Wiedemann-Rautenstrauch neonatal progeroid syndrome: report of three new patients

Humberto Arboleda, Luis Quintero, Emilio Yunis

Abstract

Wiedemann-Rautenstrauch (WR) syndrome is known as a neonatal progeroid syndrome, with only few published case reports. We describe three additional patients, two of them sibs, showing the clinical features of WR syndrome. Skeletal abnormalities are reported and assays of hormones and lipids are presented in one patient. Disturbance in bone maturation and lipid and hormone metabolism appear to be involved in this neonatal progeroid syndrome.

(*J Med Genet* 1997;**34**:433–437)

Keywords: neonatal progeroid syndrome; Wiedemann-Rautenstrauch syndrome; autosomal recessive disorder; bone maturation-lipid-hormone

Instituto de Genética, Universidad Nacional de Colombia, Santafé de Bogotá, Colombia
H Arboleda
L Quintero
E Yunis

Correspondence to:
Dr Arboleda.

Received 15 August 1996
Revised version accepted for publication 4 December 1996

Case reports

CASE 1

Case 1 was the first daughter of a healthy, unrelated 23 year old mother and 28 year old father. Delivery was normal at 30 weeks of gestation. Both the paternal grandparents and great grandparents were cousins; three of the father's phenotypically normal sibs (two brothers and one sister) died from unknown causes (fig 1). The patient's brother (case 2) showed a similar clinical picture. Table 1 shows the clinical features of the patient.

Physical examination at birth showed apparent macrocephaly with frontal and biparietal bossing, large fontanelles and wide sutures, sparse scalp hair, and prominent scalp veins; hypoplasia of the facial bones, small and beak shaped nose; upward slanting palpebral fissures; hypertelorism, sparse eyebrows and eyelashes; and very low set, small, dysplastic ears with absent lobes. The mouth, with one incisor, was small and retracted, with a small linear dimple below the lower lip; the chin was sharp and pointed. All these features conferred a progeroid appearance to the patient (fig 2A, B).

The thorax showed a broad base and there were no cardiac murmurs. The external genitalia were of a normal female. The limbs were slender with flexed articulations and the hands and feet appeared large. There was generalised deficient subcutaneous fat, with the exception of excessive fat on the buttocks. The skin was thin, dry, and shiny. She was hypertonic and died at 2 weeks of an undetermined cause.

Radiographs showed craniofacial disproportion and severe dysostosis. The ilia were hypoplastic with a trident configuration of the acetabula, the metaphyseal end plates of the long bones, mainly the femora and tibiae, were irregular, and the diaphyses were thin (fig 3A, table 2). Chromosome study showed a normal karyotype, 46,XX.

Table 1 Clinical features in Wiedemann-Rautenstrauch syndrome. Comparison of the features of our patients with previously reported cases

