SYNDROMES PRESENTING ADDUCTED THUMB WITH/ WITHOUT CLUBFOOT AND DUNDAR SYNDROME

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Summary: Syndromes presenting adducted thumb with/without clubfoot and Dundar syndrome: Congenital adducted thumb has been called variously as congenital clasped thumb, thumb in palm deformity or flexion adduction deformity of the thumb. This condition can be an isolated anomaly or associated with several genetic disorders. The syndromes that include adducted thumb as a cardinal feature such as Dundar Syndrome are few in the literature. This syndrome is an autosomal-recessive very rare disorder characterized by typical facial appearance with dysmorphic features that includes wasted build, hyperextensible, thin and translucent skin with atrophic scarring, severe congenital contractures of fingers and thumbs, club feet, severe kyphoscoliosis, joint instability, muscular hypotonia, and ocular involvement. Heart, kidney, and/or intestinal defects can also be observed. Up to date the syndrome is described in few families in the literature.

Here we discuss the syndromes that include adducted thumb as a cardinal feature and also the differential diagnosis of the Dundar Syndrome according to the literature.

Key-words: Adducted thumb - Adducted thumb-clubfoot syndrome - Dundar syndrome - Ehlers-Danlos syndrome musculocontractural type.

INTRODUCTION

A congenital flexed adducted thumb has been called variously as congenital clasped thumb, thumb in palm deformity or flexion adduction deformity of the thumb. This condition can be an isolated anomaly or associated with several genetic disorders. Congenital clasped thumb refers to a wide spectrum of thumb anomalies. It can be a result of mild deficiencies of the thumb extensor mechanism (extensor pollicis brevis or longus or both) or severe abnormalities of the extrinsic and intrinsic muscles, web space and soft tissue and joint contractures (3). According to the most useful classification that proposed; type I is supple clasped thumb with absence of hypoplasia of the extensor muscles, the thumb can passively abducted and this condition is seen without other digital abnormalities. Type II clasped thumb is a complex type with additional findings of hand contractures as joint contractures and collateral ligament abnormalities. In this form the thumb cannot be passively abducted and extended. Also other digital anomalies can be seen. Type III clasped thumb is associated with related syndromes especially arthrogryposis group. In this type the extensor mechanism can be deficient or normal (17, 20, 28). This condition should alert the

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clinician for various genetic syndromes (30).

Dundar Syndrome (Ehlers-Danlos Syndrome, Musculocontractural Type), Christian Adducted Thumbs Syndrome, Escobar or multiple pterygia syndrome, MASA Syndrome, Arthrogryposis Multiplex Congenita, Distal, Type I, Arthrogryposis, Distal, Type 2a are some of the most common syndromes that include adducted thumb as a cardinal feature.

**SYNDROMES**

**Dundar Syndrome** (Ehlers-Danlos Syndrome, Musculocontractural Type, Adducted Thumb – Club Foot Syndrome, Arthrogryposis, Distal, with Peculiar Faces and Hydronephrosis, MIM ID #601776) is a rare syndrome that was originally described by Dundar et al. in male and female first cousins (4). Later on Sonoda and Kouno and Janecke et al. reported similar cases (10, 26). Up to date there are few reports published related with the syndrome. This syndrome embraces a broad spectrum of features. It is characterized by typical facial appearance that comprises frontal bossing, late-closing anterior fontanelle, telecanthus, downslanting palpebral fissures and deep set/ posteriorly rotated ears, downturned angles of mouth, facial clefting. The dysmorphic features include wasted build, thin and translucent skin, ocular anterior chamber abnormalities, distal arthrogryposis with arachnodactyly and adducted thumbs, club feet, joint instability and coagulopathy. The heart, kidney, and/or intestinal defects can also be observed (4, 5).

