Eur J Pediatr (1985) 144:348–354

European Journal of
Pediatrics

De Barsy syndrome—an autosomal recessive, progeroid syndrome*

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Abstract. We report two families with seven siblings with de Barsy syndrome. Characteristic features include severe mental retardation, hypermobility with athetoid movements, grimacing, muscular hypotonia, laxity of small joints and brisk deep tendon reflexes, progeroid aspect with cutis laxa, atrophy of skin with hyperpigmentation, isolated depigmentations, reduction of subcutaneous fatty tissue, translucent vein pattern, short stature, frontal bossing in the young child, large prominent ears with dysplastic helices and corneal clouding or cataracts. The syndrome probably has autosomal recessive inheritance.

Key words: De Barsy syndrome – Progeroid syndromes – Cutis laxa

Introduction

In 1968 de Barsy et al. [1] reported on a girl with "dwarfism, oligophrenia and degeneration of the elastic tissue in skin and cornea". This girl had a characteristic face and athetoid movements. In the following years eight further similar observations were reported [2–5, 7]. Riebel [6] was the first to identify the syndrome in sibs (cases 1 and 2 in this report). This family has recently been re-evaluated by one of us. Two additional affected siblings will be described in this paper. Furthermore we present a family from Western Australia with three affected siblings.

Case reports

Family 1. The healthy Turkish parents were without consanguinity. The father and mother were 44 and 40 years old respectively, at the birth of the last affected child. A half-brother and half-sister of the paternal grandmother were said to be phenotypically abnormal and mentally retarded. After the birth of the oldest child (case 1), three siblings were born in Turkey. They were said to have normal birth data and normal appearances, but died from unknown illnesses in early infancy. The mother gave birth to seven additional children, three of whom were affected.

Case 1: K.Y., male was born 1.11.1963. Pregnancy and delivery were normal. Birth measurements reportedly were normal. Corneal opacities developed at the age of 2 months. Psychomotor retardation was noted by 5 months. At the age of 4 years, microcephaly was diagnosed. At this age the child was unable to walk without support and had no perception of its surroundings. At age of $5^{10}/_{12}$ years the child was admitted to the Department of Pediatrics, University of Berlin: his length was 93 cm (14 cm below the 3rd percentile), weight 12 kg (25th percentile in relation to length) and head circumference 43 cm (4 cm below the 3rd percentile). The boy presented with oligophrenia, athetoid movements, ataxic gait, muscular hypotonia, and genua recurvata. Pneumoencephalography revealed marked dilatation of the fourth ventricle, large cisterna magna and hypoplastic cerebellum. Cutis laxa and atrophoderma were noted, as well as corneal opacities bilaterally. Biopsy of the liver revealed no signs of storage diseases. All laboratory investigations yielded normal results, including growth hormone and insulin tests.

The child was re-admitted at the age of $11^{3}/_{12}$ years when his height was 114 cm (27 cm below the 3rd percentile), weight 17.2 kg (1 kg below the 3rd percentile in relation to height), head circumference 46 cm (5 cm below the 3rd percentile). He had a progeroid facial appearance (marked nasolabial folds, thin lips, reduction of the subcutaneous fatty tissue), bilateral corneal clouding, large dysplastic prominent ears, frontal bossing. The other findings were unchanged. The last examination of the age of 20 years showed: height 142 cm (20 cm below the 3rd percentile), weight 29.4 kg (25th percentile in relation to height), head circumference 49 cm (5 cm below the 3rd percentile). He also had a narrow face, thick black curly hair, generalised hypertrichosis, synophrys, hairy tip of a prominent nose, discrete corneal clouding bilaterally (incomplete surgical removal of annular concentric pannus in Bowman's membrane of the cornea), normal sclerae, large prominent dysplastic ears, thin lips, normal teeth, microgenia (Fig. 1a); hyperextensibility of finger and toe joints, the motility of the large joints being rather restricted. His nails were normal. There was thin, atrophic, wrinkled inelastic skin, especially at the extensor-sides of the large and small joints (Fig. 2a). There was a general reduction of subcutaneous fat, transluent vein pattern, hyperpigmentation and isolated depigmentations of the trunk. Athetoid movements, grimacing, muscular hypotonia, generalised hyperreflexia, severe mental retardation and no development of speech were observed.

