Dubowitz syndrome

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Abstract
The Dubowitz syndrome, first reported in 1965, is defined as a multiple congenital anomalies (MCA), mental retardation (MR), growth failure condition with immune defect predisposing to allergies and eczema, hematologic malignancies and neuroblastoma. Clinical manifestations include pre- and postnatal growth retadation, microcephaly, mild to moderate mental retardation, and eczema. The patients are often hyperactive with short attention span. Facial appearance is characteristic with high or sloping forehead, flat supraorbital ridge, scanty lateral eyebrows, short palpebral fissures, ptosis, abnormally modeled ears, broad and flat nasal bridge, and unusual configuration of the mouth. Genital abnormalities include hypospadias and cryptorchidism. Affected individuals may also have sacral dimple, clinodactyly of the 5th fingers, and cutaneous syndactyly of the 2nd and 3rd toes. To date, more than 150 patients with this condition have been reported. The pathogenesis is unknown. The condition appears to be an autosomal recessive trait.

Keywords
Dubowitz syndrome, growth failure, immune defect, mental retardation, facial dysmorphy.

Disease name and synonyms
Dubowitz syndrome

Diagnosis criteria / definition
Diagnosis is mainly based on characteristic clinical manifestations including pre-and postnatal growth retardation, microcephaly, mild to moderate mental retardation, eczema, hyperactive behavior, characteristic facial appearance, and genital abnormalities.

Differential diagnosis
Some of the findings in the Dubowitz syndrome are similar to those of the fetal alcohol syndrome. They include pre and postnatal growth retardation, mild to severe mental retardation, microcephaly, and similar minor facial anomalies. However, lack of history of prenatal exposure to ethanol, and an overall pattern of clinical manifestations different from that of the fetal alcohol syndrome make the distinction easy. Other important differential diagnostic considerations include Bloom

syndrome and Fanconi anemia; patients with these condition may also manifest growth and mental retardation, skin abnormalities (not eczema), and hematological and immunological abnormalities. However, facial appearance and other clinical manifestations are different from those seen in the Dubowitz syndrome. Studies on chromosome instability have been performed infrequently, and the association of the Dubowitz syndrome with chromosome instability remains unresolved.

Prevalence
To date, more than 150 patients with this condition have been reported.

Clinical description
Although these clinical findings could exist in Dubowitz Syndrome, they are not constantly present among all patients with this syndrome.

Growth
Pre- and postnatal growth retardation is common.

Psychomotor development
The level of intellectual functioning ranges from severe mental retardation to average intelligence.

Neonatal problems
Respiratory problems include tachypnea, stridor, respiratory distress, rhinorrhea and pneumothorax. Feeding difficulties include poor suck, vomiting and gastro-esophageal reflux.

Facial anomalies
Facial anomalies are perhaps the most diagnostic of all physical signs.

- ***Skull***: Microcephaly, triangular face, facial asymmetry and/or weakness, craniosynostosis, narrow bifrontal diameter, dolichocephaly, trigonocephaly, small face, narrow face, brachycephaly, large open fontanelle, prominent occiput, flat occiput, and posterior hair whorl.
- ***Forehead***: High (sloping) forehead, flat supraorbital ridge, narrow bifrontal diameter, low frontal hairline, low (small) forehead, and prominent glabella.
- ***Eyes***: Blepharophimosis and ptosis were usually present. Other minor facial anomalies include telecanthus, hypertelorism, scant eyebrows, upslant of palpebral fissures, downslant of palpebral fissures, epicanthus, arched eyebrows, hypotelorism, and a prelobular mass of the cheek.
- ***Nose***: Broad nasal bridge, prominent round tip, flat nasal bridge, large long nose, broad tip, anteverted nostrils, short nose, long philtrum, flat philtrum, prominent nose, hypoplastic alae nasi, beak-shaped, and parrot-like.
- ***Ears***: Dysplastic ears, apparently low-set, posteriorly angulated, large and prominent, simple, large, small, hypoplastic helices, anteverted auricle, prominent, lack of antihelix, prominence of lower antihelix , hearing loss, forward-set, folded helix, hypoplastic tragus, right ear fistula , cup-shaped, and right preauricular fistula.
- ***Mouth*****:** Large mouth, and small mouth.
- ***Lips***: Flat philtrum, thin vermilion border of the upper lip, and long upper lip with prominent philtrum.
- ***Palate***: high (narrow) palate, submucous cleft palate, cleft palate, cleft uvula, and big adenoid and tonsils. Submucous cleft palate is common and early detection is recommended strongly for prophylaxis of middle ear infections.
- ***Chin***: Micrognathia, and prognathism, narrow chin, and Robin sequence.
- ***Neck***: short, webbed, and long.

