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Studies of Malformation Syndromes of Man XXIV B: The Dubowitz Syndrome. Further Observations*

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Abstract. This paper reports observations on 6 new patients with the Dubowitz syndrome which was first defined by Grosse *et al.*, in 1971 and which is a recessively inherited, pleiotropic malformation syndrome including variable degrees of intrauterine growth retardation and primordial shortness of stature, microcephaly, mental retardation, eczema, and a characteristic appearance, voice and combination of minor anomalies. Data in the present report show that eczema can be absent, and patients can be of normal height, and of normal intelligence in spite of a head circumference which has so far always fallen below the third percentile. So far 11 patients (8 females and 3 males) are known with the Dubowitz syndrome; in one family the parents were first cousins.

Key words: Recessive inheritance — Parental consanguinity — Mild mental retardation/normal intelligence — Intrauterine growth retardation/shortness of stature/normal height — Catch-up growth — Microcephaly — Malformation syndrome.

Grosse *et al.* (1971) defined a syndrome of intrauterine and postnatal growth retardation, microcephaly, characteristic appearance and combination of minor anomalies with variable degrees of mental retardation and apparent predisposition to eczema. This condition, which was thought to be due to the homozygous state of an autosomal recessive mutant, was designated the Dubowitz syndrome. This paper provides further data in support of this genetic hypothesis and documents the phenotypic manifestations of 6 additional patients, 1 studied at the University of Wisconsin, 3 in Münster, and 2 in Jersey City. Dr. Dubowitz provided further data on his original patient A.R.

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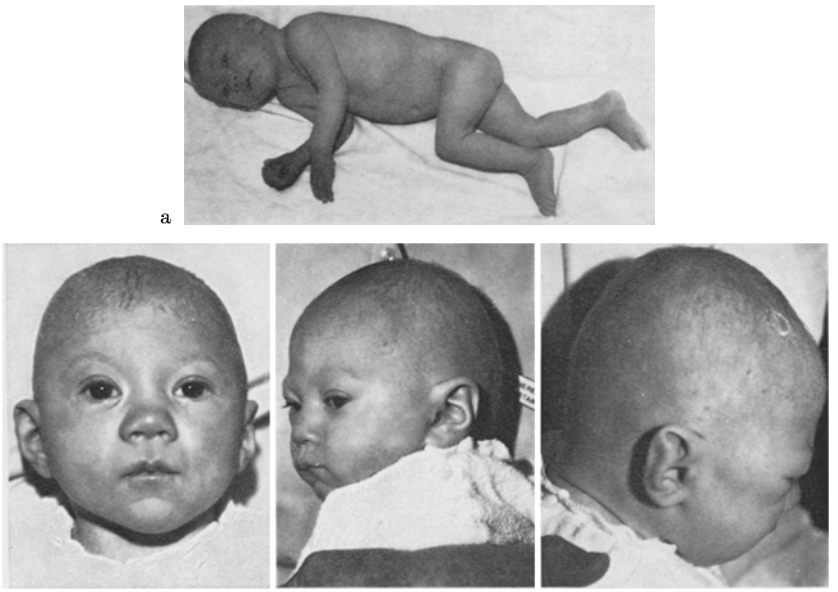
Case Reports

Case 1 (A. J., UWH No. 626271). This white female was born on 16 January 1971 to young, non-consanguineous parents after an uneventful 43 week gestation during which the mother gained 15.87 kg. For 2 years after marriage the mother was unable to conceive and she was treated for hypothyroidism. The patient represents her first pregnancy. Labor and delivery were normal, but an unspecified "anomaly" of the umbilical cord and placenta was noted at birth. The infant weighed 2807 g and she was supposedly 53.3 cm long; unfortunately, her birth head circumference is not known. She appeared pale at birth. She regained her birth weight in less than 10 days, and she went home with her mother at 4 days on an artificial formula. At home she manifested considerable irritability and she regurgitated much of her formula; at times she had postprandial projectile vomiting and "loose stools". However, during these first few weeks of life her growth and weight gain was normal. Since the first week of life she has had chronic rhinorrhea. Her formula was changed to skim milk with temporary improvement of the vomiting and diarrhea. At 9 weeks of age vomiting recurred and she again had loose stools; for this she was admitted by Dr. J. Tankersley to St. Francis Hospital in La Crosse where she was found to have an abnormal EEG, ("bioccipital dysrhythmia, grade II"), a hemoglobin of 8.7 g and a periosteal hyperostosis of the right humerus. Her vomiting stopped after she was treated with clear fluids; it was thought that her condition represented a type of encephalopathy. At 3½ months she was admitted to the University of Wisconsin Children's Hospital after a recurrence of intermittent, non-projectile, postprandial vomiting.

