

Familial Low Birthweight Dwarfism with an Unusual Facies and a Skin Eruption

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Though a number of dwarfs are readily recognized as belonging to a particular eponymous group, cases are still encountered that do not quite fit into any category.

The following patient is described in detail because of the unusual facies, the associated 'eczema', the apparent familial incidence and the resemblance to a number of cases reported in the American literature. It probably forms a distinct syndrome which should be recognizable on clinical grounds.

Case History

Amanda R. was born at term weighing only 5 lb. 6 oz. (2437 g.). From the outset she was a poor feeder and her weight gain was very slow. When she was referred to the Children's Hospital, Sheffield, at the age of 9 months, because of failure to thrive, her weight had only reached 9 lb. 9 oz. (4337 g.).

A skin eruption, mainly on the cheeks and round the eyes, first appeared at the age of 1 month. It disappeared within a few days of the application of a bland skin cream, but recurred later. At about 7 months an eruption varying in severity developed behind the knees and persisted. There was also a slight eruption in the elbow flexures and on the extensor surface of the forearms. There had not been any obvious correlation between the severity of the rash and exposure to sunlight, but there was no rash on unexposed parts of the body.

The mother could not recall the earlier milestones, but the girl sat unsupported in her pram at 7 months and on the floor at 9 months. She reached out for and grasped objects at 7 months, and at 8 months was able to chew, wave bye-bye, and play pat-a-cake.

On examination the most striking feature, apart from her small size, was the unusual facies (Fig. 1 and 2), with large and low set ears, a receding lower jaw, and the bridge of the nose in line with the forehead. An eruption resembling infantile eczema was present over the butterfly area of the face, at the angles of the mouth, around the ears, and in the flexures of the knees and elbows.

The head circumference at 14 $\frac{1}{2}$ in. (37.8 cm.) was commensurate with the body weight, both being at the 50th percentile for a 5-week-old infant. She was alert and took an active interest in her surroundings. She reached for objects with a mature two-finger grasp (Fig. 3), and was able to sit unsupported for short periods. She had a very soft high-pitched cry and voice.

Radiographs of the wrist showed only one small epiphysis corresponding to a bone age of about 2 months. Radiograph of the skull was normal. An intravenous pyelogram showed normal renal excretion and structure.

The blood count was normal; the serum Na 135 mEq, K 4.1 mEq, Cl 101 mEq, alkali reserve 22 mEq, urea 30 mg./100 ml.; Ca 10.8 mg./100 ml., and sugar 98 mg./100 ml. Routine urine examination was normal. There was no abnormal aminoaciduria on chromatography. Urinary steroids per 24 hours were 17 keto-steroids 0.4 mg., 17-ketogenic steroids 0.5 mg., 17-hydroxycorticoids 0.7 mg. A three-day fat balance: dried faeces 7 g., total fat 34.5%, daily output of fat 0.8 g.

Course and Progress. Her motor and mental development advanced steadily. At 10 months she started to crawl, was able to sit up from the supine, and to pull herself into a standing position. When assessed at 13 months she was saying two words with meaning, and was able to feed herself from a cup with a spout or from her bottle. She stood with support and walked with both hands held (Fig. 4). She was able to match two cubes and to place one on the top of the other. Her weight was 12 lb. (5443 g.) (50th percentile for 3 months) and length 25 in. (63.5 cm.) (50th percentile for 6 months). The crown to pubis length was 15 in. (38.1 cm.) and the arm span 23 in. (58.4 cm.). The circumference of the head was 16.5 in. (41.8 cm.), of the chest 16 in. (40.6 cm.), and of the abdomen 15 in. (38.1 cm.).

The eruption on the face varied in severity and was most marked around the ears. During a brief spell of sunshine, when she was 1 year old, she had developed marked erythema over the legs, arms, and neck. At 13 months there was still marked 'eczema' of the knee flexures, the outer aspect of the lower legs and the elbow flexures (Fig. 5 and 6). The face was also slightly affected.

