Lethal short rib-polydactyly syndromes: further evidence for their overlapping in a continuous spectrum

Maria-Luisa Martínez-Frías, Eva Bermejo, Miguel Urioste, Héctor Huertas, Ignacio Arroyo

Abstract

We report two new unrelated infants with short rib-polydactyly syndrome (SRPS) whose clinical and radiological features overlap the four established forms of lethal SRPS, so that it is difficult to classify them into any one particular type. One of the babies had one of the most radiologically severe SRPS ever published. The patients presented here support the previously reported hypothesis that this group of disorders might be a continuous spectrum rather than separate entities.

(*J Med Genet* 1993;30:937-41)

The features of the established lethal forms of short rib-polydactyly dwarfism syndromes (SRPS)¹⁻⁴ overlap so much that it has become difficult to distinguish between them.⁵⁻⁸ Consequently, there is controversy as to whether these types are the result of point mutations at different loci, different alleles at a single locus, or variability in the expression of the same mutant gene.^{5,9}

We present two cases of SRPS that overlap all the previously described types. These cases were identified through the Spanish Collaborative Study of Congenital Malformations (ECEMC).¹⁰

Case reports

CASE 1

The female proband (fig 1, tables 1 and 2) was stillborn to a G2,P2, 33 year old mother and a 31 year old father. The parents were healthy and non-consanguineous. The family history was negative except for a distant relative with Down's syndrome.

The pregnancy was complicated by vaginal bleeding in the eighth month and the mother suffered from migraines. She was treated with antiemetics (during the first four months), alllstrenol (second and third months), aspirin (first and ninth months), propyphenazone and caffeine (first and third trimester), vitamin B (second month), and antibiotics (eighth month). She drank some beer at weekends. She had abdominal x rays in the eighth month, but there were no occupational exposures.

Delivery was by spontaneous breech presentation at 40 weeks of gestation. Birth weight was 3600 g (75th centile) and head circumference 39 cm (> 97th centile). The macerated infant had hydrops (fig 1A, table 1), a flat face, flat nasal bridge, cleft upper lip, malformed

ears, very short limbs, postaxial polydactyly, narrow chest, and a small, sexually ambiguous vaginal opening.

Radiological examination (fig 1B-D, table 2) showed frontal bossing, flat occiput, short cranial base (fig 1C), a marked shortening of the ribs and long tubular bones particularly in the mesomelic segment, small, rounded scapulae, small and flattened vertebral bodies (fig 1B), small iliac bones, and longitudinal metaphyseal spurs (fig 1D). There were premature ossification nuclei in the humeri and femora (fig 1B,D). In place of the tibia and fibula there was only one very short bone in each leg (fig 1D).

Necropsy and karyotype could not be performed.

CASE 2

This child (fig 2, tables 1 and 2), a female, was the second pregnancy of a G2,P2, 30 year old mother and a 33 year old father. They were healthy and non-consanguineous, even though three of the four grandparents came from the same small village. There was nothing remarkable in the family history except for a brother of the mother who had died shortly after birth of unknown cause.

The pregnancy of the proband was complicated by polyhydramnios, and the mother had mild morning sickness during the first two months. Fetal movements were first perceived at 4 months. The mother had taken mineral and multivitamin supplements from the fourth month to the end of pregnancy and occasionally aspirin. She had one beer and two cigarettes weekly, and one cup of coffee and a soft drink (cola) daily. There were no occupational exposures.

Breech delivery took place spontaneously at 28 weeks of gestation. The baby died two hours after birth. Her birth weight was 1220 g (75th to 90th centile). On physical examination, the infant had a narrow chest, short limbs, postaxial polydactyly of the right hand, and oedema (fig 2A, table 1).

