Introduction to $RYR1$-Related Diseases

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RYR-1 International Family Conference
July 14, 2018
For ALL individuals with congenital myopathies around the world who teach us everyday what true strength is
Congenital Myopathies

Beginning in the 1950s and 1960s muscle biopsy histochemical and ultrastructural techniques were used in recognizing congenital myopathy subtypes:

- central core disease (CCD)\(^1\)
- multi-minicore disease (MmD)\(^2\)
- centronuclear myopathy (CNM)\(^3\)
- nemaline myopathy\(^4\)


Images from: Jungbluth et al. *Nat Rev Neurol.* 2018
RYR1 as the Causative Gene for Central Core Disease:

Mutations in the ryanodine receptor gene in central core disease and malignant hyperthermia

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RYR1 mutations are the most frequent genetic cause of congenital myopathies
RyR1 = ryanodine receptor type 1

*a skeletal muscle sarcoplasmic reticulum calcium release channel*
Mutations in *RYR1* can result in:

- Central core disease (CCD)
- Multiminicore disease (MmD)
- Centronuclear myopathy
- Congenital fiber-type disproportion
- Core-rod myopathy

*Clinical course is typically either static or slowly progressive*
**RYR1-Related Myopathy Imaging: Muscle Ultrasound**

**Muscle Ultrasound:**

- A non-invasive means of assessing muscle appearance
- Can be performed at bedside
- Relative sparing of the rectus femoris muscle is a pattern highly suggestive of RYR1-related myopathy

**Quadriceps = 4 muscles:**
1. rectus femoris (RF)
2. vastus lateralis (VL)
3. vastus intermedius (VI)
4. vastus medialis (VM)
**RYR1-Related Myopathy Imaging: Muscle MRI**

**Upper leg:** rectus femoris (RF), adductor longus (AL) and gracilis (G) are relatively spared – and may be hypertrophied

**Lower leg:** tibialis anterior (TA), extensor digitorum longus (EDL), tibialis posterior (TP) and gastrocnemius medialis (GM) are relatively spared
“Core” Myopathies

Named for the muscle histological appearance of focally reduced oxidative enzyme activity

Central Core Disease (CCD)
- centrally located cores
- well demarcated cores

Multiminicore Disease (MmD)
- multiple cores
- less well-defined cores

Jungbluth. Orphanet J Rare Dis. 2007

Jungbluth et al. Semin Pediatr Neurol. 2011
Central Core Myopathy: Clinical Picture

• Hypotonia, congenital hip dislocation and scoliosis are common

• Extraocular muscle involvement, respiratory involvement, facial weakness and bulbar weakness are often mild

• Most patients achieve independent ambulation
Multiminicore Myopathy

Clinical Picture

• Can be caused by autosomal recessive mutations in RYR1 (or SEPN1)

• External ophthalmoplegia (in RYR1-related Multiminicore Myopathy) and prominent axial and proximal muscle weakness are common

• Severe cases with antenatal onset and arthrogryposis and respiratory insufficiency can occur
**Clinical features:**

- Congenital symptoms
- Extraocular muscle weakness
- Bulbar weakness
- Proximal muscle weakness
Severe Neonatal Presentation of \textit{Ryr1}-Related Myopathy

Clinical features:

- Myopathic face
- Respiratory involvement
- Poor feeding
- Ophthalmoplegia
- Hypotonia
- Arthroygryposis
“congenital fiber-type disproportion”

- A muscle pathology descriptive term
- Type 1 fiber hypotrophy compared to type 2 fibers
- Not specific for RYR1-related myopathy
“core-rod myopathy”

- a muscle pathology finding of both cores and rods
- not specific for RYR1-related myopathy
- has been reported in association with a severe form of neonatal RYR1-related myopathy

Congenital myopathy genes

Gonorazky, Bönnemann and Dowling. *Hand Clin Neurol*. 2018
Late-onset axial myopathy due to dominant \textit{Ryr1} mutations

- 77-year-old with 5-10 years of progressive trunk extension weakness
- dominant mutation in \textit{Ryr1}

- Onset in 60s of progressive trunk extension weakness
- dominant mutation in \textit{Ryr1}
RYR1-Related Myopathies: WIDE Phenotypic (Clinical) Spectrum

- Severe neonatal form
  - With respiratory involvement
  - With poor feeding
  - With arthrogryposis

- Congenital myopathy
  - With restricted extraocular movements
  - With hypotonia
  - With scoliosis

- Congenital myopathy
  - With clear proximal weakness during childhood and predominantly limb girdle weakness in adulthood

- Late-onset axial myopathy
  - Late adult onset weakness of trunk extension
**RYR1 genetics**

With the increased availability of next generation sequencing, the clinical spectrum associated with RYR1 mutations will likely continue to expand.