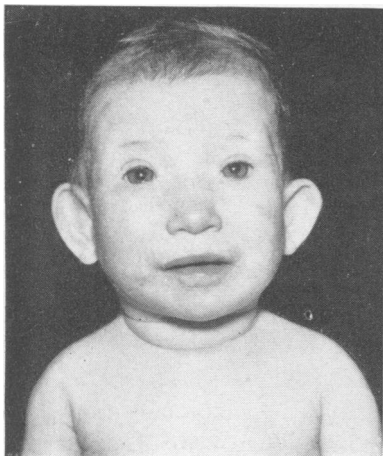


FIG. 1. Note unusual facies with large low-set ears. Eczema at angles of mouth and on cheeks.

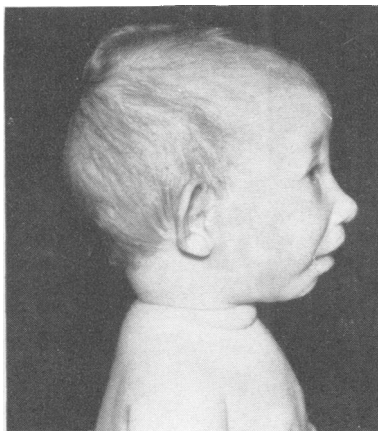


FIG. 2. Note facies, receding jaw and eczema.



FIG. 3. Aged 9 months. Shows sitting posture and mature grasp.

Four teeth had erupted, two lower medial incisors and two upper teeth corresponding in position to the lateral incisors.

Radiograph of the upper dentition showed four deciduous incisors but only two permanent incisors (Fig. 7).

There was still only one small epiphysis on a repeat radiograph of the wrist, with little change from that at 9 months (Fig. 8).

The blood count was again normal. The serum Ca was 12 mg./100 ml., phosphorus 6 mg., and alkaline phosphatase 19 units (Jenner and Kay). On repeat analysis the Ca was 10.8 mg., phosphorus 4.9 mg., and alkaline phosphatase 16.0 units. The sodium was 138 mEq, potassium 4.6 mEq, chloride 104 mEq, alkali reserve 23 mEq, and urea 24 mg./100 ml.; transaminases: SGOT 106 units, SGPT 68 units; serum albumin 4.4 g./100 ml., globulin 2.4 g./100 ml.; total

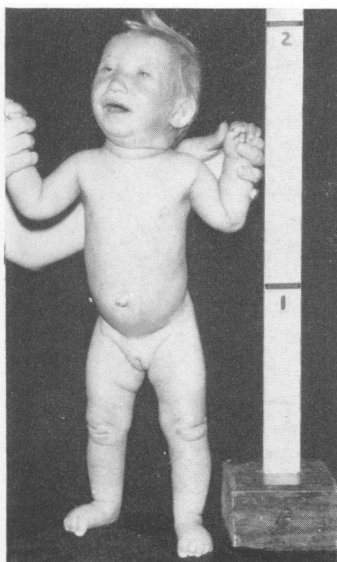


FIG. 4. Aged 13 months. Ability to stand with support.



FIG. 5. Eczema of knee.

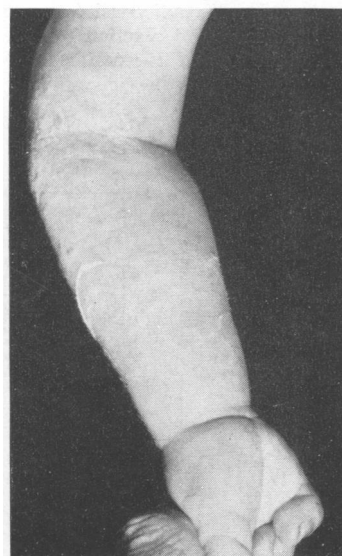


FIG. 6. Eczema of elbow and forearm.



FIG. 7. Radiograph showing absence of upper lateral incisors in permanent dentition.

serum lipids 400 mg./100 ml., serum cholesterol 77 mg./100 ml.; vitamin A 86 units/100 ml. (26 μ g./100 ml.). The sweat sodium was 40 mEq/litre. When repeated the total lipids were 610 mg./100 ml; and the total cholesterol was 150 mg./100 ml. Electrophoresis showed a normal lipid distribution with α and β fractions present.

Skin and leucocytes were cultured for chromosome analysis and showed a normal female karyotype.

The skin over the lumbar region was tested for sensitivity to ultraviolet light. The E_1 dose of the lamp was 2 minutes. Testing doses of $1\frac{1}{2}$, $1\frac{3}{4}$, 2, and $2\frac{3}{4}$ minutes were given with resultant E_1 response for the first two exposures and E_2 response for the second two. The latter two exposure sites became pigmented and were still readily visible five months later, indicating the increased reaction to the ultraviolet radiation.