Physical examination showed an alert, healthy, reasonably well nourished infant with the characteristic appearance of the Dubowitz syndrome (Fig. 1a—d). Her height was 60.8 cm ($> 25 < 50\%$ile), weight was 4990 g ($> 3 < 10\%$ile), and head circumference was 36.3 cm ($< 3\%$ile). When relaxed she was a pleasant child who smiled socially and was able to fix, focus and follow light normally, but whose general psychomotor development was on a two rather than a 3½ months level. She was unusually jittery, hyperreactive to light, touch and auditory stimuli, and most of the time she appeared irritable, unhappy and "colicky". During the examination intestinal/gastric peristalsis was visible through the abdominal wall and she vomited once in a projectile manner. Examination also showed a round, asymmetric, microcephalic skull, with a somewhat fleeting forehead, relatively flat supraorbital ridges, complete bilateral inner epicanthic folds, slight telecanthus, blepharophimosis and ptosis bilaterally, apparent microstomia and micrognathia. The tip of the nose was relatively flat, broad and anteverted. A submucous cleft was palpable. Scalp hair was sparse, and she had scalp seborrhea. The left auricle was slightly posteriorly angulated and showed relative prominence of the lower antihelix; the right auricle also was somewhat angulated and showed trifurcation of the upper antihelical crura with an open helical fold, and unusual prominence of the lower portion of the antihelix. In addition this infant's voice had the same characteristic quality as had been noted in other children with this syndrome, and voice alone would have permitted diagnosis with the patient unseen. The anterior fontanel was small but still open; all skull sutures appeared to be closed, but they were not ridged. There was asymmetry of thigh folds and of the sacral/gluteal folds. There was a bilateral slight metatarsus varus foot deformity more pronounced on right than on left.

Neurologically she impressed observers as being quite immature; she did not have a Moro or tonic neck reflex, but an active tail reflex, and a bilateral Babinski reflex. The thigh adductors were tight and there was a DeLange sign ("scissoring") of the legs.



a b c d

Fig. 1 a—d. A. J., case 1, at 3½ months of age. See text

Dermatoglyphics, right hand: *t* axial triradius, no thenar or hypothenar pattern, third interdigital distal loop, five whorls on fingertips; left: *t'* axial triradius, without thenar, hypothenar or interdigital patterns; the fingertips showed 1 twin loop, 2 whorl, 3 ulnar loop, 4 and 5 ulnar pocket loop. There was a distal loop in both hallucal areas.

Studies in the hospital showed normal serum electrolytes and normal urinalysis; a microcytic normochromic anemia (hematocrit 28%, hemoglobin 9.5 g/100 ml) with normal white blood cells and platelets; normal EEG; and "possible right ventricular hypertrophy" on ECG. There were no abnormal intracranial calcifications; the chest roentgenogram was normal and the bone age was approximately 6 months (at a chronological age of 3½ months); the thoraco-lumbar spine was normal but there was a periosteal reaction along the right humerus and both femora (considered "physiological for a child of this age" by the radiologist). Cytomegalovirus, rubella and toxoplasmosis studies gave normal results. Serum immunoelectrophoresis showed essentially normal infantile pattern.

The family history is unremarkable; mother and father were 21 and 20 years old, healthy and normal in all respects when A. J. was born; their parents, 16 sibs, and 39 nieces and nephews were all normal; father's oldest sib was stillborn for unknown reasons.

