Lethal acrodysgenital dwarfism: a severe lethal condition resembling Smith-Lemli-Opitz syndrome

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SUMMARY We report eight cases of a lethal association of failure to thrive, facial dysmorphism, ambiguous genitalia, syndactyly, postaxial polydactyly, and internal developmental anomalies (Hirschsprung's disease, cardiac and renal malformation). This syndrome is likely to be autosomal recessive and resembles Smith-Lemli-Opitz (SLO) syndrome. However, the lethality, the common occurrence of polydactyly, and the sexual ambiguity distinguishes this condition from SLO syndrome. A review of published reports supports the separate classification of this syndrome for which we propose the name lethal acrodysgenital dwarfism.

In September 1985, at the meeting of the European Club of Genetic Counselling, we reported three cases of children with a syndrome reminiscent of the Smith-Lemli-Opitz syndrome. However, it seemed to us to differ from the latter because of the extent of the genital abnormality and the rapidly fatal evolution.¹ Since then, we have encountered five new cases very similar to the first ones. Independently, Donnai *et al*² have reported three similar cases. In this paper, we discuss our eight cases and compare them to other published cases. It appears that this syndrome constitutes a new entity which we propose to name lethal acrodysgenital dwarfism.

Case reports

Cases 1, 2, 3, 4, 6, and 7 were encountered during genetic counselling sessions. Cases 5 and 8 were ascertained from anatomical and pathological records.

CASE 1

Case 1, a female, was the first child of young parents. She was born in the breech position in a state of fetal distress, weighing 2370 g and measur-

ing 44 cm. The face was dysmorphic with a narrow forehead, anteverted nares, broad and prominent nasal bridge, angioma on the forehead, narrow and antimongoloid palpebral fissures, blepharoptosis, and marked micrognathia. The head circumference was 31.5 cm and the neurological state very poor (fig 1).

In addition, there was bilateral clinodactyly of all five fingers, proximally placed thumbs, and postaxial polydactyly on the left hand. The feet also showed bilateral postaxial polydactyly, with syndactyly of the second and third toes. The fingers and toes were clenched. On examination, she was small for her age with very widely spaced nipples, female external genitalia, and a sacral dimple. No gonads were palpable.

X ray examination showed a dense base to the skull, thin ribs, and narrow iliac bones. On the left hand, the polydactyly affected the bones and the first metacarpal was short. On the right foot, there were only four metatarsals of which the last two were in the form of a Y thus giving rise to the polysyndactyly. On the left foot, the fourth and fifth metatarsals were joined proximally and the sixth had no bone (fig 2).

An examination of the eyes revealed bilateral congenital cataract. The karyotype was male (46,XY) and revealed the sexual ambiguity up-

FIG 1 Case 1 showing female external genitalia, polydactyly, low set ears, anteverted nares, broad nasal bridge, and micrognathia.

FIG 2 X ray of feet of case 1.

suspected until then. The child died of pulmonary complications on day 45.

Necropsy showed an ectopic left kidney, dilatation of the cavities of the right heart, and a macrophagic infiltration of the lungs. The uterus was absent but there were two male gonads and an epididymis. Histologically, the seminiferous tubules were immature and the interstitial cells were poorly developed.

CASE 2

The second child of a young couple was born after induced labour at 38 weeks. Ultrasound examination at 35 weeks showed retarded growth which was confirmed at birth (length 40.5 cm, birth weight 2250 g, head circumference 30 cm).

There was marked dysmorphism including an antimongoloid slant of the palpebral fissures, marked micrognathia, and broad alveolar ridges. The tongue had a multicystic appearance and there was excessive skin on the back of the neck. Syndactyly of the second and third toes was noted as well as duplication of the fifth left toe. The child had club feet and dislocated hips. A sacral dimple was present. In the genital region, a voluminous mass was noted, as well as two large folds surrounding a vaginal cleft. No gonads could be palpated.

The child died shortly of respiratory distress. The karyotype was 46,XY.

Necropsy showed an atrial septal defect, a unilobar left lung, and a rudimentary uterus with two well formed fallopian tubes; the gonads had undergone male differentiation.

CASE 3

This child was of indeterminate sex, born at 35 weeks, in the incomplete breech position, birth weight 2180 g, length 43 cm, head circumference 30 cm. The father and mother were 20 and 21 years old, respectively. The dysmorphism consisted of microcephaly with brachycephaly, poorly formed ears, a flattened nose with anteverted nares, cleft

palate, and flat angiomas on the forehead and eyelids. All four extremities were abnormal: a bilateral vestigial sixth finger implanted in the proximal phalanx of the fifth finger, a sixth toe, and syndactyly between the second and third toes. There was talipes valgus and the cry was weak. The karyotype was 46,XY and the child died on day 24.