Case 2: B.Y., female was born 13.9.1973 after a normal pregnancy and birth. Her birth weight was 3650 g, length 53 cm, head circumference 33 cm. She was an in-patient at the age of 10 months when her length was 73 cm (75th percentile), weight 7.7 kg (5th percentile), head circumference 43 cm (3rd

* Dedicated to Prof. H.-R. Wiedemann on the occasion of his 70th birthday

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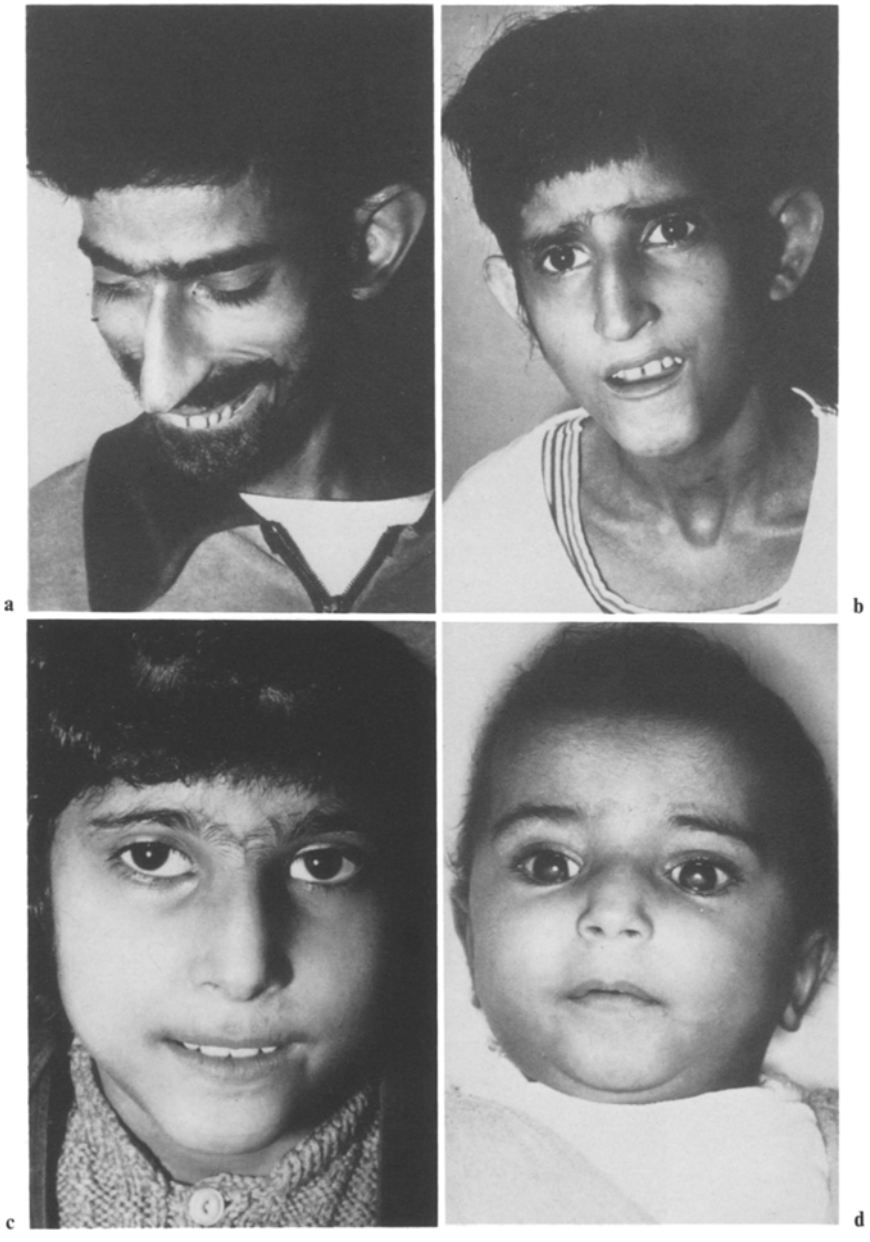

Fig. 1. a Case 1, 20 years old. **b** Case 2, $9^{9}/_{12}$ years old. **c** Case 3, $7^{5}/_{12}$ years old. **d** Case 4, 6 months old

percentile). Progeroid facies, lax and dry skin, reduction of subcutaneous fat, bilateral corneal opacities, frontal bossing, dysplastic prominent ears, thin upper lip, muscular hypotonia of lower and hypertonia of upper extremities, brisk tendon reflexes were present. The last examination was at $9^{9}/_{12}$ years when her length was 134 cm (25th percentile), weight 29.5 kg (25th percentile), head circumference 46 cm (1 cm below the 3rd percentile). She had a narrow face, black, curly hair, generalised hypertrichosis, synophryns, prominent nose, no corneal clouding (post-operative), normal sclerae, large prominent dysplastic ears, thin lips and small mouth (Fig. 1b), normal teeth, marked hyperextensibility of the small joints, the larger joints partially being fixed. The hyperpigmented skin was atrophic and inelastic on the extensor surfaces of the joints (Fig. 2b). There was a reduction of subcutaneous fat, prominent translucent veins and isolated leukoderma of the trunk. Athetoid movements, muscular hypotonia, brisk deep tendon reflexes, severe mental retardation and no speech were observed.