The parents were advised of a 25% recurrence risk, a slow but gradually accelerating pattern of psychomotor development with ultimate intellectual performance falling probably within normal limits, and about the possibility that A. J. might develop some eczema. Treatment for the apparent iron deficiency anemia was recommended.

Immediately after discharge from the University Hospitals she developed fever and dehydration due to a severe urinary tract infection which required hospitalization but which responded immediately to antibiotic therapy. Her first two teeth erupted at 4 and 5 months of age. At 5½ months she weighed 6200 g (10%ile) and had unilateral otitis media; at 6 months she weighed 6750 g (> 10 < 25%ile). At 7 months she had febrile bronchitis; she was beginning to walk in an infant walker.

When she was reexamined at the University of Wisconsin at 8 months, it was found that she had undergone remarkable psychomotor maturation to a nearly normal level; her height of 68.7 cm was on the 50%ile, but her head circumference of 39 cm still fell below the second percentile. She had four incisors; the upper central incisors appeared to be bifid. She had apparent eczema on her cheeks, the dorsum of both hands and in the popliteal and antecubital fossae. The characteristic quality of voice persisted; the anterior fontanel appeared to have closed completely. There were no focal neurological abnormalities, however, the deep tendon reflexes of the lower extremities were still somewhat hyperactive, a Babinsky reflex could still be elicited intermittently and the child continued to be slightly irritable and to give a somwhat immature impression. She was healthy, but she still had a slight anemia.

Conversation with the parents on A. J.'s second birthday revealed continuing, nearly normal psychomotor development, minimal popliteal fossa eczema, good health (only one bout of otitis media in 1972), and surprisingly normal growth with a weight of 11.8 kg (> 25%ile), height of 87 cm (> 50%ile), and a head circumference of 44.5 cm (< 2%ile).

Summary. Postmature, microcephalic baby girl followed till 8 months of age with initial neurological immaturity, irritability, vomiting, loose stools, slow psychomotor development, advanced bone age, normal height, submucous cleft of palate, bifid upper central incisors, voice and facies characteristic of the Dubowitz syndrome, periosteal reaction of right humerus and both femora, right ventricular hypertrophy on a single ECG, grade II bioccipital dysrhythmia on an EEG at 3 months (normal at 3½ months), slightly hypochromic or normochromic, microcytic (iron deficient) anemia, and mild eczema. Diagnosis: Dubowitz syndrome.

Case 2. R. Z., born 10/30/1962, a male, was delivered at home after a normal pregnancy, weighing 2000 g, and measuring 44 cm in length. He had neonatal feeding difficulties with projectile vomiting. Initially normal motor development (sat at 7 months, walked at 1 year). Because of poor appetite and recurrent infections, he was studied at $2^{3}/_{12}$ years at which time he weighed 7080 g and was 74 cm tall; it was noted "that his gait was normal, that he was definitely microcephalic (head circumference 39 cm), that his forehead was sloping, but that he had a normal dentition. His testes were undescended. He was thought to have the mental age of 12 months. A pneumoencephalogram was technically unsatisfactory, but a skull film was normal. The anterior portions of both first ribs are fused. The EEG was normal."

The patient was examined in the University Children's Hospital in Münster at the age of $5^{1}/_{12}$ years, and was found to be a small, gracefully built and unusually active boy. Anthropometric data are summarized in Table 1. The boy appeared normally proportioned, but he was evidently microcephalic; his forehead was sloping. He had microretrognathia but no cleft of palate. He had an epicanthic fold on the

right, an extremely thin subcutaneous fat pad, cutis marmorata, and bilateral cryptorchidism. The remainder of the physical examination was normal.

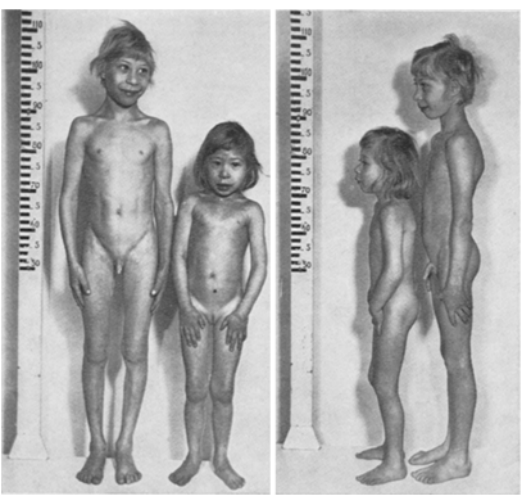
His IQ was estimated at 76; this probably an unreliable result since the patient tired easily and was too playful, active and uncooperative.