Radiological examination (fig 2B,C, table 2) showed marked shortening of the long bones and ribs and widening of the metaphyseal area with longitudinal spurs (see fig 2D for histology), which were also evident in the ribs and pelvis. The pelvic bones were abnormally contoured. The vertebral bodies were small. The femora were bowed and the tibiae and fibulae were equally short. Corticomedullary differen-

ECEMC Coordinating Group and Departamento de Farmacología, Facultad de Medicina, Universidad Complutense, 28040 Madrid, Spain.
M L Martínez-Frías

ECEMC Coordinating Group, Facultad de Medicina, Universidad Complutense, Madrid, Spain.
E Bermejo

ECEMC Coordinating Group and Hospital Universitario San Carlos, Facultad de Medicina, Universidad Complutense, Madrid, Spain.
M Urioste

ECEMC Peripheric Group and Servicio de Pediatría, Hospital Gutiérrez Ortega, Valdepeñas, Ciudad Real, Spain.
H Huertas

ECEMC Peripheric Group and Servicio de Neonatología, Hospital San Pedro de Alcántara, Cáceres, Spain.
I Arroyo

Correspondence to Dr Martínez-Frías.

Received 30 March 1993.
Revised version accepted 8 June 1993.

Figure 1 Case 1. (A) Postmortem photograph. (B) Anteroposterior x ray. (C) Lateral radiograph. (D) Radiological examination of pelvis and lower limbs.

Table 1 Non-radiological diagnostic criteria for the four forms of SRPS and comparison with our cases.

	Non-Majewski SRPS				ECEMC cases	
	Saldino-Noonan (type I)	Verma-Naumoff (type III)	Beemer-Langer (type IV)	Majewski SRPS (type II)	1	2
External appearance						
Cleft upper lip	—	Pseudocleft	+	+	+	—
Preaxial polydactyly	—	—	1 case ¹¹	+	—	—
Postaxial polydactyly	+	+	+	+	+	+
Syndactyly	+	+	—	+	?	—
Omphalocele/umbilical hernia	—	—	+	—	—	—
Systemic abnormalities						
CNS						
Holoprosencephaly	—	—	+ ²¹²	1 case ¹³	?	—
Hydrocephalus	—	—	+ ^{11 13 14}	+ ²¹⁵	?	+/-*
NTD	—	—	+ ²¹⁶	+ ²¹⁶	?	—
Hypoplastic epiglottis	—	—	—	—	?	—
Urinary tract anomalies	+	+	+	+	?	+
Renal agenesis	+	—	—	—	?	—
Genital abnormalities	+	+	+	+	+	—
Other						
Polyhydramnios	+	+	+	+	?	+
Oligohydramnios	+	+	—	—	?	—
Inheritance	AR	AR	AR?	AR	?	—/sib
Consanguinity/affected sib	+	+	+	+	—	+
Normal karyotype	+	+	+	+	?	+
Sex ratio (M:F)	4:9	5:3	8:5	1:1	—	—
Sex					F	F

* Mild cerebral ventricular enlargement.

Table 2 Radiological diagnostic criteria for the four forms of SRPS and comparison with our cases.

	Non-Majewski SRPS				ECEMC cases	
	Saldino-Noonan (type I)	Verma-Naumoff (type III)	Beemer-Langer (type IV)	Majewski SRPS (type II)	1	2
Short cranial base	—	+	?	—	+	+
Macrocephaly	—	—	+	—	+	—
Flat occiput	+	+	?	—	+	—
High clavicles	—	—	+	—	+	—
Rounded scapulae	+	—	—	—	+	—
Vertebral anomalies	+	+	+	—	+	—*
Pelvic abnormalities	+	+	+	—	+	+
Abnormal contour	+	—	+	—	+	+
Flat acetabulum	+	+	—	—	—	—
Trident shaped	+	+	—	—	—	—
Tibiae shorter than fibulae	—	—	—	+	†	—
Ovoid tibia	—	—	—	+	?	—
Bowed femora	—	—	+	—	—	+
Good corticomedullary differentiation	—	+	+	+	?‡	?‡
Metaphyseal spurs	+	+	Min	Min	+	+
Longitudinal	+	+	—	—	+	+
Premature ossification nuclei	+	—	—	+	+	—

* Vertebral bodies were small, but the gestational age was 27 weeks.
† In place of the tibiae and fibulae there was only a very short bone.
‡ Corticomedullary demarcation was difficult to assess.

Figure 2 Case 2. (A) Clinical appearance. (B) Anteroposterior x ray. (C) Lateral radiograph. (D) Histological examination of the growth plate in long bones.

tiation was difficult to assess (fig 2B). The cranial base was shortened.