Case 3: H. Y., female was born normally on 16. 11. 1976 after a normal pregnancy. Measurements of the newborn were reported to be normal. Clinical investigation at the age of $7^{5}/_{12}$ years showed: height 111 cm (4 cm below the 3rd percentile), weight 17.7 kg (25th percentile in relation to length), head circumference 47.5 cm (3rd percentile). She had a progeroid facies, thick black hair, generalised hypertrichosis, synophryns, slightly hooked nose, no corneal clouding (postoperative), normal sclerae, large dysplastic prominent ears, thin lips (Fig. 1c) and normal teeth. There were hyperextensible small joints with normal mobility of the large joints. The nails were normal. The skin was atrophic, wrinkled, thin and hyperpigmented, especially over the regions of the joints (Fig. 2c) with isolated depigmentations. There was general hypermobility and hypotonia of muscles with increased reflexes. Some delay of mental development was noticed with nearly normal speech.

Case 4: H. Y., male was born 29. 1. 1982. Pregnancy and birth were normal. The birth weight was 4250 g, length 55 cm, head

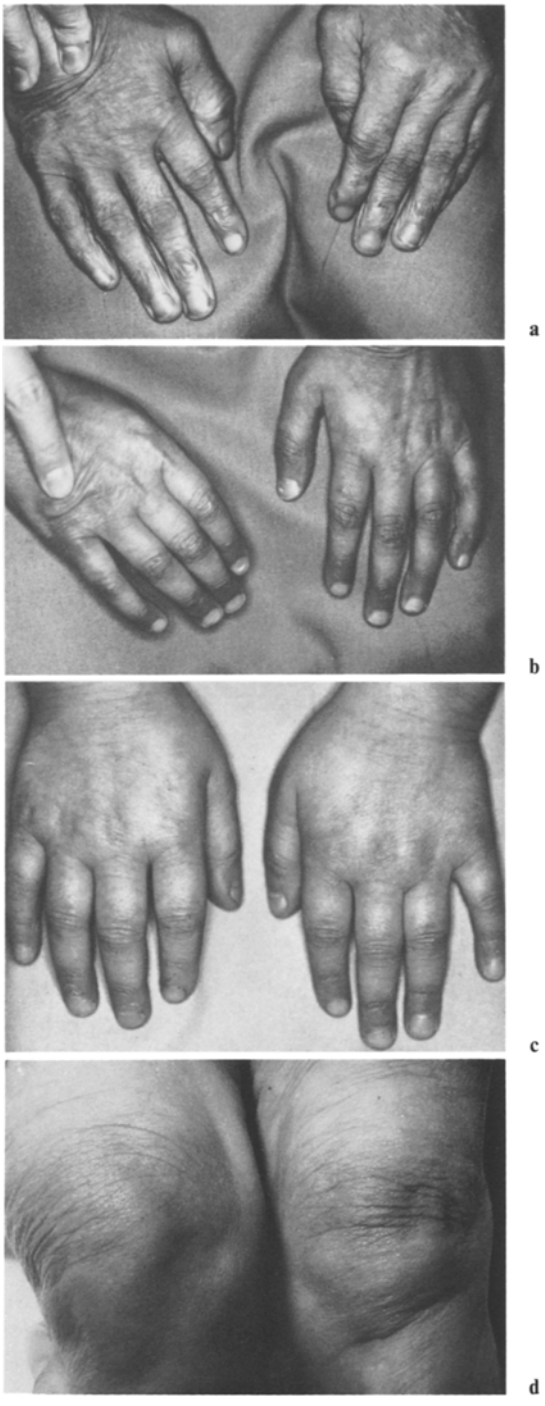

Fig. 2a–d. Patients as in Fig. 1a–d with wrinkled, hyperelastic, atrophic skin on the extensor surfaces of the joints

circumference 35 cm. Examination at the age of 6 months showed: length 69 cm (97th percentile), weight 7.5 kg (50th percentile), head circumference 43 cm (50th percentile). There were synophryns, prominent nose, band-like corneal clouding bilaterally (Fig. 3), normal sclerae, large dysplastic prominent ears and microgenia (Fig. 1d). Hyperflexibility of the small joints and normal mobility of the large joints was observed. There was atrophy of the skin, especially over the extensor surfaces of the large joints, where it was wrinkled and inelastic (Fig. 2d). Except in these areas the skin was hyperpigmented. Subcutaneous fat was reduced and there were