Roentgenograms indicated hypoplasia of the first and second ribs which were fused anteriorly; vertebrae and pelvis were normal. Bone age was 2¼ to 2½ years (at a chronologic age of 5½). EEG was normal.

Fundi showed unusually convoluted retinal vessels as well as peripheral pigmentation reminiscent of a fine-grained salt and pepper pigmentary dysplasia or degeneration. The electroretinogram was slightly abnormal: amplitude of *a* and *b* waves was diminished.

Serum electrolytes, complete blood count and erythrocyte sedimentation rate were normal. Blood glucose levels varied between 80—120 mg%. Glucose tolerance test was normal; the highest blood sugar level (152 mg%) was attained after 30 min. After a dose of ½ unit insulin the blood sugar fell from 96 to 49 mg%, with associated somnolence. Insulin induced hypoglycemia was followed, after 2 hrs, by a rise of the serum growth hormone value from 4.5 to 13 ng/ml. Two 17-ketosteroid excretion determinations gave values of 0.28 and 0.94 mg/24 hrs; corresponding gonadotropin excretion values were 15 and 30 units. Following a dose of 750 mg of metopiron the ACTH response appeared to be diminished; urinary corticosteroid values rose to maximum values of only 1.1 and 1.8 mg/24 hrs. I^{131} was stored in amounts appropriate for age; scans showed an even, normal distribution of I^{131} over the thyroid gland. The PBI was 6.7 γ%.

The patient was last seen at the age of 9 years (Fig. 2a and b). He attended third grade in a special school but was barely able to keep up; transfer to a trainable-retarded educational program will probably be necessary. His appearance was unchanged and his hyperactivity was barely manageable. Psychologic testing showed considerable resistance to an educational setting, shyness, easy fatigueability, reluctance to cooperate, hyperactivity more pronounced in the presence of parents



a b

Fig. 2a and b. R. Z., case 2, and B. Z., case 3, at $8^{10}/_{12}$ and $4^{8}/_{12}$ years respectively

and sister, and an overall percentile IQ value of 69. He did not have eczema; his hair was of a light blond color and rather sparse, his forehead was sloping. He had bilateral epicanthic folds, a highly-pitched voice, retrognathia, a normal palate, and relatively large and carious teeth. There was no syndactyly of toes; and with the exception of a slight clinodactyly of both fifth fingers, the hands were unremarkable. The skin did not show unusual pigmentation. Bone age was 5½—6 years. Dermatoglyphics are summarized in Table 2.

Case 3 (B. Z., born 5/21/67, the sister of case 2). During her pregnancy, the mother suffered from hyperemesis gravidarum; she may have had rubella. A female infant was delivered 5 days after the expected date of confinement, and was admitted immediately for investigation. It was determined that she did not have ornithosis, listeriosis, leptospirosis, or toxoplasmosis. The anterior fontanelle allegedly closed during the 12th week of life.

At the age of 6 months she was first examined in the University Children's Hospital in Münster. Her measurements are listed in Table 1. This very small infant had evident microcephaly and a suggestive "bird-faced" appearance. The anterior fontanelle was barely palpable, the auricles were dysplastic. There was slight antimongoloid slanting of the palpebral fissures and an epicanthic fold bilaterally. The scalp hair was sparse and straight. Palate was normal. She had a raised, pigmented nevus immediately to the left of the linea alba, about half-way between the umbilicus and symphysis pubis. The right thumb was bifid and had two separate nails (Fig. 3). There was brachyclinodactyly of both fifth fingers with hyperextensibility of joints. Dermatoglyphics are summarzed in Table 2. The subcutaneous paniculus was underdeveloped (especially on the trunk). Rest of the physical examination was unremarkable.

