Eur J Pediatr (1986) 144:574–578

European Journal of
**Pediatrics**


# The Dubowitz syndrome

**W. Küster and F. Majewski**

Institute of Human Genetics and Anthropology, University of Düsseldorf, Federal Republic of Germany

**Abstract.** The Dubowitz syndrome is a rare, autosomal, recessively inherited disorder of intrauterine and postnatal growth retardation leading to microcephaly, moderate mental retardation and such characteristic facial anomalies as telecanthus, epicanthic folds, blepharophimosis, ptosis, broadening of the bridge and tip of the nose, abnormal ears and retrogenia. Further findings include hyperactivity, eczema, cryptorchidism in the affected males, and brachy-clinodactyly of the fifth fingers. Thirty-three cases with this syndrome have been reported in the literature. Five additional patients are presented. All five are sporadic cases. The diagnostic symptoms and the differential diagnosis are discussed.

**Key words:** Dubowitz syndrome – Genetics – Growth retardation

## Introduction

In 1965 Dubowitz described an infant girl with intrauterine and postnatal growth retardation, microcephaly, peculiar face, eczema, hyperactivity and moderate mental retardation. Further reports brought the number of patients with the syndrome to 33 [1, 2, 4–11]. We have examined five children with symptoms of the Dubowitz syndrome. We present the case reports and try to define the major diagnostic signs.

## Case reports

*Case 1: A. S., male*

The family history is unremarkable. The mother has two healthy daughters and has had two abortions. The parents are healthy and unrelated. During pregnancy bleeding occurred in the 24th week of gestation. Delivery was at the 42nd week of gestation with a birth weight of 2400 g, a birth length of 48 cm, and a head circumference of 33 cm. The newborn was cyanotic. At the age of 4 weeks a bilateral inguinal hernia was treated chirurgically. Retarded wound healing was observed. The statomotor development was delayed. The child learned sitting by 11 months. Evaluation at the age of 2 11/12 years (see Fig. 1a, b) showed a height of 90.5 cm (−1.6 SD), a weight of 11.5 kg (in relation to height age: −0.7 SD), and a head circumference of 47.5 cm (in relation to height age: −1.7 SD). The child had sparse, blond scalp hair. Epicanthic folds, a telecanthus, and a broad bridge and tip of the nose were noted. The dorsally positioned ears showed no dysplasias. There were full lips, a high narrow palate, and irregular-standing teeth in the upper jaw. The chin was reduced. Both cheeks showed a red skin with fine scaling. Other abnormalities included a soft heart murmur, bilateral cryptorchidism, and a small scrotum. Brachy- and clinodactyly of both fifth fingers and a pes valgum were found. Neurological examination revealed muscular hypotonia of the trunk and the upper limbs and hypertonia of the lower extremities. There was no free walking, no speech ability and a marked hypermobility. The karyotype was 46,XY.

*Case 2: G. V., male*

The family history is unremarkable. Both unrelated parents, a brother and a sister of the patient are healthy. There was premature labour beginning in the 7th month of gestation. Caesarean section was done 3 weeks preterm because of a narrow pelvis. Birth weight was 2650 g, birth length 50 cm and head circumference 35 cm. The APGAR score was 2-9-9. Recurrent infections were observed in the first 2 years. Bilateral inguinal hernias were treated chirurgically. Seizures of the grand mal type were observed at the age of 2 years. Statomotor development was retarded. The child was able to sit at 12 and to walk at 20 months. He could speek his first words at 17 months.

Physical examination at the age of 2 years (see Fig. 2a, b) revealed a height of 82 cm (−1.7 SD), a weight of 9.2 kg (in relation to height age: −1.9 SD), and a head circumference of 47.6 cm (in relation to height age: −0.3 SD). The occiput was prominent, and the forehead high. The child had silver-blond, fine scalp hair. There was a mongoloid slanting of the somewhat narrow palpebral fissures and epicanthic folds. The bridge of the nose was flat. Low set dysplastic ears were present. The lips were full and the mandible markedly hypoplastic. Palate and teeth were normal. Reduced subcutaneous fatty tissue was noted. Brachy- and clinodactyly of both fifth fingers were observed, whereas the limbs otherwise were normal. Bilateral cryptorchidism was found. The child suffered from a general muscular hypotonia and a severe hyperactivity. The voice was high-pitched and the speech development markedly delayed.