Necropsy showed hypertrophic left cardiac cavities, small and immature lumbar-pelvic intra-abdominal testes, Müllerian remnants behind the bladder, and dilatation of the lateral ventricles.

CASE 4

This was a first child born at 35 weeks in the breech position, with slight intrauterine growth retardation (length 46 cm, birth weight 2800 g, head circumference 33.5 cm). The parents were both 34 years old. The child presented the characteristic Smith-Lemli-Opitz facial dysmorphism, associated with a cleft palate, postaxial hexadactyly of all four limbs (fig 3) with syndactyly of the second and third toes, and a bilateral simian crease. The external genitalia were very hypoplastic, but male (fig 5). The karyotype was 46,XY.

The child died on day 16. Necropsy showed absence of internal male genital organs and the presence of a common mesentery and infiltration in the lungs.

CASE 5

The discovery of oligohydramnios and of major hypotrophy led to termination of pregnancy at 29

FIG 3 X ray of hand of case 4 showing postaxial polydactyly.

FIG 4 Foot of case 4 showing polysyndactyly of the toes.

FIG 5 Case 4 showing hypoplastic external genitalia.

weeks. The fetal karyotype was 46,XY. The external genitalia were female with a blind vagina. At necropsy, severe micrognathia, slanted palpebral fissures, and bilateral urethral duplication were noted. There were no fallopian tubes, uterus, or ovaries, but there were two small abdominal masses resembling testes and a common mesentery.

CASE 6

This child was both small for dates and premature (born at 30 weeks), birth weight 1850 g, head circumference 29.5 cm (<25th centile). She was born by caesarian section because of breech position and multiple malformations. She was phenotypically female and showed micrognathia, broad nasal bridge, anteverted nares, a high palate and horizontal palpebral fissures. The neck was short with an apparent excess of skin. The limbs seemed short with club feet, postaxial hexadactyly

FIG 6 Case 7 showing micrognathia, polydactyly, excess of loose skin on the neck, pectus excavatum, and low set ears.

of the left hand and foot, and syndactyly of the second and third toes. A sacral dimple was noted. Necropsy showed pulmonary hypoplasia and an interventricular septal defect. The gonads resembled testes but there was a very hypoplastic uterus. The right kidney was small and ectopic. The karyotype was 46,XY, inv(9).

CASE 7

This small for dates female child, born at term (birth weight 2480 g), was admitted to hospital because of her dysmorphic appearance characterised by micrognathia, a flattened nasal bridge, an arched palate, low set and poorly formed ears, postaxial polydactyly of all four extremities, and hypertrophic labia majora. The neck was short with excess loose skin (fig 6). X rays revealed a sixth lumbar vertebra (sacral dimple), confirmed the polydactyly (synostosis of the fifth metacarpal), and showed a short first metacarpal and brachymesophalangy of the sixth. The child died of heart failure with a patent ductus arteriosus. Necropsy showed large and lobular kidneys. The karyotype was 46,XX.

CASE 8

This girl was born to a 17 year old mother of gypsy origin whose parents were consanguineous, but whose precise relationship was not known. As early as the 20th week, ultrasound suggested a low weight gain which was confirmed at birth (birth weight 2050 g, head circumference 31 cm, length 42 cm). She

presented with multiple congenital abnormalities and died after 16 days of life.

The karyotype was 46,XY. The face showed characteristic dysmorphology with cataracts and a cleft palate. Postaxial polydactyly was noticed on the hands and feet with a bilateral simian crease and syndactyly of the second and third toes. The external genitalia were female with hypertrophic labia majora and clitoris. The gonads could not be seen.

Necropsy revealed testes in the inguinal canals and a vagina devoid of Müllerian duct derivatives. There were no other anomalies of the internal organs with the exception of a retro-oesophageal subclavian artery and a patent ductus arteriosus. On examination of the skull, slight distension of the lateral ventricles and heterotopic cell clusters were observed. The pancreas appeared immature with large islets of Langerhans.

Discussion

The eight infants we have described obviously show the same pattern of malformations. The major element consists of the genital anomalies with an XY karyotype but complete failure of masculinisation of the external genitalia or even a true sex reversion. The testes were undescended, small, and appeared immature. The presence of a hypoplastic uterus or Müllerian remnants was noted in four out of the seven cases with a male karyotype.