Vessels of the fundi appeared normal, but there was a peripheral salt and pepper pigmentary change with a few larger pigment spots. The ERG was also slightly abnormal.

The fasting serum growth hormone level was rather high at 10.5 ng/ml but did not rise 30 min after insulin-induced hypoglycemia.

The girl was reexamined at 2 and 4 years; her appearance and clinical condition had remained unchanged. She had learned to walk at a normal time. Her deciduous dentition was normal. A café-au-lait spot was seen on the left side of the back. The

Table 1
Anthropometric measurements on the Z. siblings with the Dubowitz syndrome

		Weight (g)	Height (cm)	OFC (cm)
R. Z. (case 2)	Birth	2000	44	?
	$2^{3}/_{12}$	7080	74	39
	6	10100	95	40.5
	7	11300	99	40.5
	$9^{5}/_{12}$	14000	110	41
B. Z. (case 3)	Birth	2000	42	28
	$^{3}/_{12}$	2160	?	32
	$^{6}/_{12}$	4300	58	32.5
	$2^{1}/_{12}$	7250	76	37
	$4^{10}/_{12}$	10000	88.5	37

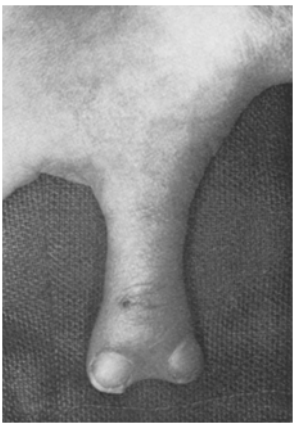


Fig 3. Bifid right thumb of case 3

Table 2. Dermatoglyphics of the Z. family

Person	Side	Palms							Interdigital areas			
		d	*c*	*b*	*a*	*t*	*hy*	*th*	1	2	3	4
Father	R	11	9	7	5	*t*	0	0	0	0	L	L
	L	11/7	9	5	?	*t*	0	L/Q	0	L	L	?
Mother	R	11	0	7	5′	*t′*	A/L^c	0	0	0	0	?
	L	11	0	7	5	*t′*	L^r	0	0	0	0	?
R.Z. (case 2)	R	11	9	7	5′	*t′*	A/A	0	0	V	0	?
	L	11	9	7	5′	*t′*	A/A	0	0	V	0	?
B.Z. (case 3)	R	11	0	7	4	*t′*	A/A	0	0	V	0	?
	L	11	0	7	3	*t*	A/A	0	0	0	0	?

	Side	Fingers				
		I	II	III	IV	V
Father	R	W	W	R	W	W
	L	W	U	?scar	W	U
Mother	R	U	A	A	A(U)	A(U)
	L	U	A	A	A	A
R.Z. (case 2)	R	W	U	U(A)	U	A
	L	U	U	U	U	U
B.Z. (case 3)	R	W	U	U	U(A)	A
	L	A	A	A	A	A

mother stated that the child sweated rather strongly. In 1972 excoriations were noted on the trunk, but no sign of eczema could be discovered. She had sparse, blond hair, and a sloping forehead, retrognathia, and a carious deciduous dentition.

Syndactyly was not present. Bone age (in 1969) corresponded to a chronological age of 2 years; the distal phalanx of the right thumb was duplicated.

Play-observations showed the girl to lack endurance; alone, she manifested considerable anxiety. She was able to name objects correctly, and acted in an altogether reasonable and well-oriented manner. In the presence of her (affected) brother her behavior changed and she became extraordinarily vivacious and loquacious.

Family history shows that mother (born 12/2/1940, 154 cm tall) and father (born 5/1/1942, 182 cm tall) are both healthy, but *related to each other as first cousins* (the patients' paternal grandfather is a brother of their maternal grandmother). An older brother, born in 1961, is healthy. Family history is otherwise unremarkable. These two siblings were first presented by RAP in 1969 at the Meeting the European Society of Pediatric Research.

Case 4. (S. D.) was born on 27 July 1966 when her father and mother were 38 and 26 years old respectively. A sister, born in 1969, is healthy.