	Wiedemann[2]		*Rautenstrauch et al*[1]		*Devos et al*[3]	*Rudin et al*[5]	*Obregon et al*[6]	*Castiñeyra et al*[7]	*Bitoun et al*[8]	*Leroy et al*[9]		*Present report*		
												1	*2*	*3*
Birth weight (g)	2200	2550	2380	2110	2110	2500	2300	1450	1950	2150	1300	1500	1700	2120
Birth length (cm)	45	49	48	47	48	45	NR	47	42	45	34	43	45	47
Head circumference (cm)	NR	NR	32.5	32	33	34	36	31	35	31	28.5	29	30	NR
Sex	M	M	F	F	F	M	F	F	M	F	M	F	M	M
Consanguinity	–	–	–	–	+	–	–	–	+	–	–	–	–	–
Senile aspect	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pseudohydrocephalus	+	+	+	+	+	+	+	+	+	+	NR	+	+	+
Wide open sutures	+	+	+	+	+	+	+	+	+	NR	NR	+	+	+
Widened fontanelles	+	+	+?	+	+	+?	NR	+	+	+	+	+	+	+
Sparse scalp hair	+	+	+	+	+	+	+	+	–	–	NR	+	+	+
Prominent scalp veins	+	+	+	+	+	+	+	+	+	+	NR	+	+	+
Hypoplasia of the facial bones	+	+	+	+	+	+	+	+	+	NR	NR	+	+	+
Low set ears	+	+	+	+	+	+	+	NR	+	+	NR	+	+	+
Beak shaped nose	+	+	+	+	+	+	+	+	–	+?	NR	+	+	+
Intraocular abnormalities	–	–	–	–	–	–	–	NR	–	–	–	–	–	–
Dentition present at birth	2	4	2	2	1	4	2	2	–	–	–	1	4	4
Slender limbs	+	+	+	+	+	+	+	+	+	–	–	+	+	+
Large hands and feet with long fingers and toes	+	+	+?	+	+	+	+	+	NR	+	+	+	+	+
Hypertonia	NR	NR	NR	NR	NR	NR	NR	NR	–	–	NR	+	+	+
Prepucial hypoplasia	NR	NR				NR			–	NR	NR		+	+
Large penis	+	+				NR			–	NR	NR		–	–
Cryptorchidism	NR	NR				+			–	NR	NR		+	+
Gynaecomastia	NR	NR	NR	NR	NR	NR	NR	NR	–	–	NR	–	+	–
Fat accumulation in buttocks	+	+	NR	NR	+	+	+	+	–	–	NR	+	–	NR

NR: not reported.

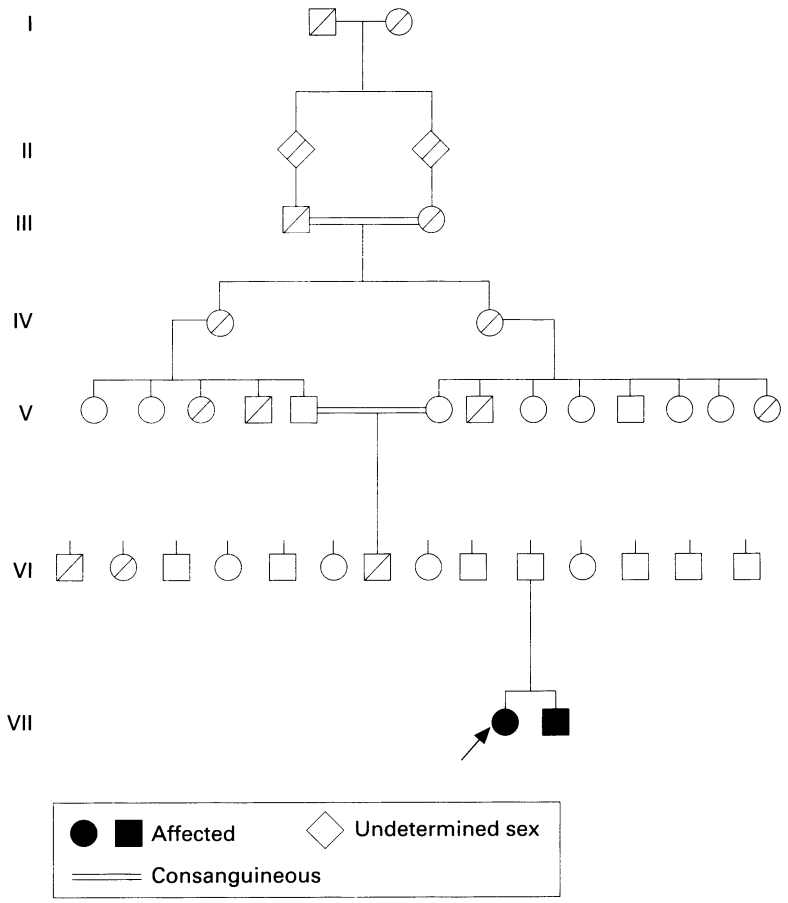

Figure 1 Family pedigree of cases 1 and 2.