*Offprint requests to:* Dr. W. Küster, Hautklinik der Universität, Moorenstr. 5, D-4000 Düsseldorf, FRG

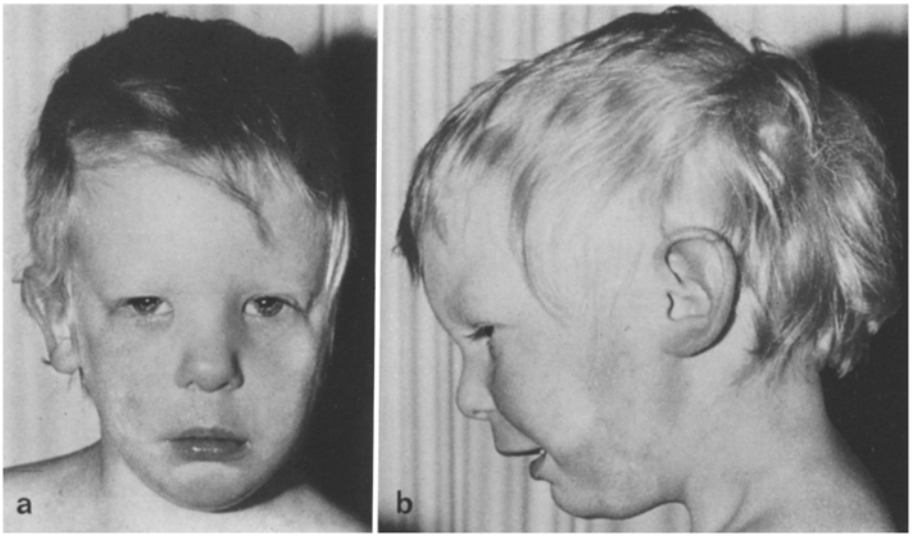


**Fig. 1a, b.** Frontal **a** and lateral **b** view of case 1. Note epicanthic folds, broad bridge and tip of the nose, full lips and retrogenia

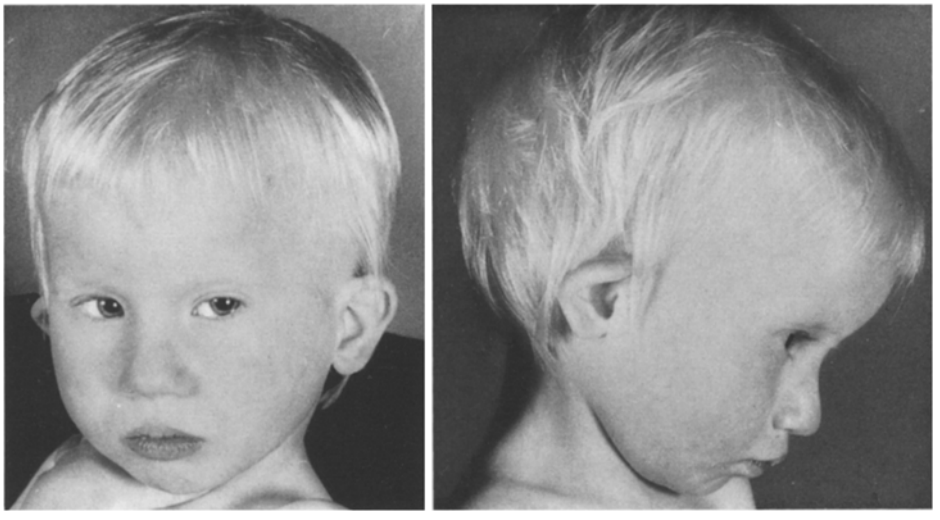


**Fig. 2a, b.** Appearance of case 2. Note fine scalp hair, epicanthic folds, low set dysplastic ears, full lips and retrogenia

*Case 3: P. D., male*

The family history is unremarkable. Both parents are healthy and unrelated. He is the first child. During pregnancy spotting was observed in the 4th week of gestation. Labour was induced in the 42nd week of gestation. Birth weight was 2710 g, birth length 50 cm, and head circumference 32 cm. The APGAR score was 8-9-10. Catheterization revealed a VSD, anomalies of the coronary vessels, an arteria lusuria and a right descending aorta. The statomotor development was nearly normal.