Ocular manifestations
Ocular problems include strabismus, esotropia, microphthalmia, myopia, hyperopia, iris coloboma, cataract, nystagmus, anisocoria, megalocornea, iris hypoplasia, paresis, poor vision, astigmatism, blue sclerae, and deep optic nerve cupping and immature retinal vessels.

Dental manifestations
Tooth problems (anomalies) include delayed eruption, caries, crowded teeth, microdontia, malocculsion, malalignment (irregular), diastema, conical, oligodontia, macrodontia, missing upper central incisors, fused, doubled, bifid incisors, rotated lower incisors, and incomplete true fusion of the primary right mandibular canine and first molar.

Cutaneous manifestations
Sparse or thin hair and eczema were the most prominent cutaneous manifestations. The site of eczema varied from the entire body except face, to a limited area of the body: face, popliteal fossa, elbow-flexures, neck, gluteal areas, scalp, trunk, "extensor area", arms and legs, hands, and perianal area. Age of appearance ranged from 1 month to 2 years. Chronic severe eczema with intense itch was associated with excoriation, lichenification and crusting. The eczema often clears by age 2 to 4 years. It occasionally lasts after infancy, and in some cases until adult life. Topical medication including hydrocortisone cream is effective in some cases, but ineffective in others. Dietary modification may be helpful in

alleviating the. In severe cases, sleep may be disturbed through the night.
Other skin manifestations include dry skin, reduced subcutaneous fatty tissue, photosensitivity, hyperpigmentation, pigmented nevi, capillary hemangioma, seborrheic dermatitis, erythema, cutis marmorata, hyperkeratosis, diastasis recti , café-au-lait spot, umbilical hernia, congenital lymphedema, edema of feet, vascular marking, accessory nipple, hypotrichosis, atopic dermatitis, keloid scar, pityriasis, hypopigmentation, subcutaneous lymphangioma, and retarded wound healing.

Gastro-intestinal manifestations
Feeding difficulties during the neonatal period and infancy are common and are characterized by regurgitation, vomiting, and occasional projectile emesis. Since these symptoms are related mostly to gastroesophageal reflux, and rarely to vascular abnormality, a search for the underlying cause is recommended. Congenital constipation associated with anal stenosis, rectal prolapse and hiatal hernia were also reported.

Skeletal manifestations
Skeletal abnormalities involved limbs more prominently than other parts of the body.

- ***Skull***: Large anterior fontanelle, delayed closure of the cranial sutures, unusually pointed symphysis of the mandible, and stenosis of the external auditory canal.
- ***Central nervous system***
  Absence of corpus callosum, hypoplasia of the pituitary gland and stalk
- ***Hands***
  - Fingers: Clinodactyly of the 5th fingers, short fingers (brachydactyly), polydactyly, cutaneous syndactyly of fingers, nail hypoplasia, clinodactyly of the 2nd fingers, short metacarpals, radially deviated 5th fingers, ulnarly deviated 3rd fingers, overlapping fingers, mild hypertrophy of the interphalangeal joints, and small hands.
  - Thumbs: Broad thumb, camptodactyly, proximal thumb, finger-like thumb, right bifid thumb with separate nail, hypoplastic thumb, and adducted thumbs.
- ***Feet*** Cutaneous syndactyly of toes 2 and 3, club foot(pes planovalgus, pes equinovalgus), flat feet (pes planus), broad first toes, nail absence or hypoplasia, small feet, overlapping(crowded) toes, diastasis of 1st and 2nd toes, cutaneous syndactyly of toes 3 and 4, short 5th toes, short toes, cutaneous syndactyly of toes 4 and 5, wide 2nd toe, short 1st metatarsals , brachymetatarsy, metatarsus varus, and adducted metatarsals.
- ***Joints:*** Hyperextensible joints, genu valgum, and Osgood-Schlatter's disease.
- ***Chest:*** Pectus excavatum, pectus carinatum, and rib synostosis.
- ***Hips:*** Hip dysplasia, congenital dislocation of the hips, and coxa valga.
- ***Vertebrae :*** Sacral (pilonidal) dimple, scoliosis, *spina bifida* occulta, sacral cleft, kyphosis or hyperlordosis, dysplasia of a cervical vertebral body, prominence of the lower portions of the sacrum, dysplastic cervical vertebrae.