CASE 2

Case 2 was the brother of patient 1 and was the product of the second pregnancy, three years after the first. Pregnancy was normal and vaginal delivery was at term. Table 1 shows the clinical features of this patient.

A progeroid appearance was evident with frontal and parietal bossing, wide sutures and large fontanelles, almost total alopecia, and small capillary haemangiomas in the metopic, interparietal, and occipital regions. Prominent scalp veins were present (fig 2C). There was craniofacial disproportion with small facial bones, depressed frontonasal angle, ocular proptosis, small, beak shaped nose, small and low set ears with a normal configuration, a downward slanting mouth with four teeth, two yellowish maxillary and two mandibular incisors, and a V shaped palate. There was evident gynaecomastia without milk secretion, a short prepuce, and bilateral cryptorchidism.

The extremities appeared thin, with long hands and feet (fig 2D), stiff articulations, and prominent muscle mass and venous circulation. In general, the skin was thin and hyperaemic, with deficient subcutaneous fat. The finger and toenails were normal.

Ophthalmic examination showed normal anterior poles, clear lens and vitreous, and hypopigmented fundi. Neurologically he was hypertonic and his cry was weak.

Results of lipid determination are shown in table 3. Hormone assays showed high levels of prolactin (140 ng/ml, normal values (NV) <15 ng/ml), testosterone (2.4 ng/ml, NV <0.1 ng/ml), oestradiol (107 pg/ml, NV 3-10 pg/ml), and T4 (19.3 µg/100 ml, NV 7.3-15 µg/100 ml). TSH analysis gave results within normal limits (0.65 µIU/ml, NV 0.5-5 µIU/ml); T3 assay was not reported. Chromosome study showed a normal karyotype, 46,XY.

Failure to thrive was evident one month later and the same clinical features were present at 6

