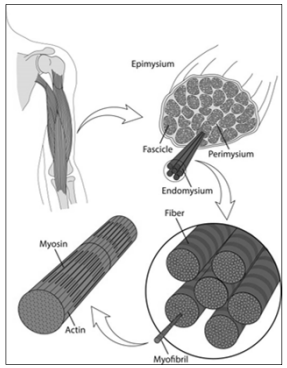
MYOPATHY WITH CONTRACTURES

Asst. Prof. Chaiyos Khongkhatithum. MD
Division of Neurology
Department of Pediatrics
Faculty of Medicine Ramathibodi Hospital

MYOPATHY WITH CONTRACTURES

- 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
-

Mathewson MA. Phys Med Rehabil Clin N Am. 2015;26:57-67

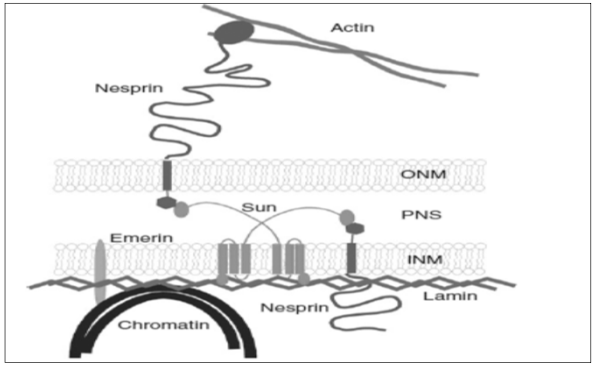
MYOPATHY WITH CONTRACTURES

- 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 author
- 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)

LINKING THE NUCLEUS TO THE CYTOSKELETON COMPLEX (LINC)



Handbook of Clinical Neurology. 2011; Vol. 101

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

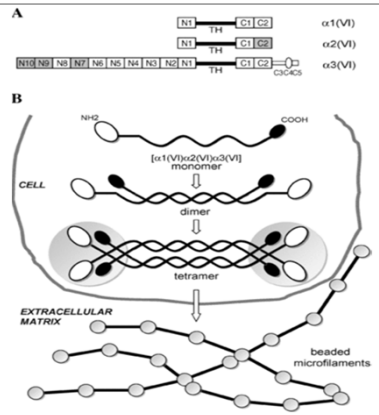
ULLRICH CONGENITAL MUSCULAR DYSTROPHY & BETHLEM MYOPATHY

- 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

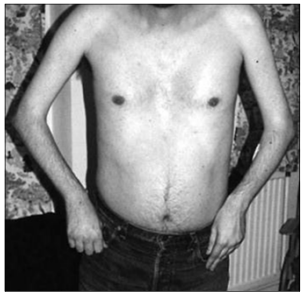
- early onset weakness (newborn)
- Congenital hip dislocation
- Delayed ambulation
- Lost ambulation around 10-20 yr
- Proximal joint contractures
- Distal joint hyperextensibility
- Normal IQ
- Skin:
  - Follicular hyperkeratosis
  - Abnormal scar formation
- Early & progressive RLD
- Nocturnal BiPAP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

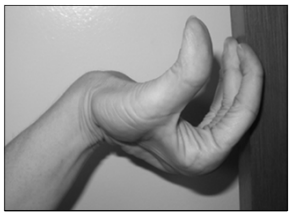
❖ Bethlem Myopathy

- 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

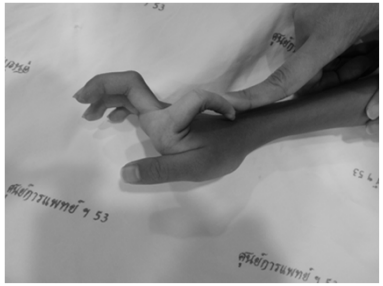
UCMD = Ullrich Congenital Muscular Dystrophy
BM = Bethlem Myopathy, RLD = Restrictive lung disease