Pregnancy was normal except for hyperemesis gravidarum. Delivery occurred 13 days before the expected date of confinement; at birth her weight was 2550 g, length 44 cm, head circumference 30 cm (all less than 3rd %ile for gestational age). Infancy was normal except for initial feeding difficulties, later enuresis, and distinct light sensitivity of the skin. The skin is frequently rough on the extensor surfaces of the extremities; there is facial erythema. Psychomotor development was normal.

First examination in 1967 at $1^{4}/_{12}$ years: height 70 cm (< 3%ile); this was regarded as a normal variant, but the skull appeared to be too small. The EEG was normal.

In 1970 (at $3^{10}/_{12}$ years) she was 90 cm tall (> 3 < 10%ile), but her bone age was normal; at that time she had enuresis.

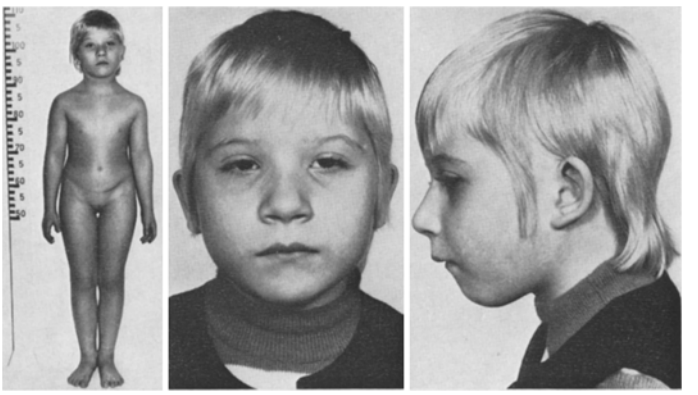
At $5\frac{1}{2}$ years she was 104 cm tall (> 3 < 10%ile), but her head circumference of 46 cm was below the 3%ile. Examination at the University Pediatric Clinics in Köln suggested slight hypothyroidism for which the child has been treated since then. She was also found to have left vesico-ureteral reflux, hyperopia (+ 2.5 d OU), and albinotic fundi with increased vascular tortuosity.

In 1972 (at $5^{7}/_{12}$ years) she was 106 cm tall (> 3 < 10%ile); her ECG was normal.

All biochemical studies yielded normal results. In 1970 and 1972 she was found to have normal intelligence (IQ values of 102 and 104 respectively); she has never been irritable.

Examination at $6^{7}/_{12}$ years: height 110.5 cm (> 3 < 10%ile), weight 19 kg (> 10 < 25%ile), and head circumference 47.5 cm (< 3%ile). Facial appearance suggests the Dubowitz syndrome; she was found to have microcephaly with head length and width of 16.1 and 12.9 cm respectively, a relatively low forehead, thin and straight whitishblond scalp hair, mongoloid slanting of palpebral fissures, bilateral upper epicanthic folds, relatively small (short and narrow) palpebral fissures with slight bilateral ptosis and hyperopia; inner and outer canthal distances of 30 and 78 mm respectively; anteverted nostrils, slight micrognathia, relatively small, "plump" and slightly anteverted auricles; high and narrowly arched anterior hard palate; deciduous teeth being replaced, no significantly increased caries; short broad fingers and toes and toe and finger nails. The fith fingers were relatively short and clinodactylous. Rest of the physical examination was unremarkable, but she is said not to show any particular resemblance to her parents.

Case 5. J. C., a 9-month-old white boy of Irish ancestry was referred by his pediatrician to the New Jersey Medical School Genetics Unit because of slow growth, which was first appreciated at the age of $2\frac{1}{2}$ months; at 4 and 8 months he had the bone age of a newborn. PBI was normal at 8 months of age. A high-pitched cry had



a b c

Fig 4a—c. S. D. at $6^{7}/_{12}$ years of age

been noted in earlier infancy. There had been no feeding problems, vomiting or diarrhea. Food intake was apparently adequate, and he had no urinary tract symptoms.