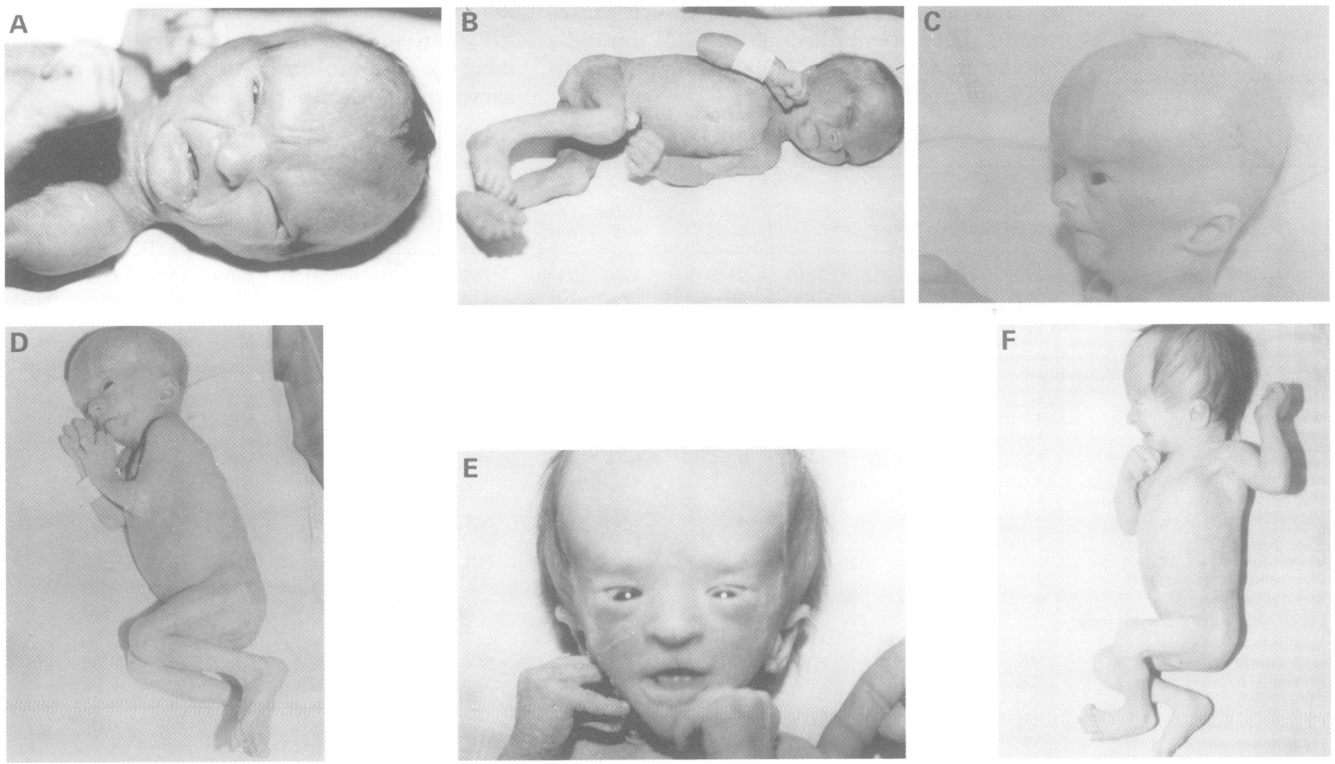

Figure 2 Photographs of the three patients, at birth (case 1), 5 months (case 2), and 8 days after birth (case 3). (A, B) Case 1. (C, D) Case 2. (E, F) Case 3.