In addition to these genital anomalies, facial

dysmorphism and a general pattern of malformations was observed. The facial dysmorphism was reminiscent of Smith-Lemli-Opitz syndrome. The most characteristic features were the anteverted nostrils and micrognathia. In three cases out of eight, a cleft palate was associated with the above, and an arched palate was noted once. Enlargement of the alveolar ridges was noted in one case. There was a constant flattening of the nasal bridge, sometimes abnormally shaped ears, an excess of skin on the back of the neck (five cases out of six), and frontonasal angiomas.

However, the dysmorphic facial pattern found in our cases is not very specific as it does in fact consist of features found not only in the Smith-Lemli-Opitz syndrome, but also in other syndromes. On the other hand, the other abnormalities are more specific. Polysyndactyly was present in seven out of eight cases and was of variable expression, affecting at times a single hand, at other times all four limbs. Associated with this were other limb abnormalities, club feet or talipes valgus and short thumbs. The abnormalities of the genitalia, of the face, and of the extremities were accompanied by malformations of the internal organs. Renal hypoplasia was the most frequent and the heart may be affected (septal defect or patent ductus arteriosus). Cerebral abnormalities have also been noticed, such as ventricular dilatation as well as pulmonary abnormalities (lobulation abnormalities one case, pulmonary hypoplasia one case, pneumopathy three cases) (table 1).

The pattern of malformations described here is not in itself new. Without mentioning the earlier observations of Foerster and Casper, certain cases

of the so called Ullrich-Feichtiger syndrome 'typus rostockiensis', such as those of Weber and Schwarz, seem quite similar to ours. Certainly, the Ullrich-Feichtiger syndrome has proven to be extremely heterogeneous.⁴ In Feichtiger's initial observations (1943) the 'Würzburg' type is similar to trisomy 13 or Meckel syndromes, whereas the 'Rostock' type, which is associated with preauricular appendages and deafness, micrognathia, triphalangy of the thumbs with bilateral polydactyly of the hands, no external ray to the feet, anal atresia, and hypospadias, is similar to what is currently designated the Townes-Brock syndrome.⁵ The existence of this syndrome was questioned as early as 1975 by Pfeiffer and Slavaykoff.⁶ They described a sister and brother who died after only a few days of life both presenting with postaxial polydactyly, the boy also having hypospadias. While considering the possibility of Ullrich-Feichtiger syndrome, these authors concluded that it was more likely to be Smith-Lemli-Opitz syndrome.⁷ Other more recent observations mention Smith-Lemli-Opitz syndrome with early lethality, in which the severely affected phenotype is accompanied by polydactyly.⁸⁻¹¹ Based on their personal experience and other published reports, Cherstvoy *et al*¹² found a significant difference between the Smith-Lemli-Opitz cases that are associated with polydactyly and those that are not. The former seem to them to constitute a separate entity, characterised in particular by an earlier death, a higher frequency of renal anomalies, and different cerebral malformations.

Coincidental with our first three observations Donnai *et al*¹³ published three cases in which the

TABLE 1 Features of lethal acrodysgenital dwarfism.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Total
Chromosomes	46.XY	46.XY	46.XY	46.XY	46.XY	46.XY	46.XX	46.XY	7M, 1F
Phenotype	F	F	F	M (hypospadias)	F	F	F	F	
Müllerian remnants	-	+	+	-	+	+	+	-	
Immature testes	+	+	+	No testes	+	+	-	+	
Weight (g)	2370	2250	2180	2800	Terminated	1850	2480	2050	8/8
Dwarfism	+	+	+	+	+	+	+	+	8/8
Microcephaly	+	+	+	-	?	+	+	+	6/7
Micrognathia	+	+	+	+	+	+	+	+	8/8
Anteverted nares	+	+	+	+	+	+	+	+	8/8
Low set ears	+	+	+	+	+	+	+	+	8/8
Cleft palate	-	-	+	+	-	+	-	+	4/8
Excess of skin on the neck	-	+	?	+	?	+	+	+	5/6
Postaxial polydactyly	+	+	+	+	?	+	+	+	7/7
Simian crease	+	+	+	+	?	+	+	+	7/8
Syndactyly of toes 2-3	+	+	+	+	+	+	+	+	8/8
Club foot (valgus)	-	+	+	-	?	+	-	+	4/6
Sacral dimple	+	+	-	-	?	?	+	-	4/6
Cataract	+	-	-	-	?	?	-	+	2/7
Urinary tract malformation	+	-	-	?	+	+	+	-	4/7
Cardiac defect	+	+	+	?	-	+	+	+	6/8
Pulmonary lobulation abnormality	+	+	?	+	?	-	-	-	2/4