Physical examination at the age of 13 months revealed a height of 70 cm (−2.3 SD), a weight of 6390 g (in relation to height age: −2.1 SD), and a head circumference of 42.6 cm (in relation to height age: −1.3 SD). The child had fine, but not sparse scalp hair. There were epicanthic folds, somewhat small palpebral fissures with mongoloid slant (like the mother), but no ptosis. Markedly reddened cheeks were observed. The palate was normal. A minimal retrogenia was found. The ears were normal. A marked systolic murmur was present. The child showed reduced subcutaneous fatty tissue. Both testicles were descended. A small but deep sacral dimple was noted. Hands and feet were normal. The child suffered from moderate muscular hypotonia and marked hyperactivity.

*Case 4: N. S., female*

This is the first child of healthy and unrelated parents. The mother had had three spontaneous abortions. During pregnancy an EPH-gestosis was observed. A Caesarean section was performed in the 38th week of gestation because of suspected plancental insufficiency. The birth weight was 1590 g, the birth length 39 cm, and the head circumference 30.5 cm. After birth the child suffered from an infection of the urinary tract, and severe anaemia (haemoglobin 7.6 g %, reticulocytes 6‰) was found. Muscular hypertonia was present. The girl walked unaided at the age of 14 months and spoke her first words at the age of 14 months.

Physical examination at the age of 17 months (see Fig. 3a, b) showed a height of 73 cm (−2.3 SD), a weight of 8.3 kg (in relation to height age: −1.3 SD), and a head circumference of 44 cm (in relation to height age: −0.8 SD). The child had blond, but not sparse scalp hair. Epicanthic folds and a telecanthus were noted. The bridge of the nose was flat and broad and the nose shortened. There were low set ears without dysplasias. Mouth and palate were normal. The chin was reduced. There were normal external female genitalia and a deep sacral dimple. A brachydactyly of both fifth fingers was present, the extremities otherwise being normal. The tonus of

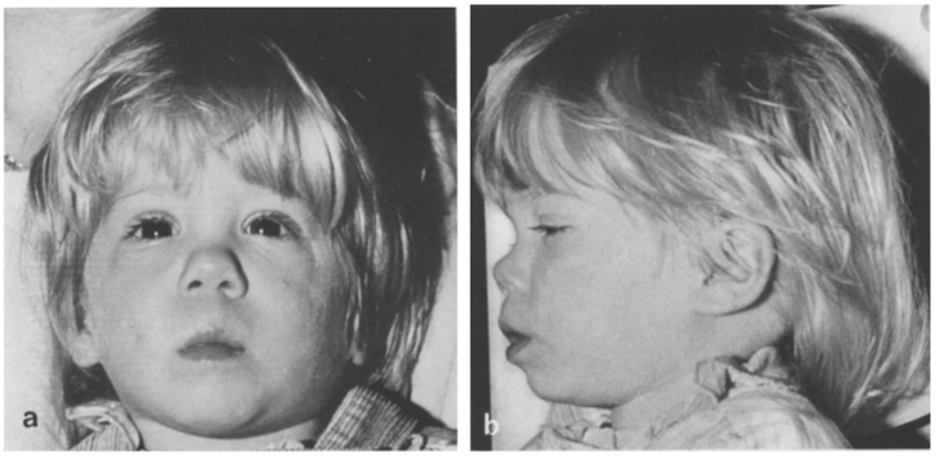

**Fig. 3a, b.** Frontal **a** and lateral **b** view of case 4. Note epicanthic folds, broad bridge of the nose, low set ears and moderate retrogenia