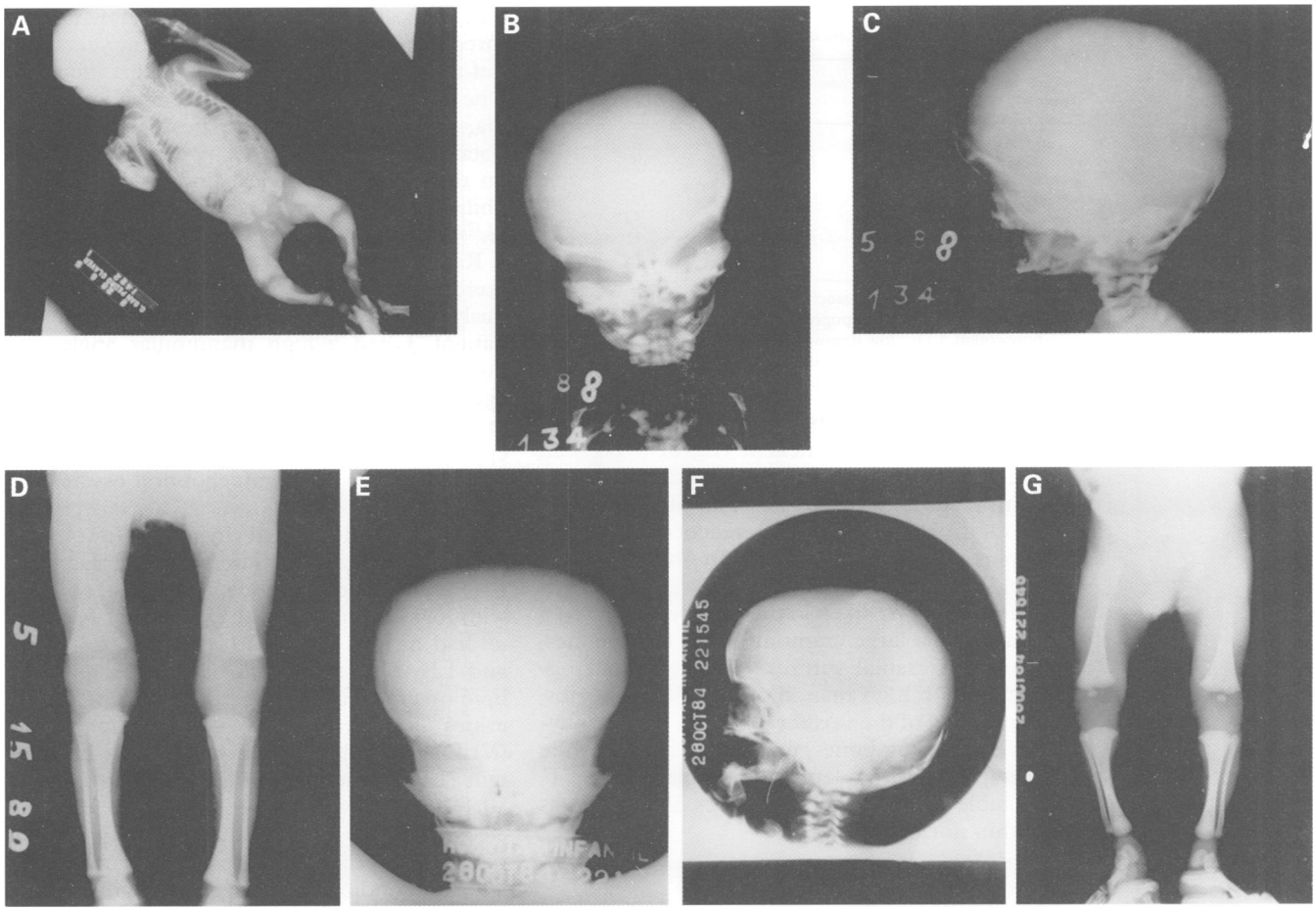

Figure 3 X rays of the three patients, at birth (case 1), 5 months (case 2), and 8 days after birth (case 3). (A) Case 1. (B, C, D) Case 2. (E, F, G) Case 3.

months of age with global hypotrophy and slow psychomotor development. There was no accumulation of adipous tissue in the lumbosacral area.

Radiographs showed craniofacial disproportion, large sutures and fontanelles with evident severe dysostosis, frontal and parietal bossing, elongated orbits, global hypoplasia of the facial bones, and thin long bones with enlarged metaphyseal end plates in the femora and tibiae (fig 3B, C, D, table 2). At the age of 6 months, bone age was 3 months; by then the patient was in hospital with leucoplastic keratitis and pneumonia which led to his death.

CASE 3

This male was the second child of healthy, young, unrelated parents (mother 21 and father 25 years old); pregnancy and delivery were normal. His older brother is healthy.

Physical examination at 8 days showed (table 1): apparent macrocephaly with frontal and parietal bossing, wide sutures and fontanelles, alopecia, and prominent scalp veins. The face appeared progeroid and triangular with a depressed nasal bridge, small, beak shaped nose with thin skin, upward slanting palpebral fissures with epicanthic folds, prominent lower eyelids, blue sclerae, and alopecia of the eyebrows and eyelashes. He had right sided esotropia, low set ears with square lobes, a long philtrum, thin lips, a pointed chin, and a high palate (table 1). There were four natal teeth, lost during the first week of life (fig 2E).

The neck was short with redundant skinfolds and the chest was short and showed a broad base without cardiac murmurs or abdominal visceromegaly. There was gynaecomastia, hypoplastic prepuce, and cryptorchidism. The limbs were thin with enlarged and rigid articu-

Table 2 Radiographic findings in Wiedemann-Rautenstrauch syndrome. Comparison of 13 patients