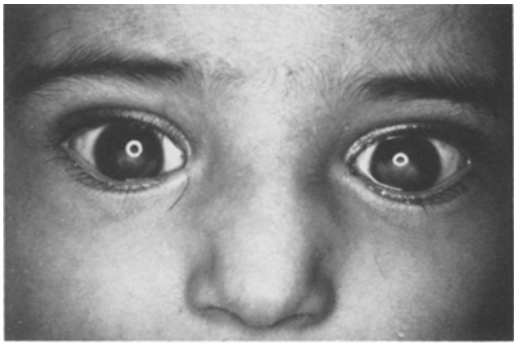

Fig. 3. Band-like corenal opacities (case 4)

Fig. 4 (Cases 5 and 6 at 6 years and 4 years). Note prominent forehead, apparently large skull, flexed fingers and elbow and knee joints in both sibs

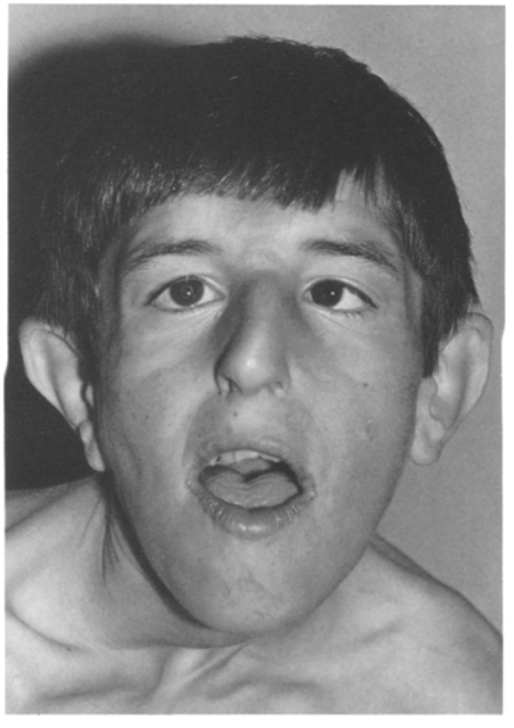

Fig. 5. Case 5 at age 13 years. Note microcephaly, large ears with poor modelling, antimongoloid slanting of palpebral fissures, convergent strabismus and right-sided cataract

Fig. 6. Case 5 at age 13 years: note reduced subcutaneous fat, pectus excavatum and grimacing