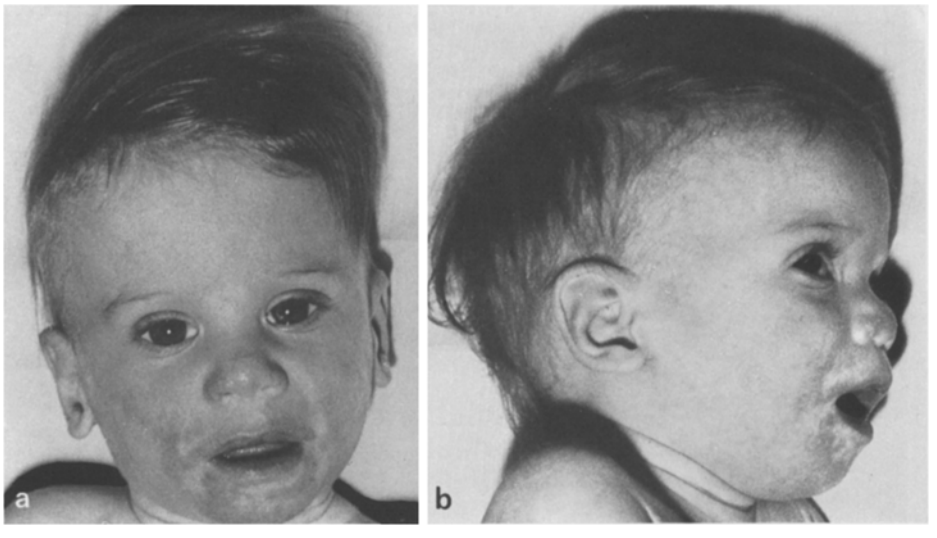

**Fig. 4a, b.** Frontal **a** and lateral **b** view of case 5. Note epicanthic folds, broad bridge and tip of the nose, normal philtrum and lips, eczema and retrogenia

the muscles was normal, the statomotor development was nearly within normal limits. The speech abilities were found to be markedly delayed. The mother reported a marked hypermobility at home.

*Case 5: R. W., male*

Both parents are healthy and non-consanguineous. Another female child (birth weight 3050 g) expired shortly after birth because of aspiration. During pregnancy the mother smoked 30 cigarettes daily and drank sometimes six glasses of beer in the evening, but obviously she was not alcohol-dependent. Delivery was at term. The birth weight was 1750 g, the birth length 43 cm, and the head circumference 30 cm. A lumbar meningomyelocele was repaired after birth. No hydrocephalus, but a paralysis of the bladder and anus was observed. Sucking was poor. Hospitalization was necessary because of respiratory infection.

Physical examination at the age of 13 months showed a girl with a height of 66 cm (−3.7 SD), a weight of 5630 g (in relation to height age: −3.7 SD), and a head circumference of 42 cm (in relation to height age: −0.7 SD) (see Fig. 4a, b). The child showed red-blond and fine scalp hair. The forehead was narrow and the occiput prominent. The anterior fontanel was 1 × 1 cm. Epicanthic folds and an epicanthus inversus were noted. There was no distinct telecanthus. A moderate ptosis of the upper lids, a deep and broad bridge and a broad tip of the nose were observed. The vermilion border of the upper lip was normal. The first incisivi were large, and the palate normal. A moderate retrogenia and dorsally positioned and low set ears without dysplasias were seen. A marked erythema was present with scaling on both cheeks, the tip of the nose and periorally. On the extensor parts of all extremities a partly linear and patchy erythema with slight scaliness was seen with further erythema of the perianal region. There was no brachydactyly, but a moderate clinodactyly of both fifth fingers. The subcutaneous fatty tissues were reduced. The child had a normal penis but the scrotum was small and empty. There was no hypotonia of muscles. The child was able to sit, but free walking was not possible. Marked hyperactivity was noted.