CLINICAL PHENOTYPE

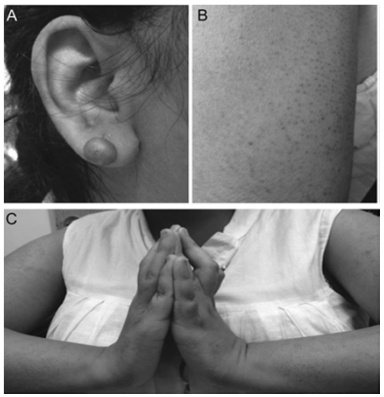


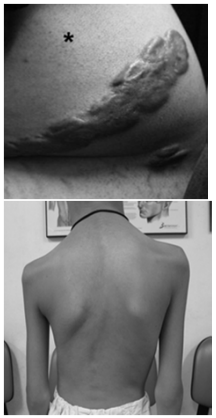


HYPERLAXITY OF DISTAL JOINTS



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

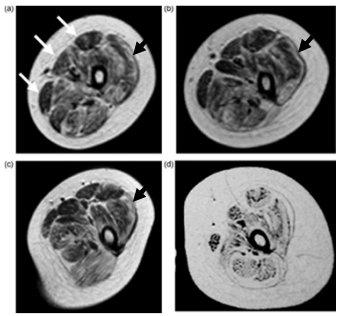




Liew W K , and Darras B T Neurology. 2013;81:44-45

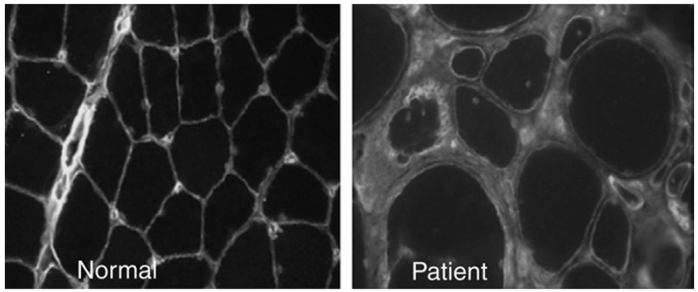
MUSCLE MRI

- 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”



Bonnemann CG. Handbook of Clinical Neurology. 2011; Vol. 101 (3rd series)
Mercuri E, et al. Neuromuscul Disord. 2005;15:303–310

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

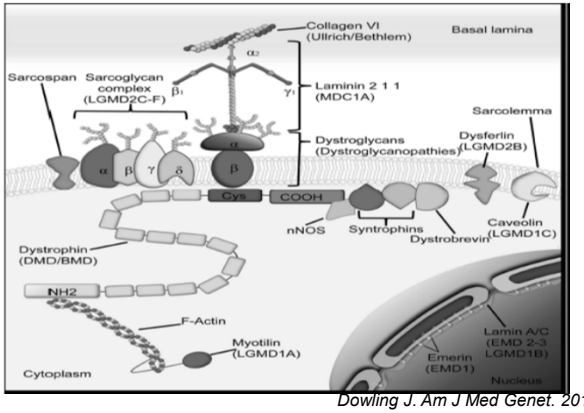


Bönnemann CG. Handb Clin Neurol. 2011 ; 101: 81–96

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

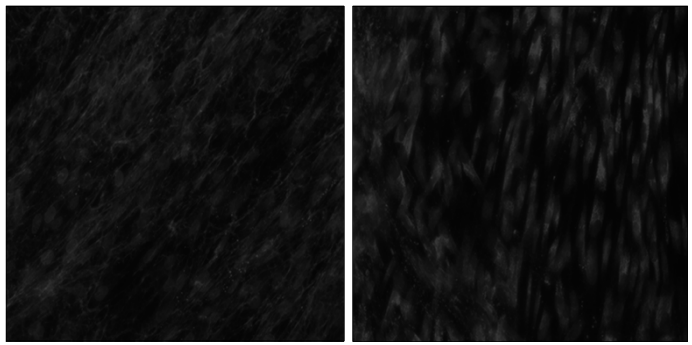
DYSTROPHIN ASSOCIATED GLYCOPROTEIN COMPLEX AND RELATED PROTEINS



Dowling J. Am J Med Genet. 2017;1–38.

Immunostaining of Collagen VI in Cultured Fibroblasts

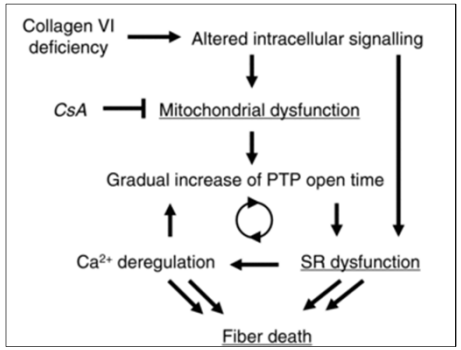
with Tx-100 20x overlayer



Normal **UCMD #13**

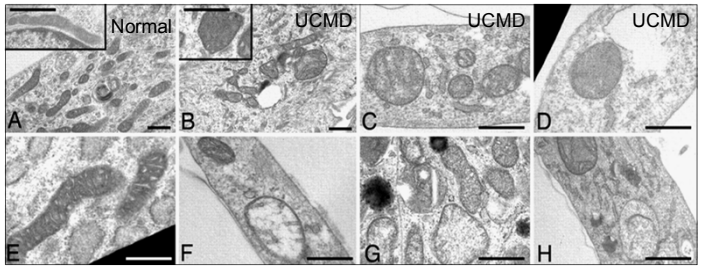
C. Bonnemann, Philadelphia

COLLAGEN VI AND MITOCHONDRIA



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

MITOCHONDRIAL DYSFUNCTION IN UCMD



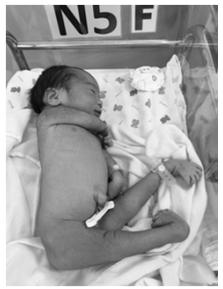
Angelin A, et al. Proc Natl Acad Sci U S A 2007;104