	Wiedemann[2]		*Rautenstrauch et al*[1]		*Devos et al*[3]	*Rudin et al*[5]	*Obregon et al*[6]	*Bitoun et al*[8]	*Leroy et al*[9]		*Present report*		
Patient No	1	2	1	2					1	2	1	2	3
Large skull	+	+	+	+	+	+	+	+	−	−	+	+	+
Unossified skull bones					+			+	+	+	+	+	+
Small facial bones	+	+	+	+		+	+	+			+	+	+
Wide cranial sutures	+	+	+	+		+	+	+			+	+	+
Partly unossified atlas						+	+					+	+
Thin ribs							+	−	+	+	+	+	+
Hypoplasia of vertebral bodies							+	−	+	+	+		+
Abnormal iliac bones						+	+	−			+		+
Trident configuration of the acetabula						+	+	−			+		+
Unossified ischia						+	+	−			+		+
Irregular end plates of the metaphyses						+	+	−	+	+	+		−

Table 3 Comparison of lipids in three patients with Wiedemann-Rautenstrauch syndrome

	Rautenstrauch et al[1]	Rudin et al[5]	Present report
Patient*	2		2
Age (y)	4	0	0
Cholesterol	N	N	
Triglycerides		H	
HDL	N	N	L(7.4)†
VLDL	N	H	H(89.3)†
LDL	N	L	L(3.3)†

* Patients 2 of Rautenstrauch *et al*[1] and present report.
HDL: high density lipoprotein, VLDL: very low density lipoprotein, LDL: low density lipoprotein.
N: normal range, H: high range, L: low ranges.
† Percentage by electrophoresis.

lations and the hands and feet were large with arachnodactyly and flexion (fig 2F). He had rocker bottom feet. The skin was dry, thin, and shiny with generalised absence of subcutaneous fat. He had normal reactions but was hypertonic. Chromosome study showed a normal karyotype, 46,XY.

Radiographs taken in the first week showed a skull with a large cranium, small facial bones, and wide cranial sutures. There was micrognathia with high mandibular angles, thin ribs, hypoplasia of the vertebral bodies, thin diaphyses of the long bones, mainly the fibulae, wide metaphyses of the femora and tibiae (fig 3E, F, G, table 2), and small iliac bones. Bone age was within normal limits.

Discussion

Wiedemann-Rautenstrauch syndrome is recognised as a neonatal progeroid syndrome. Ten cases have been reported so far,[1-8] and another two patients were reported at a clinical genetics meeting.[9]

This syndrome was delineated as a new progeroid syndrome by Wiedemann[2] based on two personal observations and two sisters reported by Rautenstrauch and Snigula.[1] The major physical features remain unchanged in survivors.[10 11] Evidence for an autosomal recessive pattern of inheritance has been presented in four reports,[1 3 7 8] with possibilities of prenatal diagnosis by ultrasound.[8]

We describe three additional patients, two of them sibs, providing further evidence for this pattern of inheritance. The striking resemblance to the previously reported children with the Wiedemann-Rautenstrauch syndrome is obvious in our three patients.

Patients with this syndrome can be recognised at birth because of a wide spectrum of abnormalities (table 1), among which are short stature, failure to thrive, progeroid appearance, apparent macrocephaly with frontal and parietal bossing, wide fontanelles and sutures, prominent scalp veins, hypoplasia of the facial bones, sparse scalp hair, eyebrows, and eyelashes, and generalised lipoatrophy. Most patients showed neonatal teeth, which were lost early. In one patient we found gynaecomastia without milk secretion; case 2 and case 3 had cryptorchidism and short prepucial folds.

The majority of these patients die during the first days or months after birth. Two of our patients survived for two and six months. The date of death of the third is not known. Only three patients have survived for some years,[6 8 11] but the other cases have had a short life span. One of our patients died of bronchopneumonia. Because no pathological details were obtained in these patients, we cannot comment on the neuropathological findings of sudanophilic leucodystrophy reported by Martin *et al.*[12]

Radiographs of our three patients showed skeletal abnormalities that have been previously described[6] (table 2). In addition, our patient 3 had a high mandibular angle and bone age in agreement with his chronological age. Moreover, it appeared that dysostosis involved the metaphyseal area more than the epiphyseal. Nevertheless we think that membranous rather than endochondral ossification is involved.