Necropsy showed mild dilatation of the cerebral lateral ventricles, hypoplastic lungs, VSD, and hepatic fibrosis. There were also glomerular and renal tubular cysts, existing multiple visceral microhaemorrhages, and hyaline membrane disease.

Chromosome study performed on cultured skin fibroblasts showed a normal female karyotype, 46,XX.

This couple had a normal child who had been born one year before the proband, but we are aware that, more recently, they have had another infant with the same clinical appearance as the proband, also diagnosed as having SRPS (J I Rodríguez, personal communication).

Discussion

It has become apparent that there is an important overlap in both the clinical and radiological findings of the different types of lethal SRPS,^{5,6,9,11} including the Majewski syndrome (type II SRPS), which had generally been considered to be easily distinguishable from the other types.¹⁷⁻¹⁹ In 1991, Yang *et al*¹² stated that the Beemer-Langer SR(P)S shows clinical and radiological characteristics that allow it to be distinguished from the others as type IV. However, Hennekam¹¹ considered that in some cases it is very difficult to distinguish Beemer-Langer SR(P)S from type II (Majewski). In a recent report⁸ we described two cases whose features overlapped all four types of lethal SRPS, and who also presented the most severe brain anomalies reported so far, such as anencephaly. One of the cases had an older sib who was also affected and these two sibs presented different clinical and radiological characteristics that were compatible with the Majewski type in one and with the non-Majewski SRPS type in the other; moreover, there was an older sib with anencephaly. Our conclusion was that, rather than representing new types of SRPS, these cases support the idea of a continuous spectrum which could include all the types of SRPS. The cases we describe here also support this conclusion since they have clinical and radiological features that overlap the four established types of SRPS; at least, we have been unable to classify them in any one of the existing types.

Case 1 showed radiological findings that seem to indicate one of the most extreme forms of lethal SRPS reported. She had a short cranial base, as is usually observed in SRPS type III, but she also had the flat occiput that has been recognised in types I and III. The rounded scapulae and vertebral anomalies together with pelvic abnormalities and the longitudinal metaphyseal spurs in this patient also make her condition compatible with SRPS type I or type III. Regarding the tibiae and fibulae, one of the two bones was absent bilaterally; it was impossible to be certain which one was missing, and the remaining one was very short. Absence of the tibia has been described recently by Sharma *et al*¹⁵ in a case

with manifestations of both the hydrolethalus syndrome and SRPS type II (Majewski), and, in 1983, Walley *et al*²⁰ reported non-ossified fibulae in a patient with the Majewski type of SRPS. On the other hand, the premature ossification of the proximal epiphyses of the humeri and femora are usually seen in type I and type II. The child also had a cleft upper lip as is observed in both types II and IV.

Case 2 also overlaps all the forms of SRPS. She had mild dilatation of the cerebral lateral ventricles (which is compatible with SRPS types II and IV), a short cranial base (seen in type III), pelvic abnormalities, non-ovoid tibiae the same length as her fibulae (which would favour types I, III, or IV), femoral bowing (type IV), and longitudinal metaphyseal spurs (which supports a diagnosis of types I or III). The absence of vertebral anomalies is compatible with SRPS type II. This case had hepatic fibrosis and renal cysts, as has been observed in some other cases of SRPS, including the non-lethal types such as Jeune syndrome and Ellis-van Creveld syndrome. Nevertheless, the clinical and radiological findings make the differential diagnosis of these non-lethal types easy.

These two cases once again show that it is very difficult to categorise some patients into only one of the four established types of SRPS, because they present some of the manifestations that are considered to be diagnostic criteria of more than one form. These findings support the existing hypothesis^{5,6,8,20,21} of there being a single spectrum of SRPS that would include all the known types.

This work was supported in part by a grant from the Dirección General de Salud Pública, Ministerio de Sanidad y Consumo of Spain. We also thank C F Warren for her linguistic assistance.