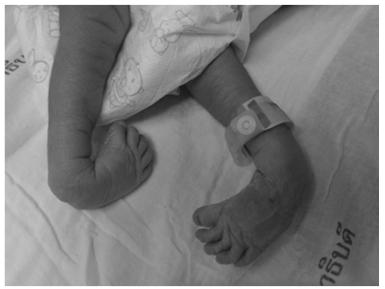
COLLAGEN VI-MITOCHONDRIA CONNECTION

- **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**

Merlini L, et al. Oxid Med Cell Longev. 2011;2011:139194

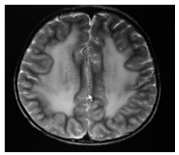
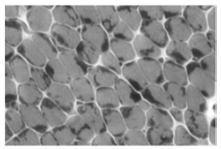
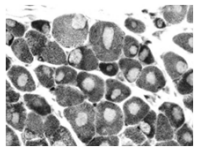
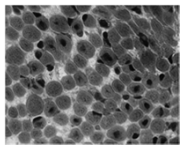
MUSCLE DISEASE WITH ARTHROGRYPOSIS





MUSCLE DISEASE WITH ARTHROGRYPOSIS

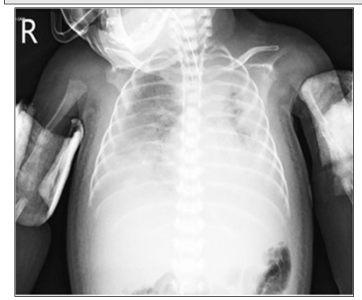
- Multiple congenital contractures at birth
- Abnormalities of muscle formation structure and/or function leading to secondarily decreased fetal movement
- Congenital muscular dystrophy (Merosin deficiency), congenital myopathies (nemaline myopathy, central core/nuclear myopathies), mitochondrial disorders

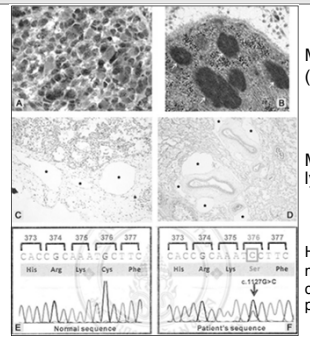
CASE REPORT Open Access

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

Jariya Waisayarat[1*], Chinnawut Suriyonplengsaeng[1,3], Chaiyos Khongkhatithum[2] and Mana Rochanawutanon[1]



CXR reveals bilateral chylothorax



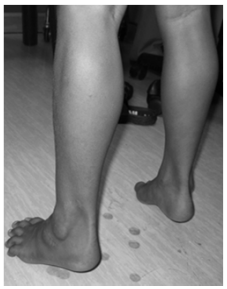
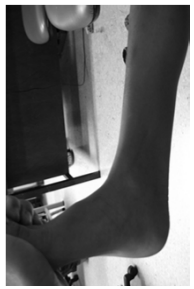
Muscle biopsy (mGT, EM)

Markedly-dilated lymphatic vessels

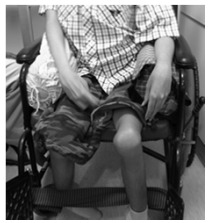
Heterozygous missense mutation ACTA1 c.1127G>C p.Cys376Ser

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

DUCHENNE MUSCULAR DYSTROPHY

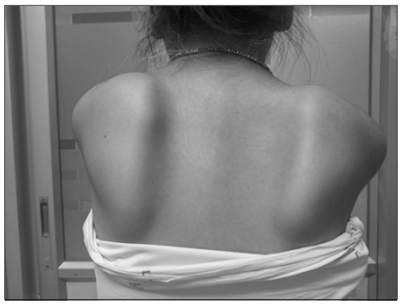
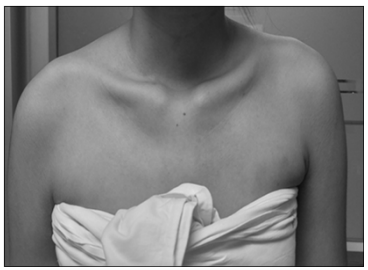



Early- before loss of ambulation

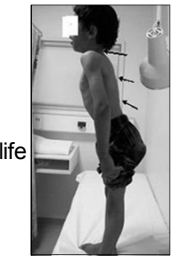
Late- after loss of ambulation

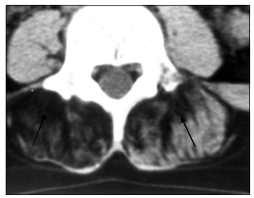
LGMD2A: SCAPULAR WINGS, MILD DELTOID ATROPHY, TOE WALKING

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





Koul R, et al. J Child Neurol. 2014;29:1436-40

FHL1-RELATED GENETIC CONDITIONS AND OTHER MYOFIBRILLAR MYOPATHIES

Myofibrillar 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