J. C. was born 25 January 1971 after a full term gestation and normal vaginal delivery with vertex presentation at Monmouth Medical Center, New Jersey. Birth weight was 2.4 kg and length 43 cm. The mother had taken heroin and LSD during the first trimester; there had been no attempts at abortion. The baby left the nursery in apparently good condition at 4 days of age. He had had bronchopneumonia at age 2 months and was hospitalized for 10 days. Immunizations with DPT and oral polio vaccine were accomplished without difficulties.

He rolled over at 2 months, crawled, smiled and cooed at 4 months, held hands together at 5 months, laughed at 5—6 months, sat up at 6 months, tried to feed himself between 6 and 7 months, walked with support and babbled at 9 months. His first tooth appeared at 8 months.

At the time of birth, the patient's mother was 19 years old, 157.6 cm tall and in good health. She was heroin addicted and used LSD until the end of the first trimester of pregnancy with the patient. She has 6 brothers and 3 sisters; an 8-year-old brother has CNS damage due to convulsions when 2 years old. Patient's father was 21 years old, 189.5 cm tall, a drug addict, imprisoned for rape. Parents were not consanguineous, and the family history was essentially unremarkable.

Physical examination at the age of 9 months: head circumference 38.5 cm (< 3%ile), length 68 cm (10%ile) weight 5.8 kg (< 3%ile); he appeared as a small-for-age, obviously microcephalic but healthy, pleasant and active boy. He was also found to have nonpalpable anterior and posterior fontanels, a prominent antihelix bilaterally, apparent minimal left microphthalmia, antimongoloid slant of the palpebral fissures, bilateral epicanthic folds, normal fundi, slightly "bulbous" tip of nose, broad maxillary alveolar ridges with a highly arched palate and micrognathia; chronic rhinorrhea; minimal syndactyly of toes 2, 3 and 4 bilaterally, whorls on all fingertips except for an ulnar loop on both middle fingers, a fibular loop in both hallucal areas; slight chordee deformity of penis, and a 1×1 cm capillary hemangioma in the midscrotal region. Rest of the physical examination was unremarkable.

All roentgenologic, laboratory, ECG and cytogenetic studies were within normal limits except for a newborn bone age.

At 11 months J. C. was taking 4 to 5 steps and talking several words, he weighed 6.4 kg, was 69 cm tall and had a head circumference of 39 cm. Physical examination was unchanged. A growth hormone assay revealed a fasting level of 4 ng% with no rise after insulin induced hypoglycemia. Subsequently the patient was seen by JMO who made the diagnosis of the Dubowitz syndrome based on the above findings, the presence of minimal eczema, hyperactivity, and characteristic voice and appearance.

During the following year he remained hyperactive; he began to use 2—3 word sentences at the age of 2 years but spoke with a peculiar high-pitched voice. He had had approximately 5 episodes of bilateral otitis media and he continued with chronic coryza. Examination at 26 months: height 84 cm, weight 9.2 kg, head circumference 41.7 cm (all below the 3%ile); he also had bilateral chronic otitis externa, small conical teeth; this hyperactive boy constantly ran on his toes.

Case 6. D. C., the sister of case 5, was born on 24 August 1972 after a normal pregnancy but premature delivery at 32 weeks. Mother denied use of drugs during this pregnancy, but she was still married to the same husband who had a growing record of criminal activity. At birth the infant weighed 1.6 kg and she was 40.5 cm long. She had initial respiratory distress, was in the newborn nursery for 1 month and was discharged weighing 2.2 kg.

At 4 months D. C. was hospitalized for 10 days for respiratory difficulties requiring oxygen therapy; at 6 months she required 10 day hospitalization for croup, and at 6½ months again for bronchitis. D. C.'s psychomotor development is probably normal, but she has the same high pitched quality of voice as her older brother.

Examination at 7½ months showed a happy, small infant with a high-pitched unusual voice, a head circumference of 35.5 cm, height of 57 cm and weight of 4.5 kg (all measurements below the 3%ile). She had microbrachycephaly with closed anterior and posterior fontanels, a small pigmented nevus on the scalp, anteversion of nostrils, relatively broad bridge of nose, highly arched palate, micrognathia, fine and sparse hair, minimal cutaneous syndactyly of toes 2, 3 and 4 bilaterally, ulnar loops on all fingertips except for whorls on the right thumb and index finger; a distal loop in both hallucal areas. Rest of physical examination was unremarkable; her mental development was judged to be at a 5—6 month level.