## Discussion

The main symptoms of our cases and the cases in the literature are summarized in Table 1. The mean values of birth weight,

**Table 1.** Symptoms of the Dubowitz syndrome

| | Published cases ($n = 33$) | Own cases ($n = 5$) |
|---|---|---|
| Sex ratio: male:female | 13:20 | 4:1 |
| Birth weight at term (mean value) | 2342 g ($n = 23$) | 2113 g ($n = 4$) |
| Birth length at term (mean value) | 44.3 cm ($n = 15$) | 45.0 cm ($n = 4$) |
| Head circumference at term (mean value) | 30.6 cm ($n = 8$) | 31.4 cm ($n = 4$) |
| Intrauterine and postnatal growth retardation | 26/33 (79%) | 5/5 |
| Microcephaly | 29/29 (100%) | 3/5 |
| Mental retardation/ Developmental delay | 14/26 (54%) | 5/5 |
| Hyperactivity | 14/21 (67%) | 5/5 |
| Muscular hypotonia | 2/ 5 (40%) | 3/5 |
| Sparse, blond hair | 20/24 (83%) | 5/5 |
| Telecanthus | 18/21 (86%) | 4/5 |
| Epicanthic folds | 14/23 (61%) | 5/5 |
| Ptosis-blepharophimosis | 19/23 (83%) | 2/5 |
| Broad tip of the nose | 14/21 (67%) | 4/5 |
| Abnormal ears | 22/24 (92%) | 4/5 |
| Retrogenia | 21/23 (91%) | 5/5 |
| Full lips | ? | 2/5 |
| High pitched voice | 15/22 (68%) | 1/5 |
| Submucous cleft palate | 7/16 (44%) | 0.5 |
| Brachy-clinodactyly of fifth fingers | 12/12 (100%) | 5/5 |
| Cutaneous syndactyly of 2nd and 3rd toes | 9/22 (41%) | 0.5 |
| Eczema | 14/24 (58%) | 1/5 |
| Cryptorchidism | 3/ 7 (43%) | 3/4 |
| Heart defects | 0/33 | 1/5 |
| Poor feeding, diarrhoea, vomiting, infections | 22/30 (73%) | 3/5 |
| Bone marrow hypoplasia | 2/33 (6%) | 0/5 |
| Malignancies | 3/33 (9%) | 0/5 |

birth length and head circumference of the published cases born at term correspondend to the 34th week of gestation. Psychomotor development ranged from severe to very mild retardation. Out of 17 cases 8 were reported to show "normal intelligence" [8]. Muscular hypotonia was present in our cases 1, 2, and 3 and in patients observed by Majewski et al. [5]. In contrast Wilroy et al. [12] and Orrison et al. [8] reported normal neurological findings. Typical morphological features of the Dubowitz syndrome include sparse, blond scalp hair, epicanthic folds, telecanthus and ptosis, broad bridge and tip of the nose, receding chin and dysplastic ears. Full lips are possibly another diagnostic sign. A high-pitched voice and a submucous cleft of the palate were frequently described. Minimal abnormalities of the hands and feet were often observed. A typical symptom is the eczema of the lower face and the flexures of elbows and knees. We saw a typical eczema in case 5 and remarkable reddened skin of the cheeks in cases 1 and 3. Heart defects or other internal malformations obviously are not typical of the Dubowitz syndrome. The heart defect in our case 3 may be due to chance. For further details see Table 1.

Repeated infections of the respiratory and the gastrointestinal tract were frequently reported, raising the possibility of an immuno-deficiency. In six out of seven patients in whom immunological studies were performed abnormal results were found: low levels of IgA (Majewski et al. [5], cases 1 and 2; Nöll-Gröne and Fuhrmann [6], cases 1 and 2), hypogammaglobulinaemia (Sauer and Spelger [10], case 1), and complete IgA deficiency (Sauer and Spelger [10], case 2). A follow-up study of a brother and a sister with Dubowitz syndrome [11] revealed aplastic anaemia with pancytopenia and severe bone marrow hypoplasia in the girl and leukopenia and spotty bone marrow hypoplasia in the boy. Three cases with malignomas have been reported: a neuroblastoma and a malignant lymphoma [10] and an acute lymphatic leukaemia [3]. Therefore the question of increased chromosome breakage and sister chromatid exchange is relevant. These examinations were done in three patients with Dubowitz syndrome, showing no abnormalities in one case [6] and a mild increased spontaneous rate of chromosome breakage, but no significant effect in clastogenic stress breakage studies in a brother and a sister [11].