Dundar et al. performed a genome-wide linkage scan, sequenced two candidate genes on chromosome 15q15, and identified homozygous mutations in the CHST14 gene in each family (5). The CHST14 gene encodes N-acetylgalactosamine 4-O-sulfotransferase 1 (D4ST1), which catalyzes the 4-O-sulfation of N-acetylgalactosamine (GalNAc) residues in dermatan sulfate and it is determined that loss of dermatan-4-sulfotransferase 1 function results in adducted thumb-clubfoot syndrome. Later on Müller et al. demonstrated locus heterogeneity in the syndrome (23). They provided evidence for the important role of dermatan sulfate in human development besides extracellular matrix maintenance (23). As a result the syndrome is the first metabolic defect specific (restricted) to dermatan sulfate biosynthesis and it is a form of congenital disorder of glycosylation (9). Miyake et al. demonstrated abnormal collagen bundle formation at a group of patients and suggested that this can be a main pathology associated with a decorin glycosaminoglycan abnormality (21). Dundar Syndrome has an autosomal recessive inheritance pattern and is caused by homozygous or
compound heterozygous mutations (5). To date nine CHST14 variants have been determined which are all related with the syndrome (5, 14, 16, 18, 21).

**Adducted Thumbs Syndrome** (Thumbs, Congenital Clasped, MIM ID 201550) that characterized by arthrogryposis, dysmyelination, craniosenosis, and cleft palate. The syndrome was originally described by Christian et al. in three infants from an inbred Amish pedigree and consisting of adducted thumbs, craniosynostosis and severe neurological abnormalities (2). Striking dysmorphic features include prominent sutures, a prominent occiput, telecanthus, an antimongoloid eye slant, strabismus, a narrow, high, or cleft palate with a bifid uvula, posteriorly rotated ears, and micrognathia. There are multiple joint contractures of the large joints, but also of the index fingers, in addition to the adducted thumbs. Muscle bulk was reduced and the infants were hypotonic (2). Kunze et al. reported a similar female infant who died at the age of 3 months. She had difficulty in swallowing with an ophthalmoplegia, hypotonia, and areflexia. There were multiple joint contractures with camptodactyly and adducted thumbs, but apparently no craniosynostosis (15). The genetic basis of this syndrome remains unknown but it was observed to have an autosomal recessive inheritance pattern.

**Multiple pterygia syndrome** (MIM ID 265000) is a form of arthrogryposis multiplex congenita which is an autosomal recessive condition and shows clinical heterogeneity. Initially it is categorized into two types; prenatally lethal and nonlethal (22). The nonlethal type, called Escobar syndrome (ES) (MIM #265000) characterized by excessive webbing (pterygia, especially of the neck, antecubital and popliteal areas), congenital joint contractures (arthrogryposis), scoliosis, syndactyly and camptodactyly of the fingers, and foot deformities (2, 15). Other variable features include intrauterine death, congenital respiratory distress, growth retardation, short stature, kyphoscoliosis and other vertebral anomalies, a mild to moderate degree of facial dysmorphism, ptosis, antimongoloid slant of eyes, low-set ears, cleft palate, cryptorchism, arachnodactyly and congenital contractures (4, 10, 11, 26). The syndrome was first reported by Bussiere in 1902 and since then, more than 60 families have been reported (11, 13). Hoffmann et al. and Morgan et al. reported that both variants of multiple pterygium syndrome can be caused by mutations in the gamma, or fetal, subunit of the nicotinergic acetylcholine receptor (AChR) gene located at chromosome 2q33–q34 (8, 22). Further, it was observed that mutations in two other related genes, CHRND and CHRNA1, also can cause the lethal type of MPS (19).
MASA Syndrome (Mental Retardation, Aphasia, Shuffling Gait, And Adducted Thumbs, Spastic Paraplegia, Type 1, Clasped Thumb and Mental Retardation, Thumb, Congenital Clasped, With Mental Retardation, Adducted Thumb with Mental Retardation, Gareis-Mason Syndrome, Crash Syndrome, MIM ID #303350) was originally described by Bianchine and Lewis (1). The cardinal clinical features of the syndrome are mental retardation, aphasia, shuffling gait, and adducted thumbs was summarized by the acronym MASA (1). The shuffling gait is thought to be caused by spasticity of the lower limbs. The clinical features also include; short stature, microcephaly, macrocephaly, strabismus, kyphosis, lordosis, pes cavus, talipes equinovarus increased reflexes and the delayed onset of speech. Structural brain abnormalities can also be seen such as agenesis of the corpus callosum, enlarged cerebral ventricles and hydrocephalus (1, 32). The condition has an X-linked recessive inheritance pattern. This syndrome is caused by mutation in the L1 cell adhesion molecule (L1CAM) gene (31).