Further Data on A.R., Patient of Dr. Dubowitz, and Case 1 of Grosse et al. (1971)

A. R. was reexamined shortly before her ninth birthday by Dr. Dubowitz who communicates these additional findings: Her eczema and sun sensitivity had disappeared. She had a submucous cleft involving the posterior one-half of the hard palate; it was 1 cm wide at the posterior end. Her speech was high-pitched. The outer one-half of her eyebrows was absent, but her scalp was essentially normal. The sacrum was prominent but not grossly abnormal. She had had extensive caries of her deciduous teeth, and two of her permanent teeth were also carious. Her fifth fingers and toes were short but not clinodactylous; there was pachyonychia of both fifth toenails. Dermatoglyphic studies showed, on palms and fingers: *t* axial triradius, hypothenar distal radial loop, third interdigital distal loop, no thenar or 1st, 2nd, or 4th interdigital patterns on either side. There was a whorl and a radial loop on the left and right thumb respectively; digits 2—5 showed the same pattern on both hands: ulnar loop, whorl, ulnar loop, and ulnar loop. There was a distal loop in both hallucal areas, and a remarkable tibial loop on the lateral aspect of the distal portion of both soles.

Discussion

This report brings the total of known cases to 11 (including A.R.'s infant sister) in 7 sibships. Eight of the patients are female, 3 are male; in three families a brother and a sister were affected, in one 2 sisters; 2 cases were sporadic. In one of the 7 families the parents were consanguineous (first cousins). These data strengthen the hypothesis of autosomal recessive inheritance of the Dubowitz syndrome; so far the parents have all appeared perfectly normal.

This report suggests that transient neonatal ECG and EEG changes, cryptorchidism, preaxial polydactyly, periosteal hyperostosis of proximal long bones, rib anomalies, and microcytic normo- (or slightly hypo-) chromic anemia may be component manifestations of the Dubowitz syndrome. The abnormal voice and remarkable behavioral phenotype are emerging as prominent characteristics of the syndrome. The female patient A.J., case 1 of this report, also shows that microcephaly can be present *without* significant shortness of stature; S.D. showed catch up growth from less than the third to greater than the 10th percentile. Although the story of multiple infections is impressive in some patients, it is not yet clear whether children with the Dubowitz syndrome are unusually susceptible to infection due to some impairment of their immune mechanism. Chronic rhinorrhea was again a prominent manifestation in A.J., J.C., and D.C.; A.J. also had unusually loose stools and feeding difficulties characterized primarily by regurgitation, vomiting, and occasional projectile emesis. In these 6 new patients eczema was a minimal problem or nonexistent.

The Dubowitz syndrome is a pleiotropic multiple congenital anomaly syndrome; however, some of the manifestations of the Z. siblings may represent the homozygous state of other recessive genes. So far, no diagnostic, physiologic or metabolic lead has emerged that would serve to explain the Dubowitz syndrome in terms of a single underlying inborn error of metabolism. To us the most remarkable feature of this syndrome is the degree of mental ability these patients can attain in spite of a head circumference which falls significantly below the second percentile.

From personal experience we have found that the most important differential diagnostic consideration involves the fetal-maternal-alcoholism (FEMAL) syndrome first described by Jones *et al.* (1973). These infants may show IUGR with PSOS, microcephaly (occasionally with signs of very severe neonatal brain damage), sparse hair, slight to severe mental retardation; on first view an appearance suggestively similar to infants with the Dubowitz syndrome (DS) but differing from it by the presence of sharp upper epicanthic folds and short palpebral fissures rather than the blepharophimosis-"dystopia canthorum"-ptosis com-

bination seen in DS children; FEMAL children have a high incidence of congenital heart disease which has not been observed in the DS. The minor anomalies in the two syndromes are also different. Since maternal alcoholism can occur during two or more pregnancies, the appearance of two FEMAL children in one sibship with phenotypically normal parents may initially suggest the presence of a recessively inherited disorder.

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