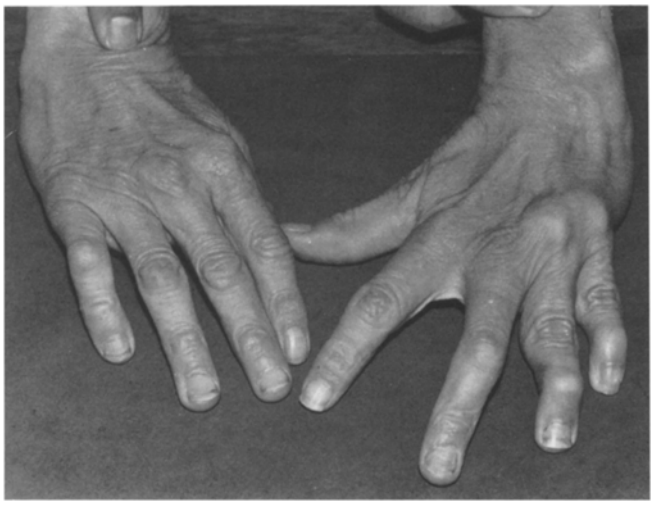

Fig. 7. Hands of case 5 with wrinkled skin and brachymetacarpia 4/5 on the left

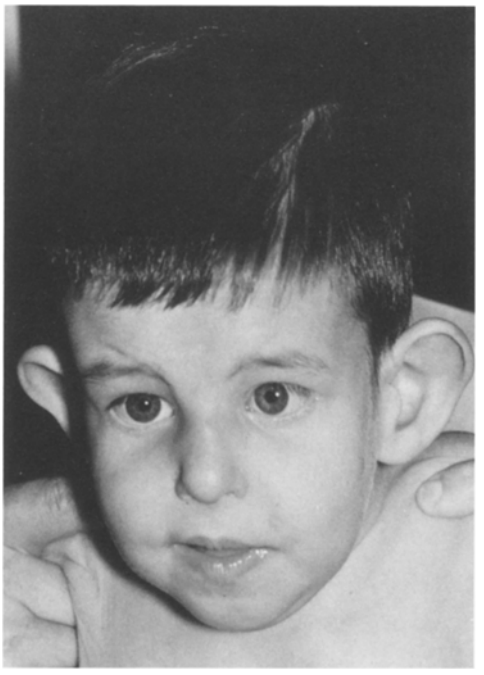

Fig. 8. Face of case 6 at age $3^1/_2$ years. Note high forehead, large ears, convergent strabismus and small mouth

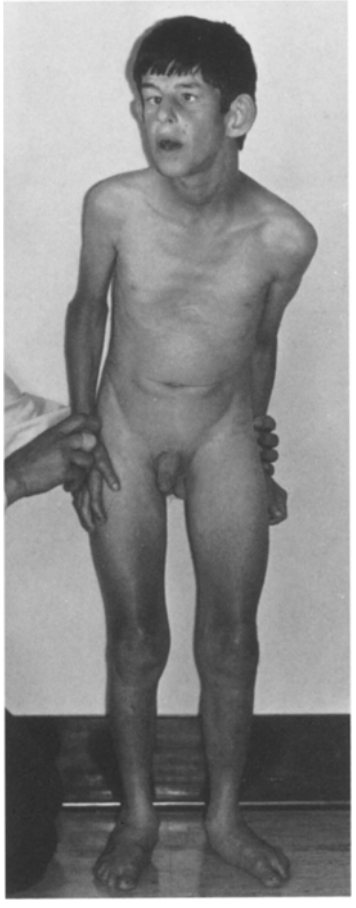

Fig. 9. Case 6 at age 11 years. Note progeroid aspect, reduced subcutaneous fat as well as growth retardation and microcephaly

many translucent small blood vessels. There was mild muscular hypotonia and brisk tendon reflexes. Statomotor development was normal (at age 2 years the mental developmental was judged to be normal by another children's hospital).

Laboratory investigations showed normal data on routine analysis, normal amino acids in plasma, normal lipoproteins,

normal excretion of mucopolysaccharides and exclusion of prenatal infections (cases 1, 2 + 4).

Chromosome analysis found normal karyotypes in cases 1, 2 + 4. X-ray investigations were unremarkable (cases 1, 2 + 4). Electroencephalography showed non-specific alterations in cases 1, 2 + 4. Skin biopsy (done in cases 1 and 2) detected marked degeneration of the elastic and collagen fibres.

Family 2: Both parents are Italian migrants coming from the same small village, but they are not known to be related. The mother has had five pregnancies, the first and third ending in miscarriages. All three children were born in Perth, Western Australia.

Case 5: A.S., male was born 29.6.1960. Birth was premature in the 30th week of gestation, birth weight 992 g (well below 3rd percentile). Despite tube feeding his weight gain was poor. At the age of 5 months the baby had a weight of 3490 g and a head circumference of 35.5 cm. The forehead bulged, the anterior fontanel was widely patent, but with normal tension. There was muscular hypotonia. The fingers were flexed and a general "arthrogrypotic" appearance was noted. The palpebral fissures were slightly anti-mongoloid and there was convergent strabismus. The mouth appeared small, the ears were large with poor modelling. The boy exhibited pectus excavatum and reduced subcutaneous fat. The movements were random and athetoid. The small joints were hyperextensible (Fig. 4, case 5 at the right side, aged 6 years). His statomotor and mental development was retarded severely (walking at age 4 years, first words at age 9 years). He suffered from a right-sided cataract (Fig. 5), which was noted first at the age of $8^1/_2$ years.