Arthrogryposis Multiplex Congenita, Distal, Type 1a (MIM ID #108120) belongs to a highly heterogeneous group. In this type the affected parts of the limbs are usually the distal parts especially hands and feet. The fingers are medially overlapping, fists are clenched and also camptodactyly, ulnar deviation of the fingers and the positional foot deformities can be seen. The other joints contractures are variable. In this type of arthrogryposis there are no associated visceral anomalies. Besides this, the patients’ intelligence is normal (7). The classic form is always sporadic but there are some authors that described families that have dominant inheritance (7, 12). The causative factor of this type of artrogryposis was demonstrated by Sung et al. and TPM2 gene that encodes beta-tropomyosin was determined (27).

Arthrogryposis, Distal, Type 2a (Freeman-Sheldon Syndrome, Whistling Face-Windmill Vane Hand Syndrome, Cranioarciptarsal Dys trophy, Cranioarciptarsal Dysplasia, MIM ID #193700) syndrome is originally described by Freeman and Sheldon (6). The syndrome has an autosomal dominant inheritance pattern and includes skeletal malformations and facial characteristics. Abnormal x-ray appearance of the floor of the anterior cranial fossa of the skull, microcephaly, camp todactyly with ulnar deviation, adducted thumbs, kyphoscoliosis, hip dislocation, talipes equinovarus, contracted toes, and vertical talus; are the common skeletal abnormalities. Facial characteristics include full forehead, mask like facies, deep-set eyes with hypertelorism and telecanthus, epicanthal folds, increased philtrum length, small nose with
hypoplastic alae nasi and a small mouth (6). Toydemir et al. screened 28 FSS probands for mutations in genes that encode myosin heavy chains and a mutation in the MYH3 gene in 26 of 28 FSS cases was reported (29).

**DISCUSSION**

At the genetic evaluation of a case with adducted thumbs the clinician must be careful while making the final decision between non syndromic adducted thumbs and syndromic forms (Table I). In a study in which twenty-five patients were included, additional features were observed in 88% of the cases (30). Neurological evaluation must be done carefully as neurologic abnormalities are commonly associated with the condition. Brain imaging should be performed and besides mental status should be evaluated (30). Up to date 27 genetic syndromes have been identified in which adducted thumbs can be a possible clinical clue (30). Before the molecular analyses, cytogenetic analyses must be performed as cytogenetic abnormalities such as interstitial 1p36 deletion, 2q inverted duplication/deletion, 3p26 deletion found to be associated with adducted thumbs (30). Dundar syndrome represents a recognizable pattern with generalized connective tissue disorders with facial dysmorphic features. Effected individuals in each of the families shared phenotypic characteristics that are atypical for previously described syndromes such as Christian Adducted Thumbs Syndrome, Escobar or multiple pterygia syndrome, MASA Syndrome, Arthrogryposis Multiplex Congenita, Distal, Type 1a, Arthrogryposis, Distal, Type 2a. With the presence of characteristic features such as typical facial appearance, wasted build, thin and translucent skin, ocular anterior chamber abnormalities, arachnodactyly and distal arthrogryposis with severely adducted thumbs, club feet, joint instability and coagulopathy, Dundar Syndrome must be investigated by performing molecular analysis for the responsible gene, CHST14 which is on chromosome 15q15. Shimizu et al. presented a comprehensive review of all 20 reported patients (25). They mentioned that, at birth some remarkable features can be seen such as large fontanelle, hypertelorism, downslanting palpebral features, multiple congenital contractures with adducted thumbs, talipes equinovarus, and cylindrical fingers and as the cases grew older spinal deformities, marfanoid body habitus, and recurrent joint dislocations can be seen. Dermatologic features can be remarkable also such as hyperextensibility, and fragility that can cause atrophic scars. Abnormal platelet function which can cause bleeding,
Table I: The clinical features of the syndromes (summarized from Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). Updated 30 August 2013). World Wide Web URL: http://omim.org/).