Jungbluth. *Orphanet J of Rare Dis.* 2007
Paroxysmal “Episodes”: related to abnormal functioning of the RYR1-encoded calcium release channel

Malignant Hyperthermia Susceptibility (MHS):
“a pharmacogenetic disorder of skeletal muscle that presents as a hypermetabolic response to potent volatile anesthetic gases such as halothane, sevoflurane, desflurane, isoflurane and the depolarizing muscle relaxant succinylcholine, and rarely, in humans, to stressors such as vigorous exercise and heat”

Signs: hyperthermia, tachycardia, tachypnea, increased carbon dioxide production, increased oxygen consumption, acidosis, hyperkalemia, muscle rigidity and rhabdomyolysis

Rosenberg et al. Orphanet J Rare Dis. 2007
King-Denborough Syndrome: may be a form of \textit{RYR1}-related myopathy

\textbf{Characteristic features:}
- ptosis
- prominent philtrum
- low set ears
- webbed neck
- short stature
- spinal rigidity
- scoliosis

- Tendency toward anesthesia-induced malignant hyperthermia (MH)
- Proximal weakness
- Characteristic features
Despite the same RYR1 mutation (p.Gly2434Arg):

Mother: recurrent rhabdomyolysis; limb-girdle weakness (5th decade)
Daughter: recurrent rhabdomyolysis
Son: baseline hyperCKemia (high CK), muscle hypertrophy

All 3 family members have ptosis (surgically corrected in mother)
Paroxysmal “Episodes” related to Channel Function

- some patients with history of proximal weakness
- episodes are later-onset (late teenage years – 30s)
- episodes of sudden, severe myalgias followed by severe weakness lasting for several hours
- episodic cramps and myalgias also common
Optimizing Care in RYR1-Related Myopathies

- Respiratory
- Nutrition
- Spine surveillance
- Physical therapy

Consensus Statement on Standard of Care for Congenital Myopathies

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The Care of Congenital Myopathy
A Guide for Families

www.curecmd.org/care-guidelines
Instead of “Reactive” Respiratory Care, “Proactive” Respiratory Care

“Restrictive” lung pattern

= most common pattern in congenital myopathies

There is restricted lung expansion due to weakness of the intercostal muscles, weakness of the diaphragm and decreased compliance of the chest wall: “extrinsic” causes of “restrictive” lung disease
Sleep Study or “Polysomnogram”

• The gold standard for assessing for nocturnal / sleep hypoventilation

• Carbon dioxide (CO₂) should be monitored throughout the sleep study

• In sleep hypoventilation, CO₂ increases in deep sleep

• BiPAP: Bilevel Positive Airway Pressure
  = the recommended form of non-invasive ventilation (NIV) for congenital muscle disease

“BiPAP is your Buddy”
Cough Assist Machine
= Insufflator / Exsufflator

• Alternates positive and negative airway pressure

• Stimulates cough (and thus helps to expectorate phlegm)

• Increased use during and immediately following respiratory infections is essential to help clear mucous: so-called “airway clearance”

• Daily use of the Cough Assist Machine (on the “Insufflation” mode) helps to promote chest wall and lung compliance
Progressing Toward Clinical Trials in the *RYR1*-Related Myopathies:

- Optimize care
- Comprehensive natural history studies
- Patient registry

“We tend to assume that the medical staff will always know what is best. I think if we enter every situation realizing that each of us has useful knowledge and experience with CM, it helps to remind us that we (parents and those affected) can contribute in helpful ways and even educate others. We are all on the same team.” - a mother of a child with CM
Editorial

Patient Organizations and Research on Rare Diseases
Julie R. Ingelfinger, M.D., and Jeffrey M. Drazen, M.D.

LAM is not the only medical condition in which patient groups have sponsored both clinical and basic research, have located patients to participate in trials, and have enlisted the help of expert clinicians and investigators. Other examples are cystic fibrosis, Huntington’s disease, Waldenström’s macroglobulinemia, oxalosis and primary hyperoxaluria, cystinosis, autosomal recessive polycystic kidney disease, and Duchenne’s muscular dystrophy, to name just a few. In each case, patients have formed groups to drive research aimed at understanding and treating their particular illness. The key to success for such groups has been to support basic research that is held to the highest scientific standards.