

Two sibs with microcephaly, hygroma colli, renal dysplasia, and cutaneous syndactyly: a new lethal MCA syndrome?

H C J P Janssen, C Schaap, N Vandevijver, P Moerman, C E M de Die-Smulders, J-P Fryns

Abstract

We report two sibs of Turkish descent with multiple congenital anomalies including severe microcephaly, hygroma colli, cystic renal dysplasia, and bilateral cutaneous syndactyly of toes IV-V. In addition, the second sib presented with bilateral fusion of the eyelids, a bicornuate uterus, and clitoromegaly. The parents are first cousins, which suggests autosomal recessive inheritance. In reviewing previously published reports, several cases were found with cerebral, renal, and digital anomalies as the main features. Several of the additional symptoms present in the second sib were suggestive of Fraser syndrome, but the severe microcephaly in both sibs is unusual. The differential diagnosis is discussed, including the possibility of an entirely new entity in the broad spectrum of syndromes with cerebral, renal, and digital anomalies.

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In the past, several syndromes have been described with cystic renal dysplasia and cerebral and digital malformations as the main features.^{1,2} In most of them the expression is highly variable, resulting in a significant overlap between the different phenotypes. In this report we present two sibs with severe microcephaly, hygroma colli, cystic renal dysplasia, cutaneous syndactyly, and an oligohydramnios sequence. In one of them, additional abnormalities of the internal female genitalia and fused eyelids were present. Despite a thorough review of published reports, a satisfactory diagnosis could not be made. Fusion of the eyelids, cutaneous syndactyly, abnormalities of the internal genitalia, and cystic renal dysplasia initially suggested Fraser syndrome.³ However, severe microcephaly in Fraser syndrome is very uncommon and it seems most appropriate to consider these two sibs as representing a new entity in the spectrum of syndromes with cerebral, renal, and digital anomalies.

Case reports

We report on two children of a consanguineous Turkish couple (first cousins). Both parents are healthy and, more specifically, ultrasound examination of the kidneys in both parents showed no abnormalities. The first pregnancy

of this couple resulted at 38 weeks' gestation in a dysmature but healthy girl. The second pregnancy is reported below as case 1. The third pregnancy ended at 27 2/7 weeks with a caesarean section because of maternal pre-eclampsia and fetal bradycardia. A dysmature/immature girl was born, who died 14 days later of complications related to prematurity (necrotising enterocolitis). The fourth pregnancy is presented below as case 2.

CASE 1

One day before delivery the mother reported absent fetal movements. Ultrasound examination showed oligohydramnios and fetal death. Spontaneous labour ensued and a stillborn girl was delivered at 29 5/7 weeks' gestation. Birth weight was 1050 g (50th centile), crown-rump length was 23 cm (3rd centile), and head circumference was 21 cm (3 cm below the 3rd centile). Examination showed a macerated female fetus with severe microcephaly and a sloping forehead (fig 1). Hypertelorism, upward slanting palpebral fissures, a broad nose with a depressed bridge, micrognathia, and a high arched palate were present. The ears were normally implanted, but had an abnormal appearance partly because of oedema of the helices. The neck was short and a large anteriorly placed hygroma colli was present. In general there was diffuse hirsutism and cutis laxa, the latter probably related to the oligohydramnios. Limb anomalies included joint contractures of the elbows, ulnar deviation of the hands, and bilaterally broad, low set thumbs. Dermatoglyphics were atypical. There was talipes equinovarus on the right side and bilateral, nearly complete cutaneous syndactyly of toes IV-V.

On the back there was a sacral dimple, but *x* ray showed no vertebral defects. The genitalia were normal female. At necropsy, both kidneys were small and cystic. Microscopically multiple cysts, rare intact glomeruli, and primitive tubules with peritubular concentric fibrosis were seen. There was no metaplastic cartilage. The ureters were filiform, but the bladder appeared normal. The lungs were hypoplastic. The liver and spleen were congested with foci of extramedullary haematopoiesis. There was no congenital hepatic fibrosis. Macroscopic examination of the brain showed no structural abnormalities. Unfortunately, microscopy was not performed. Microbiological examination of the lungs, spleen, and liver showed excessive growth of *E coli* and *Enterococcus faecalis*. Chro-

Department of
Molecular Cell Biology
and Genetics,
University of Limburg,
PO Box 1475, 6201 BL
Maastricht, The
Netherlands
H C J P Janssen
C Schaap
C E M de Die-Smulders

Department of
Pathology, University
Hospital Maastricht,
The Netherlands
N Vandevijver
P Moerman

Centre for Human
Genetics, University
Hospital Leuven,
Belgium
J-P Fryns

Correspondence to:
Dr de Die-Smulders.