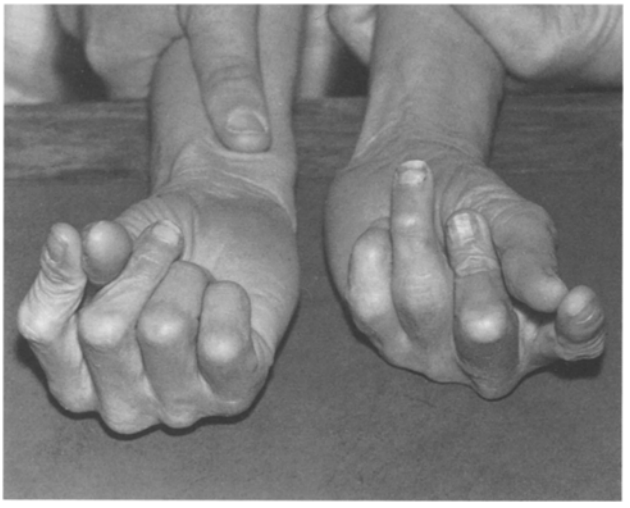

Fig. 10. Thin wrinkled skin of the hands of case 6

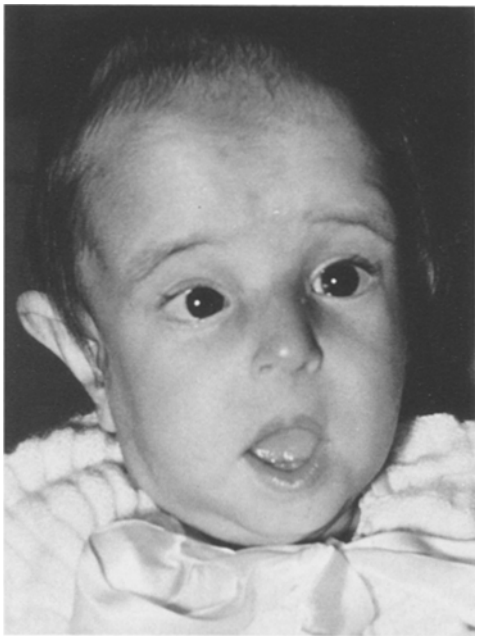

Fig. 11. Case 7 at age 5 months. Note prominent forehead

Table 1. Phenotypical comparison between all previously, known cases and our seven cases

	Published cases	Present cases							All known cases
		m	f	f	m	m	m	f	
Sex	f = 3; m = 4								f = 6; m = 8
Intra-uterine growth retardation	6/6	–	–	–	–	+	+	+	9/13
Postnatal short stature	5/6	+	+	+	0	+	±	+	10/12
Progeroid facies	6/6	+	+	±	0	+	+	+	11/13
Frontal bossing (in early childhood)	5/5	+	+	+	+	+	+	+	12/12
Large, dysplastic ears	6/6	+	+	+	+	+	+	+	13/13
Corneal clouding	4/6	+	+	+	+	0	0	0	8/13
Cataract	1/6	0	0	0	0	+	+	+	4/13
Thin lips	4/4	+	+	+	0	0	0	0	8/8
Cutis laxa	6/6	+	+	+	+	+	+	+	13/13
Atrophy of the skin	6/6	+	+	+	+	+	+	+	13/13
Degeneration of the elastic and collagenous fibres	4/5	+	+			?	?	?	6/7
Hyperflexibility of small joints	3/3	+	+	+	+	+	+	+	10/10
Muscular hypotonia	6/6	+	+	+	+	+	+	+	13/13
Brisk deep tendon reflexes	5/6	+	+	+	+	?	?	?	9/10
Mental retardation	5/5	+	+	±	(–)	+	+	+	10/12

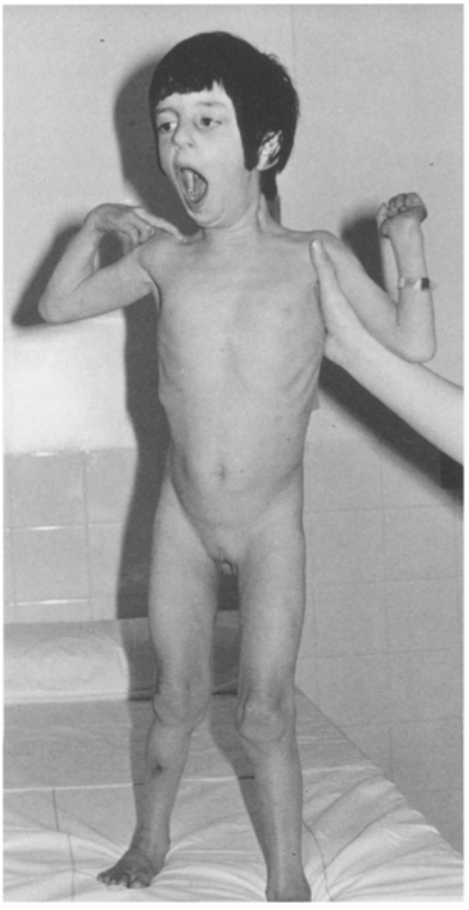

Fig. 12. Case 7 at age 5 years. Note grimacing, reduced subcutaneous fat and atypical movements of the arms