<table>
<thead>
<tr>
<th>OMIM #</th>
<th>Inheritance</th>
<th>Dundar syndrome</th>
<th>Adducted thumbs syndrome</th>
<th>Multiple pterygia syndrome, Escobar Variant</th>
<th>MASA Syndrome</th>
<th>Distal arthrogryposis type 1A</th>
<th>Distal arthrogryposis type 2A</th>
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<td>601776</td>
<td>Autosomal recessive</td>
<td>201550</td>
<td>265000</td>
<td>Autosomal recessive</td>
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<td>108120</td>
<td>193700</td>
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<tr>
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<td>303350</td>
<td>X-linked recessive</td>
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<tr>
<td></td>
<td>Autosomal dominant</td>
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<td>108120</td>
<td>Autosomal dominant</td>
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<tr>
<td></td>
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<td>108120</td>
<td>193700</td>
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</tbody>
</table>

Growth
- Severely wasted build
- Short stature
- Short stature
- Low birth weight, Failure to thrive (infancy), Postnatal growth deficiency

Head and Neck
- Brachycephaly, large fontanel with delayed closure, Cranioostoressis, microcephaly, Neck pterygia, Microcephaly, macrocephaly, Microcephaly, short neck

Face
- Broad, flat forehead, micrognathia in infancy, protruding jaw from adolescence, facial asymmetry from adolescence, Stiff, myopathic facies, Micrognathia, long philtrum, flat, expressionless face, long face, Full forehead, mask-like facies long philtrum, H-shaped chin dimple, flat face, ‘whistling’ appearance

Ears
- Low-set and rotated ears, prominent ears, hearing impairment, Low-set ears, hearing loss, conductive, Deep set eyes, telecanthus, epicanthal folds, strabismus, blepharophimosis, ptosis

Eyes
- Eye anomalies, variable, blue sclerae, hypertelorism, downslanting palpebral fissures, strabismus, myopia, glaucoma, microcornea, retinal detachment, anterior chamber abnormality, Ptosis, downslanting palpebral fissures, epicanthal folds, hypertelorism, Strabismus

Nose
- Short with hypoplastic columella, long philtrum, Broad nasal bridge, small nose, hypoplastic alae nasi

Mouth
- Thin upper lip, small mouth in infancy, high-arched palate, cleft palate, Mouth open, high-arched palate, cleft palate, Downturned corners of mouth, difficulty in opening mouth, cleft palate, high-arched palate, small mouth, Small mouth, pursed lips