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Figure 1 (A) Full body view of sib 1: note the severe microcephaly, hygroma colli, contractures of the elbows, ulnar deviation of the hands, and talipes equinovarus. (B) Detail of sib 1: severe microcephaly with sloping forehead, hygroma colli, and abnormal ears.

mosomal analysis of cultured skin fibroblasts showed a normal 46,XX karyotype.

CASE 2

During the fourth pregnancy, a structural ultrasound at 20 weeks' gestation again showed anhydramnios, microcephaly, and multicystic kidneys. The pregnancy was terminated at 20 6/7 weeks and a female fetus was delivered with a striking resemblance to case 1 (fig 2). Birth weight was 210 g (below the 3rd centile), crown-rump length was 19 cm (50th centile), and head circumference was 15 cm (2 cm below the 3rd centile). Microcephaly with a



Figure 2 Full body view of sib 2 showing severe microcephaly, hygroma colli, hypertelorism, and fused eyelids.



Figure 3 Symmetrically enlarged kidneys with multicystic renal dysplasia.

sloping forehead, hypertelorism with a broad, flat nose, a long philtrum, micrognathia, and relative macrostomia with macroglossia were present. The ears appeared large and were oedematous. There was bilateral fusion of the eyelids. The neck was short with a large circumferential hygroma colli. The palate was closed. Both hands showed a simian crease, camptodactyly of digits II and III, and a short fifth digit with only two phalanges. Both feet had almost complete cutaneous syndactyly of toes II-III and IV-V and partial cutaneous syndactyly of toes III-IV. There were contractures of all the large joints, which was probably related to the anhydramnios. Genitalia were female with a large clitoris; the anus was open and normally positioned.

Necropsy showed that the eyeballs were of normal size and microscopically normal. Both kidneys (weight 2.3 g) were symmetrically enlarged and showed multicystic renal dysplasia (fig 3). The bladder was hypoplastic. The lungs (weight 2 g) were extremely hypoplastic, but had normal lobulation. There was no laryngeal atresia. The heart displayed a situs solitus with a patent oval foramen, endocardial fibrosis of the right ventricle with a stenotic, dysplastic pulmonary valve, and a dysplastic aortic valve. There was no hepatic fibrosis. The brain weight was 5.5 g (normal weight for 21 weeks is 48 g). Microscopy of the brain showed normal development of the cortex, basal ganglia, ventricles, and cerebellum. There was a bicornuate uterus. The umbilical cord contained three vessels and was normally inserted. Chromosomal analysis on cultured skin fibroblasts showed a normal 46,XX karyotype and metabolic investigation to exclude Smith-Lemli-Opitz syndrome showed a normal 7- and 8-dehydrocholesterol and cholesterol concentration in the umbilical cord plasma.

Discussion

We report on two sibs with multiple congenital anomalies including severe microcephaly, hygroma colli, nearly complete cutaneous syndactyly of toes IV-V, and renal dysplasia. In addition, the second sib showed bilateral fusion of the eyelids, dysplastic valves of the aorta and pulmonary artery, a bicornuate uterus, and clitoromegaly. It is questionable whether fusion of the eyelids, as present in the second sib, is a true abnormality or related to gestational age.

Table 1 Syndromes with cerebral, renal, and digital malformations as the main features

	Fraser	Smith-Lemli-Opitz type II	Winter-Tsukahara	Cerebro-reno-digital spectrum ¹	This report, sib 1	This report, sib 2
<i>Craniofacial anomalies</i>						
Microcephaly	±	+	+	±	++	++
Pachygyria	-	-	+	±	-	-
Cryptophthalmos	+	-	-	-	-	±
Ptosis of eyelids	-	+	-	-	-	-
Cleft palate	+	+	-	+	-	-
High arched palate	±	+	-	-	+	-
Abnormal nose	+	+	+	-	+	+
Abnormal ears	+	-	+	±	+	+
Micrognathia	±	±	-	±	+	+
<i>Hands</i>						
Skin syndactyly	+	-	+	-	-	-
Camptodactyly	-	-	+	-	-	+
Polydactyly (postaxial)	-	+	-	+	-	-
Oedema	-	-	+	-	+	+
Contractures	-	-	-	-	+	+
Low set thumb	±	-	-	-	+	-
<i>Feet</i>						
Skin syndactyly	-	-	-	-	-	-
Toes II-III	+	+	-	-	-	+
Toes IV-V	+	±	-	-	+	+
Club feet	+	-	+	-	+	+
<i>Skin</i>						
Hygroma colli	-	-	+	-	+	+
<i>Urogenital</i>						
Renal agenesis	+	-	-	+	-	-
Renal dysplasia	±	±	+	+	+	+
Abnormal genitalia	+	+	+	±	-	+
<i>Thorax</i>						
Cor vitium	±	+	+	+	-	-
Laryngeal atresia	+	-	-	±	-	-
<i>Abdomen</i>						
Umbilical hernia	+	-	-	±	-	-
Umbilical displacement	+	-	-	-	-	-
Malrotation of gut	±	±	-	-	-	-
Anal atresia	+	-	-	±	-	-
<i>Skeletal defects</i>						
Lethal	±/+	±/+	+	±	+	±
Mental retardation	+	++	NA	+	NA	NA

NA: not applicable.

