. There was limited hip abduction, marked suprapubic and inguinal skin creases, limited movement at the knees, and metatarsus valgus. Both first metatarsals were short and there was postaxial polydactyly on the left foot with syndactyly between the fifth and sixth toes (fig 8). The occiput was prominent and the neck short. Multiple haemangiomas were present over the glabella, eyelids, philtrum, and temples. The corneae were cloudy but no cataracts were seen. The nose was short with anteverted nares and there was marked micrognathia (fig 9). The gum margins were broad and the tongue very short anteriorly but no cysts were present. The palate was high arched and cleft (fig 10). At necropsy the left cardiac ventricle was hypoplastic with a high ventricular septal defect and overriding aorta. There was only one pulmonary vein on each side draining into a hypoplastic left atrium, and the inferior vena cava was left sided passing anterior to the hilum of the left lung to enter the right atrium. Both lungs were unilobular but not hypoplastic (right 19 g, left 14.7 g). The larynx was small. The kidneys were both hypoplastic; the right had three pyramids and weighed 4.5 g and the left had two pyramids and weighed 4.6 g. The other abdominal organs were present and macroscopically

normal with female internal genitalia. The brain was macroscopically normal although the posterior fossa was shallow.

FIG 7 Case 3. Note limb shortening, abnormal facies, haemangioma, and inguinal skin creases.

FIG 8 Case 3. Note valgus deformity, short hallucus, and polysyndactyly.

FIG 9 Case 3. Note micrognathia, short neck, and short nose.

FIG 10 Case 3. Note thick upper alveolar margin, cleft palate, and very short anterior portion of the tongue.

Histological examination of the pancreas revealed increased size and number of islets. There was aganglionosis of all the large bowel and part of the terminal ileum involving the appendix. Ovarian and renal tissue was microscopically normal. Chromosome analysis showed a normal female karyotype, 46,XX

Discussion

The three cases reported here show a very similar pattern of internal and external abnormalities to the three cases (two of them sibs) reported by Rutledge *et al.*¹ We consider that the sibs reported by Kohler² bear more similarities to those of Rutledge *et al.*¹ and those contained in this report than to the Smith-Lemli-Opitz syndrome.³ The table shows the main clinical features of the eight cases. Early death was the rule and in the four cases which were male on karyotyping or on testicular histology, there were female or ambiguous external genitalia. In all cases where it was specifically stated, the limbs were reported to be moderately short. There was a

TABLE Clinical and pathological features of cases.

	Rutledge <i>et al</i> ¹			Kohler ²		This report			Total
	Case 1	2	3	Case 1	2	Case 1	2	3	
	Sibs			Sibs					
Gestation (wk)	40	37	40	38	38	35	38	40	
Birth weight (g)	2580	1880	2150	3107	2767	2325	1890	2320	
Age at death	1 d	1 d	14 d	6 h	15 h	1½ h	4 h	30 h	
External genitalia	F	F	Ambig	F	F	F	F	F	
Karyotype	46,XX	46,XX	46,XY	Testes at necropsy	'Female' at necropsy	46,XY	46,XY	46,XX	
Short limbs	+	+	?	?	+	+	+	+	6/6
Hands									
Postaxial polydactyly	-	+	+	+	+	+	-	-	5/8
Short thumbs	+	?	?	?	+	+	+	+	5/5
Transverse palmar crease	+	+	+	?	?	+	+	+	6/6
Feet									
Valgus deformity	+	+	Varus	+	+	+	+	+	7/8
Syndactyly of toes	+	+	+	+	+	+	+	+	8/8
Postaxial polydactyly	-	-	+	+	+	-	+	+	5/8
Cataracts	-	-	+	?	?	+	-	-	2/6
Low set ears	+	?	+	?	+	-	+	+	5/6
Micrognathia	+	+	+	?	+	+	+	+	7/7
Cleft/absent soft palate	-	-	-	+	-	+	+	+	4/8
Microglossia	+	+	+	?	?	+	+	+	6/6
Tongue cysts	+	+	+	?	?	-	-	-	3/6
Unilobular lungs	+	+	?	+	+	+	+	+	7/7
Cardiac defect	+	+	?	+	+	+	-	+	6/7
Hypoplastic kidney(s)	+	+	+	+	?	+	+	+	7/7
Cerebellar hypoplasia	+	+	+	?	?	-	-	-	3/6
Gall bladder agenesis	+	-	?	?	?	-	-	-	1/5
Pancreatic islets	↑ Islets, no giant cells	↑ Islet cells	No necropsy	↑ Size giant cells	↑ Size giant cells	↑ Size islets	?	↑ Size islets	6/6

characteristic valgus deformity of the feet in all but case 3 of Rutledge *et al*¹ and syndactyly between several toes. There was postaxial polydactyly in all cases of the hands or feet or both.

An unusual abnormality noted in the cases of Rutledge *et al*¹ and our three cases was the small tongue; this was not commented on in the report of Kohler.² Cleft or absent soft palate was noted in case 1 of Kohler² and all cases in this report, and cataracts in case 3 of Rutledge *et al*¹ and case 1 in this report. Unilobular lungs are an unusual finding in malformation syndromes and were present in all seven cases subjected to necropsy. Hypoplastic kidneys were present in all the necropsied cases and a cardiac defect in all but case 2 in this report. Aganglionosis was found in cases 1 and 3 in this report and may be a feature of this syndrome; large bowel histology is not available for case 2 and not reported by Rutledge *et al*¹ or Kohler.² A review of published reports of coexisting aganglionosis and Smith-Lemli-Opitz syndrome has revealed several other cases of this probably separate syndrome. Lowry *et al*⁴ reported a child with polydactyly,

cardiac defects, and hypoplastic kidneys. Patterson *et al*⁵ reported a 46,XY female with abnormal lung lobation, an abnormal kidney, but no polydactyly. Zizka *et al*⁶ reported two males with hypoplastic genitalia, joint contractures, polydactyly, and cardiac defects. Lipson and Hayes⁷ reported a male with ambiguous genitalia and polydactyly, and Greene *et al*⁸ reported two 46,XY females with polydactyly and other features similar to the cases reported here. All of the cases with aganglionosis died, the longest survival being two months.