By the age of 16 months her weight had risen to

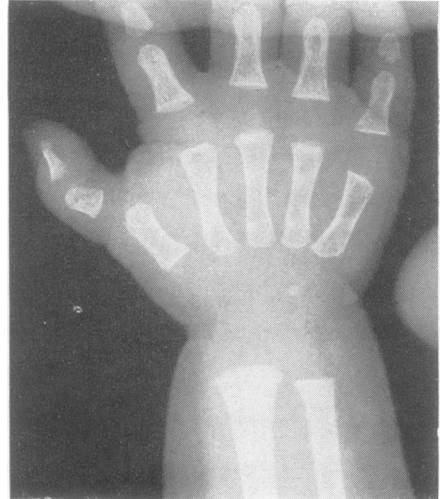


FIG. 8. Radiograph showing retardation of bone age. Taken at 13 months.

13 lb. 3 oz. (6.7 kg.). The eczema had shown some improvement with 1% hydrocortisone cream, but there was still a marked eruption, with some lichenification, in the elbow and knee flexures. No further teeth had erupted. She was walking up to six steps without support, was putting an arm out when dressed, and she helped with undressing. She was able to put a spoonful of food into her mouth. She had not learnt any new words and was still only able to put the circle into the simple formboard, and could not adapt. She matched two cubes readily but would not make a tower with them. Her manipulative ability was assessed at about the 10-month level, and she was considered to be slightly retarded for her age.

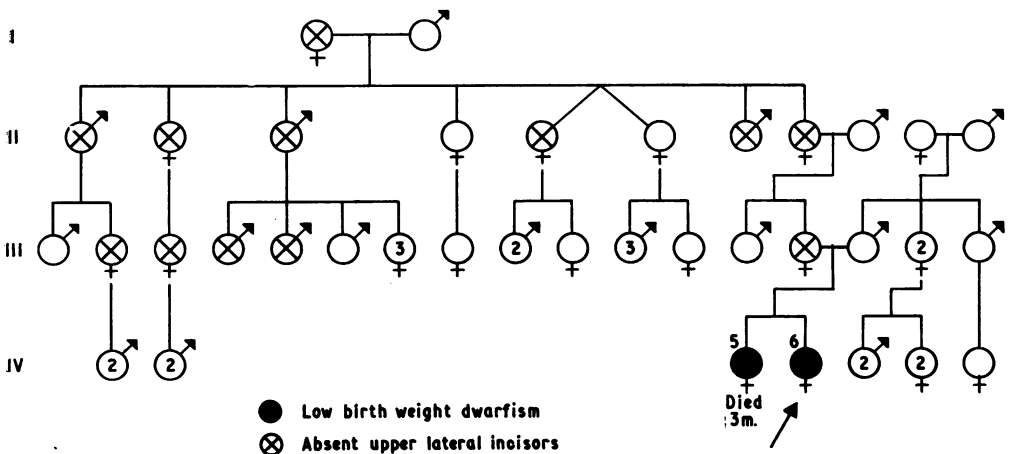


FIG. 9. Pedigree chart.

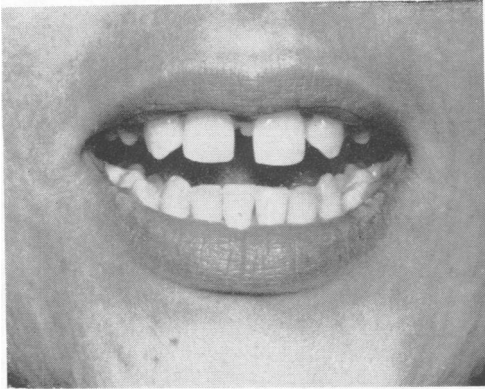


FIG. 10. Absence of upper lateral incisor teeth in mother.

of only 4 lb. (1814 g.) at full term, and she remained in hospital until her death at 3 months. Her highest weight had been 4 lb. 8 oz. (2041 g.). In addition she had webbing of the toes. There was no rash.