symptoms were comparable to those described here, and with which they associated other published cases. These authors differentiated these cases from the Smith-Lemli-Opitz syndrome as described in 1964.⁷ Indeed, if delayed development and the characteristic facial dysmorphism are also present in the SLO syndrome, the most constant features are hypospadias or cryptorchidism or both in the male, without complete failure of masculinisation, and syndactyly between the second and third toes with or without club feet and metatarsus varus. Polydactyly is seen only exceptionally and early death only occurs in 20% of the cases.

In the light of our observations, the diagnosis of Smith-Lemli-Opitz syndrome in these unusual forms seems to us to deserve close scrutiny. This is confirmed by our analysis of 47 cases published under this title and analysed according to the criteria of lethality or presence of polydactyly.

Of these cases, 20 children out of 47 died in the first few months of life and their phenotype was different to that of survivors. Facial dysmorphology did not differ significantly between the two groups, but cleft palate was present in half the cases, and enlargement of the alveolar ridges was more frequent. On the other hand, postaxial polydactyly,

most frequently affecting all four limbs, and marked sexual ambiguity seemed to be characteristic of the lethal forms (73% against 11% and 71% against 0%, respectively). Malformations of the internal organs were also more frequent, and were in themselves a measure of severity: cardiac malformations of all types, uni- or bilateral renal hypoplasia, and more particularly Hirschsprung's disease were present in eight out of the 20 fatal cases (table 2).

If we follow Cherstvoy *et al*³⁴ and classify the 47 reviewed cases of Smith-Lemli-Opitz syndrome into two groups, 'with polydactyly' and 'without polydactyly', it appears quite clear that the sexual ambiguity is more severe when there is polydactyly and the prognosis then seems to be extremely poor (table 3).

This analysis indicates the need to differentiate the Smith-Lemli-Opitz syndrome from those cases with polydactyly, marked sexual ambiguity, and early death. The results of family studies contribute a further element to support this division. It has been established that the pattern of inheritance of the Smith-Lemli-Opitz syndrome is autosomal recessive, and this is confirmed by the consanguinity found in certain families and the existence of multiple affected sibs. Within families, the degree of severity is very similar, as one would expect according to genetic heterogeneity. A possible exception is family 1 reported by Dallaire,¹⁶ in which two seriously affected children had severe polydactyly, the third child having no polydactyly. In this family, described in 1969, the author mentions an abnormally long chromosome 16 in the mother that was also present in some of the normal children as well as in some of the affected ones. Without sufficiently precise karyotype studies (marker studies) there remains doubt about the validity of the diagnosis.

A NEW PATTERN OF MALFORMATIONS

We can therefore distinguish the Smith-Lemli-Opitz syndrome from the new pattern of malformations reported here, which is also transmitted in an autosomal recessive fashion, and which we propose to name lethal acrodysgenital dwarfism.

Apart from our eight observations and the three reported cases of Donnai *et al*,¹³ and very recently the case of Scarbrough *et al*,²⁸ we can include in this

TABLE 2 *Smith-Lemli-Opitz syndrome: two forms?*

	'Classic' (n=27)	'Severe' (n=20)
Genitalia	15	14
Ambiguous or female	—	10
Cryptorchidism, hypospadias	14	4
Extremities		
Postaxial polydactyly	3	14
Short thumb	4	4
Syndactyly of toes	25	19
Face		
Microcephaly	17	15 17*
Micrognathia	19	19
Cleft/high palate	9	16
Anteverted nares	18	15
Broad alveolar ridges or cyst	3	9 9*
Malformation of internal organs		
Cardiac defect	4	15
Kidney anomalies	4	10
'Pneumopathy'	3	8
Hirschsprung's disease	—	8

*Microcephaly and broad alveolar ridges were not quoted in all observations published.