All reported children with Dubowitz syndrome are of Caucasian stock. The sex ratio is approximately 1:1 (male:female = 17:21). Five affected pairs of siblings and one pair of monozygous twins are reported [1, 4, 7, 11]. The parents of all cases were healthy and one instance of consanguinity is known [7]. These data are in favour of autosomal recessive inheritance.

In comparison with the original case of Dubowitz [1] we feel some cases demonstrate different conditions. There are at least two cases with normal birth weight (Wilroy et al. [12], case 7; Orrison et al. [8], case 5). Because there exists no diagnostic test for the Dubowitz syndrome the diagnosis in most cases remains tentative; the inclusion or exclusion of some of these cases is arbitrary.

The single symptoms including intrauterine and postnatal growth retardation, microcephaly, mental retardation, and hypermobility are non-specific, occurring in many other syndromes. The abnormalities of the face (see Table 1) are of diagnostic value, when intrauterine growth retardation and microcephaly are present. The importance of the facial abnormalities for the diagnosis will be elucidated by studying affected siblings with different manifestations. The diagnosis can be supported by a longer observation of the child's behaviour. The hyperactive restlessness often is the most serious symptom for the parents.

The most important differential diagnosis is alcohol embryopathy, which shares in common a lot of symptoms. The main differences with the Dubowitz syndrome are short upturned nose, small vermilion border of lips, congenital heart defects, haemangiomas, hernias, absence of syndactylias and eczema and the drinking history of the mother. Alcohol embryopathy may be difficult to separate from the Dubowitz syndrome, as demonstrated by our case 5. Intrauterine and postnatal growth retardation, microcephaly and hyperactivity are typical of both disorders. The minimal telecanthus and the neural tube defect are in favour of the diagnosis alcohol embryopathy, whereas the eczema, the normal philtrum and lips and the broad tip of the nose are in favour of the Dubowitz syndrome, as well as the fact that the mother is not alcohol addicted.

## References


1. Dubowitz V (1965) Familial low birthweight dwarfism with an unusual facies and a skin eruption. J Med Genet 2:12–17
2. Fryns JP, Farbry G, Willemyns F, van den Berghe H (1979) The Dubowitz syndrome in a teenager. Am J Med Genet 4:345–347
3. Gröbe H (1983) Dubowitz-Syndrom und akute lymphatische Leukämie. Monatsschr Kinderheilkd 131:467–468
4. Grosse R, Gorlin J, Opitz JM (1971) The Dubowitz syndrome. Z Kinderheilk 110:175–187
5. Majewski F, Michaelis R, Moosmann K, Bierich JR (1975) A rare type of low birthweight dwarfism: The Dubowitz syndrome. Z Kinderheilk 120:283–292
6. Nöll-Gröne C, Fuhrmann W (1983) Dubowitz-Syndrom. Poster Demonstration. 18. Tagung der Gesellschaft für Anthropologie und Humangenetik, Münster
7. Opitz JM, Pfeiffer RA, Hermann JPR, Kushnick T (1973) Studies of malformation syndromes of man XXIV B: The Dubowitz syndrome. Further observations. Z Kinderheilk 116:1–12
8. Orrison WW, Schnitzler ER, Chun RWM (1980) The Dubowitz syndrome: Further observations. Am J Med Genet 7:155–170
9. Parrish JM, Wilroy RS (1980) The Dubowitz syndrome: The psychological status of ten cases at follow-up. Am J Med Genet 6:3–8
10. Sauer O, Spelger G (1977) Dubowitz-Syndrom mit Immundefizienz und malignem Neoplasma bei zwei Geschwistern. Monatsschr Kinderheilkd 125:885–887
11. Walters TR, Desposito F (1985) Aplastic anemia in Dubowitz syndrome. J Pediatr 106:622–623
12. Wilroy RS, Tipton RE, Summitt RL (1978) The Dubowitz syndrome. Am J Med Genet 2:275–284


Received April 1, 1985/Accepted August 23, 1985