Both parents are of normal stature. The father is 70 in. (178 cm.) tall and weighs 168 lb. (76 kg.), and the mother is 65 in. (165 cm.) tall and weighs 140 lb. (63.5 kg.). It was noticed that the mother had only two upper incisor teeth (Fig. 10) and further questioning revealed a similar anomaly in the maternal grandmother and great-grandmother and a number of other members of the family (Fig. 9).

While pregnant with Amanda the mother developed blisters on both arms following exposure to the sun on three successive days. She had never previously had a severe reaction to sunlight, and usually tanned readily.

When last examined at 18 months her weight had risen to 14 lb. (6.35 kg.) and her length was 27.5 in. (69.8 cm.). Four upper and two lower incisor teeth were present.

The eruption on the face and limbs had completely cleared within two weeks of her previous attendance, while she was still having hydrocortisone cream and had not recurred after this was stopped. During this period she had not been out of doors as frequently as before.

Her walking had improved considerably but she had not learnt any new words. She placed the circle in the simple formboard and could also adapt. She placed one cube on another but would not release it. She was still considered to be slightly retarded.

Family History. A female sib, with a similar facial appearance (IV. 5, Fig. 9) had a birth weight

Discussion

The main clinical features in this patient are the low birthweight dwarfism, the peculiar facies, and the skin eruption on the face and extremities. The fact that a previous sib probably had a similar condition, while the parents are normal, suggests an autosomal recessive mode of inheritance.

The Table summarizes a number of similar cases that have been reported recently, and the following analysis is based upon it.

Skin. The condition first attracted the attention of dermatologists: in fact the first five cases listed were all shown at dermatological meetings. Torre (1954) thought that the erythematous lesions on the face resembled lupus erythematosus, but Bloom (1954a, b) suggested a congenital telan-

TABLE
SUMMARY OF SIMILAR REPORTED CASES

Case No.	Reference	Age (yr.)	Sex	Familial	Birth Weight < 2.5 kg.	Weight < Height	Bone Age	I. Q.	Absent Incisors	Rash Face	Rash Limbs	Light Sensitivity	Café au lait patches	Other Congenital Abnormalities	Facies	High-pitched Voice
1	Machacek (1953) (quoted Bloom)	3½	M	-						+						
2	Torre (1954)	2½	F	-	+					+	+	+		+		
3	Bloom (1954)	20	M	-	+			N		+	+	+	+	+	+	+
4	Brunsting (1957)	22	M	-				R		+	+	+				
5	Lewis (1957)	20	M	-				R		+	+	+	+			+
6	Hillman (1957)	6	M	-	+	+		R		+	+	+			+	
7	Korting and Adam* (1958)	37	M	-				R		+	+	+			+	
8	Katzenellenbogen (1960)	2½	M	-	+	+		PR	N	+	+	+	-	+	+	+
9	Katzenellenbogen (1960)	10	M	-	+	+		N		+	+	+	+		+	+
10	Szalay (1963)	10	M	?	+	+		R	N	+	+	+	+		+	+
11	Szalay (1963)	11	M	+	+	+		R	N	+	+	+	+		+	+
12	Szalay (1963)	8	F	+	+	+			N	+	+	+	+		+	+
13	Dubowitz (1964)	3½	F	+	+	+		R	R	+	+	+			+	+
14	Dubowitz (1964)	d. 1½	F	+	+	+							-	+		

d = died; N = normal, R = retarded.
* A questionable case.

giectatic erythema, which was more in keeping with the histological changes. In subsequent reports the clinical and histological descriptions of the skin lesions have varied considerably, but the distribution over the face and extremities has been fairly consistent. Sensitivity to sunlight was noted in practically all of them.

Facies. The striking facies may be more distinctive in this syndrome than the character of the skin eruption. Bloom (1954b) drew attention to the narrow fine-featured face of his patient, which gave the impression of precocious senility. There is a striking facial resemblance between Bloom's patient, that of Hillman, Crawford, and Talbot (1957), all three patients of Szalay (1963), the one patient illustrated by Katzenellenbogen and Laron (1960), and the present one. Brunsting (1957) and Lewis (1957) also claimed that their patients resembled Bloom's, but no photographs are included in their reports. While Korting and Adam (1958) considered their adult dwarf to have the same syndrome as that described by Bloom, the facial appearance in their illustration bears no resemblance. Case reports in the earlier literature of skin eruptions of the face and extremities in dwarfs, such as the three cases of Thomson (1923, 1936), can also be differentiated from the present syndrome on the basis of the different facial appearance. On the other hand one of the two personal cases included by Seckel (1960) in his monograph on bird-headed dwarfs probably belongs to this syndrome. This child weighed only 4 lb. 5 oz. (1956 g.) at birth and from the illustration does not appear to have a bird-like facies but bears a strong resemblance to the present case. There is, however, no mention of a skin eruption in Seckel's patient.