Cardiovascular manifestations
Congenital heart defects include ventricular septal defect, patent ductus arteriosus, atrial septal defect, coarctation of the aorta, and mitral valve prolapse.

Urogenital manifestations
- ***Male***: Genitourinary abnormalities include cryptorchidism, inguinal hernia, hypospadias, small testes, small penis, hypoplastic genitalia, hypoplastic scrotum, and bifid scrotum.
- ***Females***: Hypoplastic genitalia, hypoplasia of the clitoris and labia minora , hypoplastic labia majora, and partial vaginal septum.
- ***Kidney***: Vesicoureteral reflux, hydronephrosis, and later enuresis.

Neurological manifestations
Neurological problems include seizures, hypertonicity of the legs, migraine headaches, presence of Babinski sign, meningomyelocele, internal hydrocephalus, hydrocephalus, truncal ataxia, hyperactive deep tendon reflexes or hypoactive deep tendon reflexes, and paralysis of the bladder and anus.

Behavior problems
Behavior problems include high-pitched or hoarse voice, and hyperactivity.

Frequent infections
Recurrent infections are common in Dubowitz syndrome. Recurrent infections include repeated otitis media, urinary tract infection, upper respiratory infection, pneumonia, sinusitis, chronic rhinitis, ulcerative stomatitis, encephalitis, purulent dacryocystitis, croup syndrome, pertussis, mucositis, tonsillitis, and enteritis. Since hearing loss secondary to chronic otitis media or to Gentamycin® may occur, periodic hearing asessment is recommended.

Allergic problems include bronchial asthma and atopic dermatitis, and other allergy including food, pollen, dust, milk, or molds.

History of surgical procedures
A history of surgical treatment includes orchidopexy, ptosis, otitis media, herniorrhaphy, heart surgery, blepharophimosis, tonsillectomy, strabismus, adenoidectomy, club foot, cleft palate, or submucous cleft palate repair, tongue-tie, myringotomy, hypospadias, rectal prolapse, vocal cord cyst, removal of cartilage from the nose, meningomyelocele, chronic dacryostenosis, velopharyngeal insufficiency, subcutaneous lymphangioma, aberrant subclavian artery, bilateral tubal ligation, and polydactyly.

Complications
Velopharyngeal insufficiency associated with submucous cleft palate, vascular abnormalities, hypoparathyroidism, and hematological and malignant disorders have been reported.

Management including treatment
Regular, long-term follow-up of patients with Dubowitz syndrome is recommended. We suggest regular study of:

1) growth: plot carefully; consideration of treatment with growth hormone or anabolic steroids may be discussed with pediatric endocrinology consultant;
2) health status including regular physical examination, urinalysis and complete blood count;
3) speech and dental development, and hearing especially in those who have had multiple middle ear infections;
4) behavior/neurologic problems;
5) Developmental and intellectual quotients (D.Q./I.Q).: Denver developmental scale and other formal testing;
6) surgical needs: repair of craniofacial, limb, or urogenital anomalies;
7) surveillance for hematological and malignant (mostly neuroblastoma) disorders;
8) educational programs appropriate for individual patients.

Etiology
The cause of the Dubowitz syndrome is unknown, but is presumed to represent the homozygous state of an autosomal recessive mutation. There is a suggestion that some carriers may show mild manifestations. Familial occurrence was found 15 times in a total of 141 patients.

Diagnostic methods
Diagnosis is based on characteristic clinical manifestations.

Antenatal diagnosis
At the moment, prenatal diagnosis is not reliable.

Unresolved questions
The association of the Dubowitz syndrome with chromosome instability remains unresolved.

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