- 1 Saldino RM, Noonan CD. Severe thoracic dystrophy with striking micromelia, abnormal osseous development, including the spine, and multiple visceral anomalies. *AJR* 1972;114:257-63.
- 2 Majewski F, Pfeiffer RA, Lenz W, Müller R, Feil G, Seiler R. Polysyndaktylie, verkürzte gliedmassen und genitalfehlbindungen: Kennzeichen eines selbständigen syndroms? *Z Kinderheilkd* 1971;111:118-38.
- 3 Verma IC, Bhargava S, Agarwal S. An autosomal recessive form of lethal chondrodystrophy with severe thoracic narrowing, rhizo-acromelic type of micromelia, polydactyly and genital anomalies. *Birth Defects* 1975;11(6):167-74.
- 4 Beemer FA, Langer LO, Klep-de Pater JM, *et al*. A new short rib syndrome: report of two new cases. *Am J Med Genet* 1983;14:115-23.
- 5 Sillence DO. Invited editorial comment: non-Majewski short rib-polydactyly syndrome. *Am J Med Genet* 1980;7:223-9.
- 6 Bernstein R, Isdale J, Pinto M, Du Toit Zaaijman J, Jenkins T. Short rib-polydactyly syndrome: a single or heterogeneous entity? A re-evaluation prompted by four new cases. *J Med Genet* 1985;22:46-53.
- 7 Rodríguez JL, Gamallo C, Cuevas J, Pastor I, Collado F. Síndrome de costilla corta-polidactilia con malformaciones viscerales múltiples. *An Esp Pediatr* 1980;13:805-10.
- 8 Martínez-Frías ML, Bermejo E, Urioste M, Egúés J, López Soler JA. Short rib-polydactyly syndrome (SRPS) with anencephaly and other central nervous system anomalies: a new type of SRPS or a more severe expression of a known SRPS entity? *Am J Med Genet* (in press).
- 9 Cherstvoy ED, Lurie IW, Shved IA, Lazjuk GI, Ostrowskaya TI, Usojev SS. Difficulties in classification of the short rib-polydactyly syndromes. *Eur J Pediatr* 1980;133:57-61.
- 10 Martínez-Frías ML, Frías JL, Rodríguez-Pinilla E, *et al*. Value of clinical analysis in epidemiological research: the Spanish Registry experience. *Am J Med Genet* 1991;41:192-5.

- 11 Hennekam RCM. Short rib syndrome-Beemer type in sibs. *Am J Med Genet* 1991;40:230-3.
- 12 Yang SS, Roth JA, Langer LO Jr. Short rib syndrome Beemer-Langer type with polydactyly: a multiple congenital anomalies syndrome. *Am J Med Genet* 1991;39:243-6.
- 13 Nivelon-Chevalier A, Halfon D, Mabile JP. Chondrodysplasie letale à cotes courtes type Majewski. Diagnostic in utero. *Pediatric* 1982;6:453-9.
- 14 Lin AE, Doshi N, Flom L, Tenenholz B, Filkins KL. Beemer-Langer syndrome with manifestations of an orofacioidigital syndrome. *Am J Med Genet* 1991;39:247-51.
- 15 Sharma AK, Phadke S, Chandra K, et al. Overlap between Majewski and hydroletharus syndromes: a report of two cases. *Am J Med Genet* 1992;43:949-53.
- 16 Tsai YC, Chang JM, Changchien CC, et al. Unusual short rib-polydactyly syndrome. *Am J Med Genet* 1992;44:31-6.
- 17 Spranger J, Grimm B, Weller M, Weissenbacher G, Herrmann J, Gilbert E, Krepler R. Short rib-polydactyly (SRP) syndromes, types Majewski and Saldino Noonan. *Z Kinderheilkd* 1974;116:73-94.
- 18 Jones KL. *Smith's recognizable patterns of human malformations*. Philadelphia: Saunders, 1989.
- 19 Gorlin RJ, Cohen MM, Levin LS. *Syndromes of the head and neck*. New York: Oxford University Press, 1990:218-21.
- 20 Walley VM, Coates CF, Gilbert JJ, Valentine GH, Davies EM. Brief clinical report: short rib-polydactyly syndrome, Majewski type. *Am J Med Genet* 1983;14:445-52.
- 21 Bidot-López P, Ablow RC, Ogden JA, Mahoney MJ. A case of short rib polydactyly. *Pediatrics* 1978;61:427-32.