Weight. Hillman *et al.* (1957) pointed out that the weight of their patient was disproportionately low for the height. These corresponded to the 1½-year and 3-year level respectively in a 6-year-old patient. They suggested a hypocaloric form of dwarfism to explain this, but were unable to induce their patient to take a high calorie diet in order to prove it. The same discrepancy between height and weight was subsequently observed by Katzenellenbogen and Laron (1960) and Szalay (1963) in all their patients, and also in the present patient. The bone age has been retarded in four of the reported cases as well as in the present patient, but was normal in three others (excluding the case of Korting and Adam).

Intelligence. The intelligence has been regarded as normal in the majority of reports. No detailed studies are given and it is possible that a minimal degree of impairment, such as that of the present patient, may have been overlooked in some instances.

Biochemical Studies. Routine biochemical studies of the blood and urine were found to be normal by a number of authors and extensive investigations of thyroid and adrenal function by Bloom and by Katzenellenbogen and Laron gave normal results. The latter authors also found no benefit from anabolic steroid or insulin therapy.

Associated Defects. Associated congenital abnormalities have been recorded in a number of cases. *Café au lait* patches occurred in 5; other abnormalities include ichthyosis and pilonidal cyst (Bloom, 1954b), supernumerary fingers (Torre, 1954), hypospadias and undescended testes (Katzenellenbogen and Laron, 1960), absence of upper lateral incisors (Szalay, 1963), and webbed toes (sib of present case). The absence of upper lateral incisors in all three of Szalay's cases as well as in the permanent dentition of the present case is of special interest. This is a fairly common congenital anomaly. Röse (1906), in a survey of 15,000 persons, found degeneration or absence of the upper lateral incisors in 6% of Scandinavians, 2-4% of Central Europeans, 1.4% of Greeks, and about 1% of coloured races. It was more common in females than in males. Hrdlička (1921) found the incidence in American males to be 1.4% and in females 3%. A number of authors have reported a familial incidence; inheritance is usually dominant (Gates, 1946). This abnormality usually occurs as an isolated phenomenon, though it may be associated with other abnormalities such as hare-lip and cleft palate (Lucas, 1904). The absence of upper lateral incisors in various members of the family on the mother's side of the present case follows an autosomal dominant inheritance. However, none of them is dwarfed or has any other stigmata of the syndrome. In this family the anomaly of the teeth and the dwarfism may be coincidental, but the fact that Szalay's three patients also had absence of the upper lateral incisors suggests that there may be a linkage between the two conditions.

Genetics. Bloom's (1954b) patient was the only living child of healthy unrelated parents. A sib died at the age of 3 months of unknown cause.

The family history was negative. No mention of the family history was made in the patients of Torre (1954), Brunsting (1957), and Lewis (1957), and it is recorded as being non-contributory in the patient of Hillman *et al.* (1957). The first patient of Katzenellenbogen and Laron (1960) had healthy unrelated parents of normal stature and a healthy sib. In the second case the parents were of average height and unrelated, but the maternal grandfather was of short stature; three sibs were normal.

The possibility that the affection might be genetically determined was first suggested by Szalay (1963). The parents of his first patient were first cousins: there was no family history of similarly affected children and three sibs were normal. His second and third patients were a brother and sister, who had three normal sibs: their parents were normal and unrelated and their family history was negative.

Szalay's patients and the family recorded here suggest that the syndrome is inherited in a recessive manner. The chromosome pattern was found normal in Szalay's first patient and in the present study.

Summary

A female infant is described with low birthweight dwarfism, a peculiar facies, a skin eruption of the face and flexures, retarded bone age, slightly impaired intellectual development, and absence of the permanent upper lateral incisors. A previous sib, who probably also had the syndrome, died at the age of 3 months. Absence of the upper lateral incisors as an isolated anomaly occurs on the mother's side of the family as an autosomal dominant trait. Biochemical and chromosomal studies were normal. Similar reported cases are reviewed.

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