MYOPATHY WITH CONTRACTURES

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Contracture is the prominent feature.
One of a handful of signs in muscle disease
Distribution and onset of the contracture is a very important clue for diagnosis.
(exclude late stage muscular dystrophy & severe CMD or congenital myopathy)
Some with important cardiac manifestations, and important to recognize
Limitation of the locomotion or disability
Management of the contracture is important for ambulation

PATHOPHYSIOLOGY OF CONTRACTURE

- Changes in muscle sarcomere length, fiber type, ECM concentration, fiber and fiber bundle stiffness, mechanical properties, and even stem cell numbers
- Exhaustion of the satellite cell due to constant regeneration of muscle fibers


MYOPATHY WITH CONTRACTURES

- Emery-Dreifuss muscular dystrophy (EDMD)
- Congenital muscular dystrophy (CMD)
  - Collagen VI muscular dystrophy (Ullrich CMD & Bethlem myopathy)
  - Merosin deficient (MDC1A)
- Severe congenital myopathy
  - Central core – severe scoliosis
  - Nemaline myopathy – arthrogryposis
- Duchenne muscular dystrophy
- SEPN 1–related myopathies (rigid spine syndrome)
- FHL1–related genetic conditions and other myofibrillar myopathies
- Limb girdle muscular dystrophy 2A, Calpainopathy (ankles and elbows but sparing of respiratory muscles)
EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD)

- 1961 Dreifuss & Hogan described a large family with an X-linked form of MD
- 1966 Dreifuss & Emery reevaluated this family
- Early 1980s autosomal dominant form described by several authors
- Limb girdle weakness, prominent joint contractures, cardiac involvement
- 5 genes causing EDMD (linker of nucleoskeleton and cytoskeleton complex)
  - EMD (STA) - emerin (X-linked recessive)
  - LMNA - Lamin A & C (AD)
  - SYNE1 & 2 - synaptic nuclear envelope protein 1 & 2 (Nesprin 1 & 2)
  - SUN1 & 2
  - TMEM43 (LUMA)

CLINICAL FEATURES OF EDMD

- Normal at birth and in the first few years of life
- Contractures often develop in the second decade of life, affecting the elbows or the ankles, posterior cervical muscles (limited neck flexion)
  - Early in X-linked EDMD
- Slowly progressive muscle weakness targeting humeral and peroneal distributions
- Atrophy of biceps and triceps
- Toe-walking, slow running, and loss of balance or falling
- Early hyporeflexia or areflexia
- Loss of ambulation in the late 2nd to 3rd decade (common in AD-EDMD)

CARDIAC ABNORMALITY OF EDMD

- Sudden cardiac death is present long before the onset of muscle weakness
- Cardiac conduction system is the earliest target
- First-degree AV block, broad flat P waves, absent P waves, right bundle branch block, atrial fibrillation or atrial flutter (with no rapid ventricular response)
- Cardiomyopathy leading to heart failure (Laminopathy)
- Pacemaker implantation does not always prevent sudden death
- Internal cardioverter defibrillators might be appropriated for EDMD with LMNA mutation
- Age for implantation 20-40 years of age
ULLRICH CONGENITAL MUSCULAR DYSTROPHY & BETHLEM MYOPATHY

- Collagen VI related dystrophies (COL6-RD)
- Autosomal recessive or
- Autosomal dominant (less frequent); in Bethlem myopathy & 50% of Ullrich CMD with de novo dominant negative mutation
- Mutation in 1 of 3 collagen type VI genes (COL6A1, COL6A2, COL6A3)
- Collagen VI – triple helix heterotrimeric monomer of α1, α2 and α3 chains excreting to extracellular space (formation of collagen fibrillar network)
- Cellular adhesion and binding to extracellular matrix proteins
- Anchoring the basement membrane to surrounding CNT & cell-cycle signaling during proliferation/differentiation
- Pathogenesis and phenotypic heterogeneity are unclear

DIFFERENTIAL DIAGNOSTIC

- LAMA2-RD with partial deficiency
- LMNA-RD
- Emery–Dreifuss muscular dystrophies and FHL1-related disorders
- Kyphoscoliotic Ehlers–Danlos syndromes (type VI)

COLLAGEN VI FORMATION

Bernardi P. Ann N Y Acad Sci. 2008;1147

CLINICAL FEATURES

- Ullrich CMD
  - early onset weakness (newborn)
  - Congenital hip dislocation
  - Delayed ambulation
  - Lost ambulation around 10-20 yr
  - Proximal joint contractures
  - Distal joint hyperextensibility
  - Normal IQ
  - Skin:
    - Follicular hyperkeratosis
    - Abnormal scar formation
  - Early & progressive RLD
  - Nocturnal BiPAP after 10 yr
  - Scoliosis
  - CK 1-5X normal
  - No cardiac involvement