TABLE 3 *Smith-Lemli-Opitz syndrome: heterogeneity.*

N=47	Sexual ambiguity	Early death	Pulmonary abnormality	Malformation of internal organs
With polydactyly (n=17) ^{3 6 8-11 14-18}	83	70	70	75
Without polydactyly (n=20) ^{2 15 16 19-27}	10	25	10	50

entity the cases of Kohler,¹¹ Kretzer *et al*,¹⁰ cases 1 and 4 of Cruveiller *et al*,¹⁵ Lipson and Hayes,¹⁷ Akl *et al*,¹⁴ Kim and Bootwell,²² Zizka *et al*,⁹ Greene *et al*,⁸ Lowry,²⁹ and Pfeiffer and Slavaykoff.⁶ The cases of Cherstvoy *et al*¹² and of Pinsky and DiGeorge²⁶ are closer to the classical Smith-Lemli-Opitz syndrome. If the lack of karyotype makes us doubt the earlier observation of Weber and Schwarz³, we think we can retain the case of Patterson *et al*²⁵ in spite of the lack of polydactyly; the phenotype is female whereas the karyotype is 46,XY, the severe dysmorphology is comparable, there is excessive skin around the neck, flexion contractures of the fingers, elbows, knees and hips, and Hirschsprung's disease. This last point deserves comment. Intestinal ganglionosis, responsible for Hirschsprung's disease and found in eight cases, is a very unusual finding in syndromes of multiple congenital abnormalities and appears to be very specific. The same is true for the persistence of Müllerian remnants^{11 13 25} (our cases 2, 3, and 6). Finally, a number of other anomalies can be mentioned including cysts of the mouth and tongue, particular histological lesions of the pancreas, and cataracts^{10 13} (our cases 1 and 8).

THE DIFFERENTIAL DIAGNOSIS

We question the 'new lethal syndrome' of Rutledge *et al*³⁰ described by Donnai *et al*.¹³ If most of the abnormalities are compatible with the pattern of malformations that we describe, others are not: agenesis of the biliary vesicle, microglossia, and findings from bone x rays determine a slightly different pattern of malformations. The authors recognise that if certain signs were also found in Kohler's case, others, such as severe mesomelic dwarfism, distinguish it totally.

Similarly, the C syndrome,³¹ Hall-Pallister syndrome,³² and the hydrolethalus syndrome are easily eliminated, since the acrodysgenital dwarfism syndrome described here lacks the signs specific to each of them, namely trigonocephaly for the C syndrome, hamartomas for the Hall-Pallister syndrome, and hydramnios and hydrocephalus for the hydrolethalus syndrome. In the same way, the absence of kidney and liver cysts excludes the diagnosis of Meckel's syndrome. However, in a commentary on the variability of the Smith-Lemli-Opitz syndrome, Lowry *et al*¹⁸ questioned whether in similar cases these features could not result from Meckel's syndrome. This seemed to him to be possible in view of the absence of renal lesions, or alternatively they could be a variant of the Smith-Lemli-Opitz syndrome. The lethal acrodysgenital dwarfism syndrome is an answer to their question.

Trisomy 13 is the only other possible differential diagnosis and in this case simple karyotype analysis must be performed systematically to exclude this.

GENETIC COUNSELLING

The familial observations concerning two sibs,^{6 11} and the parental consanguinity found in the case of Akl *et al*¹⁴ and our case 8, are arguments in favour of an autosomal recessive pattern of inheritance and indicate that caution is required in genetic counselling. Prenatal diagnosis would entail a decision on the chromosomal sex (fetal karyotype) and the appearance of the fetus on prenatal ultrasonography.

Conclusion

In spite of the resemblances and of the difficulties in classifying certain cases in one category or the other, we feel justified in proposing a new syndrome, lethal acrodysgenital dwarfism, which is different from the Smith-Lemli-Opitz syndrome, with the reservations imposed by the lack of information concerning the mutations responsible, which may or may not be allelic.

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Addendum

After this paper had been submitted for publication, a report appeared in the *American Journal of Medical Genetics* in which Cynthia Curry described 19 children with a syndrome called Smith-Lemli-Opitz type II. All the features described in the above report provide further evidence of the existence of a discrete phenotype, more severe than Smith-Lemli-Opitz syndrome and to be distinguished from it. Curry's observations are fully consistent with those described in our paper. For all these reasons it could be misleading to lump this entity together with the original SLO syndrome. Although, as outlined in the *American Journal of Medical Genetics* editorial comment, the possibility of allelic mutation cannot be excluded, it seems better, at least on clinical grounds, to distinguish two syndromes. Accordingly, and bearing in mind the main differential features in our cases, as well as in those of Curry and Donnai *et al*, we propose to name this syndrome the lethal acrodysgenital dwarfism syndrome.

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