One case developed hypothyroidism.[8] At birth our patient 2 showed hyperprolactinaemia and high testosterone, oestradiol, and T4, with low normal TSH; the patient of Rudin *et al*[5] had normal levels of HGH, cortisol, FSH, and LH. However, both had disturbances in lipid metabolism, with increased serum triglycerides and very low density lipoprotein (VLDL) and diminished low density lipoprotein (LDL) fraction in the former, and raised VLDL and low levels of LDL and HDL in electrophoretic assays in the second. In another patient[1] lipoproteins were in the normal range. The lipid findings in these patients are summarised in table 3. Deficient biosynthesis of decorin has been reported, although this is a non-specific and probably secondary phenomenon.[9] As in the other previously published cases, peripheral lymphocyte chromosomes were normal in number and structure in our patients.

The aetiology of Wiedemann-Rautenstrauch syndrome is still unclear; it has been stated that it is not a malformation syndrome, but a disorder that involves mesenchymal tissue, mainly subcutaneous fat.[3] Our findings implicate a disturbance in the mechanism of bone maturation as well as lipid and hormone metabolism.

1 Rautenstrauch T, Snigula F. Progeria: a cell culture study and clinical report of familial incidence. *Eur J Pediatr* 1977;**124**:101-11.
2 Wiedemann HR. An unidentified neonatal progeroid syndrome: follow-up report. *Eur J Pediatr* 1979;**130**:65-70.
3 Devos EA, Leroy JG, Fryns JP, Van den Berghe H. The Wiedemann-Rautenstrauch or neonatal progeroid syndrome. Report of a patient with consanguinous parents. *Eur J Pediatr* 1981;**136**:245-8.
4 Ohashi H, Eguchi T, Kajii T. Neonatal progeroid syndrome: report of a Japanese infant. *Jpn J Hum Genet* 1987;**32**:253.
5 Rudin C, Thommen L, Fliegel C, Steinmann B, Buhler U. The neonatal pseudo-hydrocephalic progeroid syndrome (Wiedemann-Rautenstrauch). Report of a new patient and review of the literature. *Eur J Pediatr* 1988;**147**:433-8.
6 Obregon MG, Bergami GL, Giannotti A, *et al.* Radiographic findings in Wiedemann-Rautenstrauch syndrome. *Pediatr Radiol* 1992;**22**:474-5.
7 Castiñeyra G, Panal M, Lopez H, Goldschmidt E, Sanchez JM. Two sibs with Wiedemann-Rautenstrauch syndrome: possibilities of prenatal diagnosis by ultrasound. *J Med Genet* 1992;**29**:434-6.
8 Bitoun P, Lachassine E, Sellier N, Sauvion S, Gaudelus J. The Wiedemann-Rautenstrauch neonatal progeroid syndrome: a case report and review of the literature. *Clin Dysmorphol* 1995;**4**:239-45.
9 Leroy JG, Beavan LA, Quentin-Hoffman E, Kresse H. Deficient decorin biosynthesis in the neonatal progeroid syndrome. In: Bartsocas CS, Beighton P, eds. *Dysmorphol-*

ogy and genetics of cardiovascular disorders. Chapter 24. Athens: HTA Medical Publication, 1994:166-76.
10 Snigula F, Rautenstrauch T. A new neonatal progeroid syndrome. *Eur J Pediatr* 1981;**136**:325.
11 Rautenstrauch T, Snigula F, Wiedemann HR. Neonatales progeroides Syndrom (Wiedemann-Rautenstrauch). Eine follow-up-Studie. *Klin Padiatr* 1994;**206**:440-3.
12 Martin JJ, Ceuterick CM, Leroy JG, Devos EA, Roelens JG. The Wiedemann-Rautenstrauch or neonatal progeroid syndrome. Neuropathological study of a case. *Neuropediatrics* 1984;**15**:43-8.