- Bethlem Myopathy
  - Onset birth-2nd decade
  - Proximal weakness
    - Legs>arms
    - Extensor>flexor
  - Contractures of fingers, wrists, elbows, ankles
  - No cardiac involvement
  - Rare RLD
  - CK 1-5X normal

UCMD = Ullrich Congenital Muscular Dystrophy
BM = Bethlem Myopathy, RLD = Restrictive lung disease
CLINICAL PHENOTYPE

HYPERLAXITY OF DISTAL JOINTS

(A) keloid formation after ear piercing; (B) follicular hyperkeratosis of the arm; and (C) Bethlem sign—flexion contractures of the fingers on wrist extension

MUSCLE MRI

- Characteristic fatty and connective tissue replacement of muscle starting around the fascia surrounding or traversing the muscle
- Rectus femoris and vastus lateralis muscles
- Similar appearance can be appreciated on muscle ultrasonography, where the degeneration around the central fascia in the rectus femoris generates the appearance of a “central cloud”


IMMUNOLOCALIZATION OF COLLAGEN VI IN THE MUSCLE OF A PATIENT WITH A DOMINANT NEGATIVE MUTATION IN COLLAGEN VI

ULLRICH CONGENITAL MUSCULAR DYSTROPHY & BETHLEM MYOPATHY

- Genotype-phenotype correlation
  - Early-severe form (never walk); most had homozygous premature termination codon mutation
  - Moderate-progressive form (loss of ambulation at 4-25 years); 80% had dominant de novo exon skipping or missense mutation
  - Mild form (ambulatory until 3rd decade); 50% had absent or strongly reduced secretion of collagen VI
- Severity of dominantly acting mutations depend on the ability of mutant protein to be incorporated into the tetramer

DYSTROPHIN ASSOCIATED GLYCOPROTEIN COMPLEX AND RELATED PROTEINS

Immunostaining of Collagen VI in Cultured Fibroblasts

with Tx-100 20x overlayer

Normal UCMD #13

C. Bönnemann, Philadelphia
COLLAGEN VI AND MITOCHONDRIA

Bernardi P. Ann N Y Acad Sci. 2008;1147

MITOCHONDRIAL DYSFUNCTION IN UCMD


COLLAGEN VI-MITOCHONDRIA CONNECTION

- Mitochondrial PTP: selective channel in inner mitochondrial membrane
  - Massive swelling of mitochondria
  - Rupture outer membrane
  - Release of components that induce apoptosis
- Pore opening inhibited by Cyclosporine A


MUSCLE DISEASE WITH ARTHROGYROSIS
MUSCLE DISEASE WITH ARTHROGRYPOSIS

- Multiple congenital contractures at birth
- Abnormalities of muscle formation structure and/or function leading to secondarily decreased fetal movement
- Congenital muscular dystrophy (Merosin deficiency), congenital myopathies (nemaline myopathy, central core/nuclear myopathies), mitochondrial disorders

DUCHENNE MUSCULAR DYSTROPHY

Early- before loss of ambulation  Late- after loss of ambulation

LGMD2A: SCAPULAR WINGS, MILD DELTOID ATROPHY, TOE WALKING

Severe congenital nemaline myopathy with primary pulmonary lymphangiectasia: unusual clinical presentation and review of the literature

Waisayarat J et al. Diagnostic Pathology 2015; 10: 27

Muscle biopsy (mGT, EM)
Markedly-dilated lymphatic vessels
Heterozygous missense mutation ACTA1 c.1127G>C p.Cys376Ser
CXR reveals bilateral chylothorax
SELENOPROTEIN (SEPN 1)-RELATED MYOPATHY

- Causes a range of conditions
  - Multi-minicores
  - Congenital muscular dystrophy
  - Rigid spine muscular dystrophy
- Often remain ambulant well into adult life
- But significant respiratory weakness

FHL1-RELATED GENETIC CONDITIONS AND OTHER MYOFIBRILLAR MYOPATHIES

Myofibrill myopathies
- Disintegration of myofibrils that begins at the Z-disc
- Present between 25 and 45 years of age
- Proximal, distal or scapuloperoneal distribution of weakness
- Cardiac arrhythmias, cardiomyopathy
- Smooth muscle problems such as gastrointestinal pseudo-obstruction
- Respiratory muscle weakness and contractures

FHL1-related
- Spinal rigidity, scapular winging
- Contractures
- Respiratory muscle weakness and cardiomyopathy

THANK YOU & QUESTIONS