At the age of $13^1/_2$ years his height was 133 cm (−3.2 SD), weight 22.5 kg (−6 kg in relation to height) and head circumference 48 cm (severe microcephaly). His final height was 148 cm. He is now unable to speak any words. The skin of the hands is loose and wrinkled (Fig. 7). There were four finger lines bilaterally and brachymetacarpia 4/5 in the left hand. He is now severely growth retarded, microcephalic and underweight (49 cm, 41 kg). His movements are random and he often grimaces (Fig. 6).

All routine laboratory tests including karyotype revealed normal results. Radiographical examination showed shortened metacarpals 4/5 in the left hand.

Case 6: G. S., male was born 13. 11. 1962 at full term. His birth weight was 2012 g, length 48 cm and OFC 30.8 cm. He was noted to be affected similarly to his brother. In the first month there was failure to thrive. Later severe myopia was noted. His statomotor and mental development were severely retarded (walking at 4 years, first words at 4 years, at the present time no speech). In the first years of life, the cranium appeared relatively large (Fig. 8), but later severe microcephaly was obvious (Fig. 9). At the age of 15 years his height was 160 cm, weight 40 kg and head circumference 47.5 cm.

At the age of 15 months he suffered from generalised seizures. Further symptoms were convergent strabismus, large, poorly modelled ears, small mouth, athetoid random movements, simian creases bilaterally, and thin, wrinkled skin of the hands (Fig. 10).

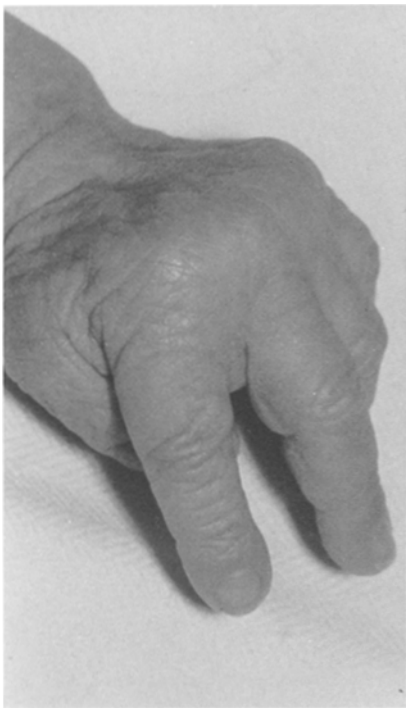

Fig. 13. Wrinkled skin of the right hand of case 7

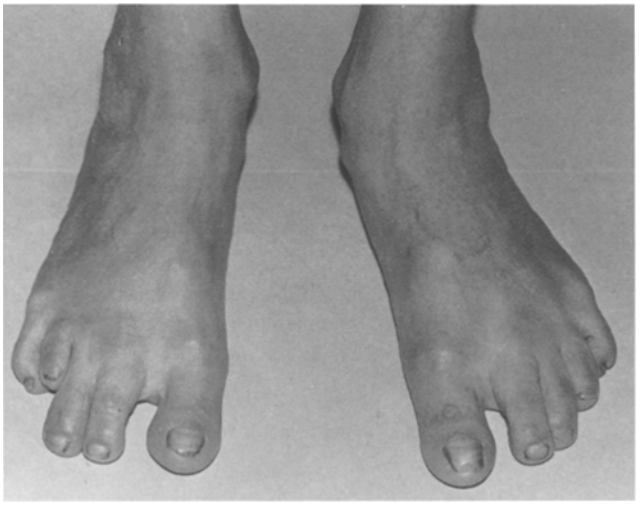

Fig. 14. Brachymetatarsia 4 the left foot of case 7

Case 7: M. S., female was born 23. 5. 1964. The birth occurred at full term, with birth weight 1870 g, length 46.5 cm and head circumference 31.5 cm. The facial abnormalities were rather similar to those of her brothers. In the first year of life, the cranium appeared relatively large with a bulging forehead. There was convergent strabismus and large, poorly modelled ears (Fig. 11). Her statomotor and mental development was severely retarded with walking at 3 years and no speech development. Her fingers were flexed and there was muscular hypotonia. She developed cataracts and severe myopia bilaterally. The cataracts were minimal at 5 months of age and dense by 8 years. There was loose wrinkled skin of the feet, knees and hands (Fig. 13) as well as pectus excavatum, little subcutaneous fat and grimacing (Fig. 12). There were simian creases bilaterally and brachymetatarsia 4 in the right foot