Cardiovascular
- Valve anomalies, atrial septal defect, hematomas, recurrent large subcutaneous
<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Hemopneumothorax</th>
<th>Respiratory insufficiency</th>
<th>Neonatal respiratory distress Pulmonary hypoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribs, Sternum, Clavicles and Scapulae</td>
<td>Pectus excavatum, flat and thin pectus</td>
<td>Rib fusion Long clavicles</td>
<td>Stiff shoulders</td>
</tr>
<tr>
<td>Breasts</td>
<td>Hiatal hernia</td>
<td>Diaphragmatic hernia, entration of diaphragm</td>
<td></td>
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<tr>
<td>Abdomen</td>
<td>Umbilical hernia, diastasis recti</td>
<td>Umbilical hernia</td>
<td></td>
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<tr>
<td>Gastrointestinal</td>
<td>Constipation, diverticular perforation, duodenal obstruction due to malrotation</td>
<td>Swallowing difficulties</td>
<td></td>
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<tr>
<td>Genitourinary</td>
<td>Cryptorchidism, hydronephrosis, bilateral, recurrent cystitis, enlarged bladder</td>
<td>Cryptorchidism, inguinal hernia, hypospadias, absence of labia majora</td>
<td>Inguinal hernia</td>
</tr>
<tr>
<td>Spine</td>
<td>Scoliosis</td>
<td>Scoliosis, kyphosis, fusion of cervical vertebrae, anterior clefing of vertebral bodies</td>
<td>Kyphosis, lordosis Mild scoliosis Kyphoscoliosis, spina bifida occulta</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Dislocation of hip</td>
<td>Hip flexion contractions, congenital hip dislocations, decreased hip abduction</td>
<td>Hip contractures</td>
</tr>
<tr>
<td>Limbs</td>
<td>Hypermobility of shoulders</td>
<td>Absent patella, dysplastic patella, dislocated radial head, flexion contractures</td>
<td>Elbow flexion contractures, knee flexion contractures Shoulder contractures Knee contractures</td>
</tr>
<tr>
<td>Hands</td>
<td>In infancy bilateral adducted thumbs, arachnodactyly, slender and/or cylindrical fingers, distal arthrogryposis, hypermobility of small joints</td>
<td>Thumbs flexed and adducted Camptodactyly, syndactyly, arachnodactyly</td>
<td>Adducted thumbs Tightly clenched fists (neonate), camptodactyly (adult), ulnar deviation (adult), absent distal interphalangeal creases, single transverse palmar creases Ulnar deviation, cortical thumbs, camptodactyly</td>
</tr>
<tr>
<td>Feet</td>
<td>Talipes equinovarus in infancy, talipes valgus and planus, progressive, hypermobility of small joints</td>
<td>Talipes calcaneovalgus, talipes equinovarus, rocker-bottom feet, camptodactyly</td>
<td>Pes cavus, talipes equinovarus Talipes equinovarus, calcaneovalgus deformities, vertical talus Equinovarus, contracted toes, vertical talus</td>
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<tr>
<td>System</td>
<td>Characteristics</td>
<td>Diagnosis</td>
<td>Findings</td>
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<td>------------------------</td>
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<tr>
<td>Skin</td>
<td>Hyperextensible skin, ecchymoses, fragile skin with atrophic scarring, delayed wound healing, hyperalgesia to pressure, palmar creases, fine to acrogeria-like, subcutaneous infections, recurrent, with fistula formation</td>
<td>Hypertrichosis</td>
<td>Pterygia of digits, neck, axillae, antecubital, popliteal, intercrural areas</td>
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<td></td>
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<td>Absent distal interphalangeal creases, single transverse palmar creases</td>
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<td>Thickened skin over flexor surface of proximal phalanges</td>
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<tr>
<td>Skin Histology</td>
<td>Fine collagen fibers predominant in reticular to papillary dermis, thin collagen bundles</td>
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<tr>
<td>Electron Microscopy</td>
<td>Collagen fibrils dispersed in reticular dermis, smooth, round collagen fibrils</td>
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<tr>
<td>Muscle, Soft Tissue</td>
<td>Hematomas, recurrent large subcutaneous, low muscle mass, hypotonia</td>
<td>Myopathy</td>
<td>Reduced muscle mass</td>
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<td></td>
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<td>Mild muscle weakness, skeletal muscle biopsy shows fiber size variability; type 1 fiber type predominance, small type 1 fibers, increased interstitial connective tissue</td>
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<tr>
<td>Metabolic Features</td>
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<tr>
<td>Neurologic</td>
<td>Gross motor developmental delay</td>
<td>Dysmyelination with excess myelin-dependent gliosis, myelin solubilization, generalized hypotonia, velopharyngeal insufficiency</td>
<td>Normal intelligence</td>
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<td></td>
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<td>Mental retardation, aphasia, shuffling gait, lower limb spasticity, agenesis of the corpus callosum, enlarged cerebral ventricles, hydrocephalus</td>
<td>Normal intelligence</td>
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<td>Mental retardation, seizures</td>
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<td>TPM2, 190990.0001</td>
<td>MYHB, 160720.0001</td>
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congenital cardiac defects, ophthalmological complications, and urolithiasis also reported (25).

Like all the syndromes early clinical diagnosis will be helpful for prediction of prognosis, the assessment of the other clinical problems of the patients and for the follow-up and therapy of the clinical conditions related with the syndrome. It is important to identify the mutation in order to inform the families for prenatal and preimplantation genetic diagnosis and as the syndrome has an autosomal recessive inheritance pattern, detailed genetic counseling must be given to families according to the literature.

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