It is known that during normal embryogenesis, the eyelids fuse around the eighth week of development and do not separate until between the fifth and seventh month of development.⁴ This makes the sole finding of fused eyelids without additional eye anomalies rather inconclusive. Nevertheless, the cutaneous syndactyly of the toes, the renal dysplasia, and the abnormal female genitalia were suggestive of Fraser syndrome, although other features present in one or both sibs were less characteristic.

In Fraser syndrome, expression is highly variable with a broad spectrum of associated malformations. Common features are cryptophthalmos, cutaneous syndactyly of the fingers and toes, abnormal genitalia, malformations of the nose and ears, laryngeal atresia, cleft lip/palate, skeletal defects, umbilical hernia, renal agenesis, and mental retardation.^{3,5} Lethality depends on the severity of the renal anomaly and the degree of laryngeal stenosis.⁵⁻¹¹ In our two sibs, microcephaly was a distinct feature, whereas in Fraser syndrome this has only occasionally been described.^{3,10} Other findings which make Fraser syndrome less likely are the absence of eye anomalies in the first sib and the lack of eyeball abnormalities in the second sib. However, cases of Fraser syndrome without cryptophthalmos or other eye anomalies have been described previously.⁶

Another syndrome to be considered in the differential diagnosis is Smith-Lemli-Opitz (SLO) syndrome. Common features here are microcephaly, hypoplastic cystic kidneys, syn-

dactyly of toes II-III, hypospadias, and male pseudohermaphroditism, and in survivors of the neonatal period feeding problems and severe mental retardation.¹² Clinical diagnosis is often difficult because of the broad clinical spectrum and the overlap with other syndromes, for example, Meckel-Gruber syndrome.¹³ Fortunately, it is now possible to rule out SLO syndrome by metabolic analysis in which the 7- and 8-dehydrocholesterol and cholesterol concentrations are assessed. In our second sib, no abnormalities in the cholesterol and 7- and 8-dehydrocholesterol concentrations in the fetal plasma were found. Therefore, SLO syndrome seems highly unlikely.

Severe cerebral anomalies in addition to renal, digital, and facial malformations have also been reported by Winter *et al*¹⁴ and Tsukahara *et al*¹⁵ and have subsequently been referred to as the Winter-Tsukahara syndrome. Winter *et al*¹⁴ reported a male infant, the result of an incestuous father-daughter relationship, with brachycephaly and simplified broad convolutions of the brain (head circumference <3rd centile), large fontanelles, hypertelorism with short palpebral fissures, and a small nose with thin nares. The ears were small with cystic pinnae. The hands were puffy with camptodactyly of the fingers and mild skin syndactyly. The kidneys were small and dysplastic and the lungs were hypoplastic. Tsukahara *et al*¹⁵ described a case of a stillborn male infant with similar features whose parents were unrelated. The brain malformation in this case was not proven.

Our two sibs share several features with these two cases, including microcephaly, dysplastic kidneys, hypoplastic lungs, and digital malformations. However, brachycephaly and, more important, pachygyria were not present in our case.

Another report combining cerebral, renal, and digital anomalies was by Lurie *et al.*¹ They presented five new cases and compiled 19 additional published case reports with cerebral, renal, and digital malformations as the main features. The majority of their cases presented with a diversity of cerebral anomalies, cystic renal dysplasia, and postaxial polydactyly. Although our two sibs share some features with these cases, including a cerebral anomaly and cystic renal dysplasia, the digital anomaly (cutaneous syndactyly) is quite different.

None of the above mentioned syndromes seems to fit our two patients, although several features are shared with each of these syndromes (table 1). Because our two cases had a strikingly similar appearance, it seems unlikely that both of them, by chance, ended up at the same extreme of one of the previously mentioned syndrome spectrums. Therefore, we propose that they constitute a new entity in which, again, cerebral, renal, and digital malformations are the main features. The fact that the malformations in the two fetuses described here show a striking resemblance and the consanguinity of the parents suggests an autosomal recessive mode of inheritance.

In conclusion, we believe that our two cases most probably constitute a new entity in the whole spectrum of syndromes with cerebral, renal, and digital malformations. Additional cases with similar features may clarify this matter. Also the discovery in the near future of the

gene for Fraser syndrome or other genes involved with programmed cell death will help to answer the question whether or not our two sibs belong to the spectrum of syndromes caused by a disturbance in programmed cell death.

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