Rutledge *et al*¹ considered several other lethal conditions in their differential diagnoses including the short rib-polydactyly syndromes, asphyxiating thoracic dystrophy, and the Ellis-Van Creveld syndrome. Like them, we dismissed these as unlikely because of the lack of characteristic radiographical and clinical features in our cases and the presence of other features not reported in those syndromes. Rutledge *et al*¹ did consider the cases by Kohler² in his differential diagnosis but rejected them since he considered that they did not have mesomelic dwarfing, tongue cysts, or laryngeal hypoplasia, and that

the renal anomaly was different. In fact, Kohler² reported that his case 2 had short limbs and his photographs confirm this. It is interesting to note that in Kohler's discussion he considered that his cases had a unique phenotype and it is only in the following editorial note that the possibility of Smith-Lemli-Opitz syndrome³ is introduced. In an editorial comment Lowry,⁹ agreeing with the suggestion of Smith-Lemli-Opitz syndrome³ for Kohler's cases, then goes on to consider phenotypic overlap between Smith-Lemli-Opitz,³ Meckel,¹⁰ and other syndromes. We believe that the cases reported and reviewed here bear such a strong resemblance to each other, and differ so markedly from the spectrum of clinical signs and clinical course usually associated with the Smith-Lemli-Opitz syndrome,³ that they should be considered as a separate malformation syndrome. In their review of the Meckel syndrome, Opitz and Howe¹⁰ cited two cases reported in German publications by Foerster and by Casper where the affected infants had renal hypoplasia and a pattern of abnormalities which would fit more closely with the syndrome reported here than with the Meckel syndrome. In the same paper, Opitz and Howe¹⁰ reviewed the Ullrich-Feichtiger syndrome; some of the cases discussed closely resemble this new syndrome although the authors stated that they are likely to be examples of the Smith-Lemli-Opitz syndrome. Pfeiffer¹¹ illustrated a presumed case of the Ullrich-Feichtiger syndrome (his case 13). He reported affected sibs who died at 48 hours of age and had polydactyly, valgus deformity of the feet, and aplasia of the kidneys, with hypospadias in the male. The illustration of the affected male bears a strong resemblance to the cases reported here. Antley *et al*¹² also considered Pfeiffer's case 13¹¹ as a possible example of the C trigonocephaly syndrome.¹³

One of the most unusual but consistent features of this lethal multiple congenital anomaly syndrome appears to be the pulmonary segmentation defect. In the computerised dysmorphology data base¹⁴ seven syndromes are listed as having this abnormality. Two of these, Fryns *et al*¹⁵ and Ivemark¹⁶ syndromes, do not have polydactyly as a feature and differ in other ways, so can be discounted. Five of the listed syndromes with pulmonary segmentation defect also have polydactyly as a feature: the anocerebrodigital syndrome of Hall *et al*,¹⁷ the C trigonocephaly syndrome,¹³ the hydroletharus syndrome,¹⁸ and the cases reported by Kohler² and Rutledge *et al*.¹

Joint contractures and short limbs, marked in cases 2 and 3 and mild in case 1, probably represent the postnatal legacy of a prenatal lack of movement. The akinesia may have been due to 'splinting' of the

limbs by oedema (thickening of subcutaneous tissue was noted on x-ray of case 3) or secondary to neurological impairment. Toriello *et al*¹⁹ have recently discussed the concept of the fetal akinesia sequence. Other conditions with joint contractures should be considered in the differential diagnosis: cerebro-oculo-facio-skeletal syndrome (COFS)²⁰ has features in common including cataracts, and Pena-Shokeir I syndrome²¹ shares pulmonary hypoplasia and early death.

Two other features are worthy of note. In the sibship of case 2 and case 3 of this report and in Kohler's² cases there was a very striking history of miscarriage at around 10 to 14 weeks. This may relate to the second point, since in the present cases 1 and 2 maternal serum oestriol levels were persistently low during late pregnancy. In both cases serum human placental lactogen levels were normal. These observations, in conjunction with the sex reversal, would be consistent with a major metabolic defect in the fetal adrenals. Rutledge *et al*¹ have speculated on the nature of a possible early error in morphogenesis common to many organs. The findings in our patients indicate that whatever the precise nature of the basic underlying defect, it is likely to extend to the adrenal glands also.

This report helps to establish the existence of a lethal malformation syndrome which has similarities to the Meckel syndrome and the C trigonocephaly syndrome but has sufficient differences to be considered as a separate condition. Four of the eight cases reported and reviewed here are sib pairs, suggesting an autosomal recessive mode of inheritance. The limb shortening, cardiac, and renal abnormalities might permit prenatal diagnosis by real time ultrasound scanning and the polydactyly, syndactyly, and cleft palate could serve as markers of the syndrome at fetoscopy.

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Note added in proof

We propose that this syndrome be called the Lowry-Miller-Maclean syndrome, since theirs was the first full description of this disorder in 1968.

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