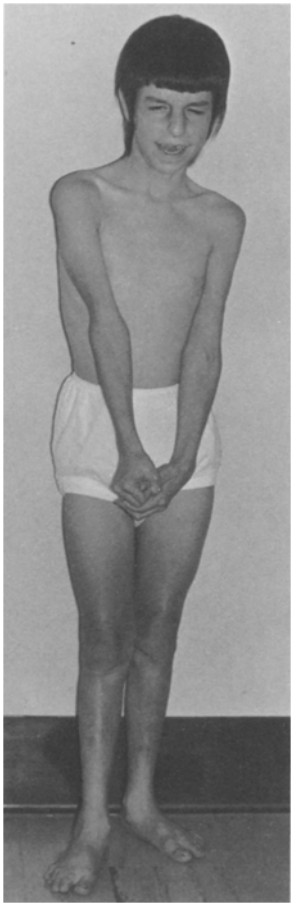

Fig. 15. Case 7 at age 9 years

(Fig. 14). The EEG was grossly abnormal with right-sided hypersynchronic potentials. She developed generalised convulsions at the age of 8 years. She was severely growth retarded. The last measurements at the age of 14 years showed: height 145 cm and weight 37 kg. Her head circumference at age 12 years was 50 cm (below the second centile) (Fig. 15).

Discussion

The main symptoms of the four sibs of family 1 are progeroid facies, frontal bossing in the young child, prominent nose, large dysplastic prominent ears, cloudy corneae, cutis laxa, atrophy of the skin, progressive short stature, choreoid and athetoid movements, grimacing and severe mental retardation (in two siblings). Most of these symptoms are observed in the three sibs of family 2 also. Differences are normal measurements at birth in family 1 and intra-uterine growth retardation in family 2 as well as corneal clouding in family 1 and cataracts in family 2. Despite these differences we think all the cases presented suffer from the de Barsy-syndrome, which hitherto has been reported in only nine cases (1–5, 7; our cases 1 and 2 included). Muscular hypotonia, brisk deep tendon reflexes and postnatal development of microcephaly are further characteristic signs. In most of the cases so far reported, there was intra-uterine growth retardation. In contrast, the sibs of family 1 had normal measurements at birth, but at least cases 1 and 3 developed pronounced postnatal growth retardation. In younger children there may be frontal bossing, while most older children become clearly microcephalic. There was no corneal clouding in the patients of Wiedemann [7], Hoefnagel et al. [5], Goecke et al. [4] and Bartsocas et al. [2]. Goecke et al. [4] noted a polar cataract in their otherwise typical patient and we observed cataracts in cases 5 and 7 of family 2 and severe myopia in cases 6 and 7. Ocular findings may include normal corneae and lenses, myopia, cataracts and corneal clouding.

Non-specific electroencephalographic changes and dilatations of the ventricles were reported by de Barsy et al. [1] and Wiedemann [7]. This may be similar to the findings noted in our case 1. Our cases 6 and 7 suffered from major seizures. Mental retardation was severe in most cases. However our cases 3 and 4 demonstrate that mental development may be only mildly impaired, or even normal. In most patients, in whom a skin biopsy was done (exception: case of Hoefnagel et al. [5]), a degeneration of elastic and collagenous fibres was observed.

A further constant sign is the hyperextensibility of small joints, while the mobility of the large joints was restricted in cases 1, 2, 5 and 6. Contrary observations with arthrochalasis are given by Wiedemann [7] and Hoefnagel et al. [5]. However, their patients were only 6 years and 6.5 years old respectively, at the time of examination.

The aetiology of the de Barsy syndrome may be clarified by our observations. Since all parents are healthy and sibs of both sexes are affected, autosomal recessive inheritance may be assumed. Wiedemann [7] also reported affected siblings, but one of these sibs died shortly after delivery. He was reported to have had an appearance similar to that of the affected sib. In contrast to all known cases with de Barsy syndrome, this newborn suffered from spina bifida and club feet.

Some signs of the de Barsy syndrome are also observed in progressive lipodystrophy Berardinelli-Seip, progeria Hutchinson-Gilford, neonatal progeroid syndrome Wiedemann-Rautenstrauch, Cockayne syndrome, Hallerman-Streiff syndrome and the cutis laxa syndromes. All these syndromes can be differentiated by characterstic, phenotypic differences.

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Received January 1, 1985 / Accepted March 12, 1985