RYR1 Myopathies

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What are RYR1 related myopathies?

- RYR1 = ryanodine receptor type I
  - Large gene on chromosome 19
  - Encodes the RyR1 protein
  - Intracellular (inside the cell) calcium channel
  - Required for converting nerve impulses into muscle contractions (excitation contraction coupling)
  - Reviewed by Dr. Bob Dirisken at 10:30am today
What are RYR1 myopathies?

• Myopathies are any conditions that result in muscle impairment as a result of muscle dysfunction
  – “static”
    • Weakness, motor delay, difficulties walking, scoliosis, facial weakness, ophthalmoparesis, inability to climb stairs
  – “dynamic”
    • Malignant hyperthermia, exercise induced rhabdomyolysis, myalgias, muscle cramps, fatigue

– Myopathies will be reviewed further by Dr. Carsten Bonnemann at 10:00am today
What is a mutation?

• How do we define mutation?
  – A change in a gene that alters the function of that gene product and causes symptoms
• Mutations can be missense, nonsense, splice site changing, intronic, deletions, duplications
  – These different types of changes may have different consequences on how the RYR1 gene is processed and expression, and what the resulting RyR1 protein looks like
• RYR1 Mutations can be inherited as dominant, recessive, or be “new” (de novo) in an individual
• Livija Medne will review mutations and other genetic concepts at 9:00am today
Who has an RYR1 myopathy?

- Anyone with:
  - (a) myopathy
  - (b) mutation in RYR1
A brief history of RYR1 mutations and human muscle disease

- 1991: Mutation found in RYR1 in porcine MH
  - (Fujii et al., Science)
- 1991: Mutation found in RYR1 in Canadian individuals with MHS
  - (Gillard et al., Genomics)
- 1993: First RYR1 gene mutation discovered in human central core disease (CCD)
  - Zhang et al. and Quane et al., Nature Genetics
- 2002: First recessive RYR1 mutation patient reported (mulit-minicore myopathy)
  - Jungbluth et al., Neurology and Ferreiro et al., Annals of Neurology
- 2005: Recessive RYR1 mutations in small cohort of patients with minicore myopathy and ophthalmoplegia
  - Jungbluth et al., Neurology
- 2010: RYR1 mutations associated with centronuclear myopathy
  - Wilmshurst et al., Annals of Neurology
- 2010- present: RYR1 mutations found in CFTD, core-rod myopathy, and nemaline myopathy
- 2010- present: RYR1 mutations found in “non-classical” myopathy settings (exertional rhabdomyolysis, isolated ophthalmoparesis, etc)
- 2013: RYR1 mutations associated with dystrophic pathology
  - Bharucha-Goebel et al., Neurology
How do we describe and/or define RYR1 myopathies?

**Gene/Mutation Based**
- (ex: RYR1, SEPN1, MTM1, NEB)
- (RYR1 related myopathy)

**Phenotype based:**
- Myopathy
- Myalgias
- Rhabdomyolysis
- Malignant
- Hyperthermia

**Pathology based:**
- Central core disease
- Core myopathy
- Multi minicore disease
- Centronuclear myopathy
- CFTD
Gene/mutation based definition: A few key points to consider

• There are many many different mutations in RYR1
  – Different mutations can have different clinical consequences
  – Some individuals may have more than one mutation
  – Individuals with the same mutation may have different clinical presentations
  – There are still “undiscovered” mutations in RYR1, including those outside of the coding sequence
RyR1 mutations in central core disease

Mutations generally cluster in 3 “hot spots”
Recessive mutations are spread throughout the gene...

Domain KEY

IP₃
MIR
RYDR
SPRY
TM

N-terminal/Region I: Exons 2-17
Central/Region II: Exons 39-46
C-terminal/Region III: Exons 85-103

● Missense
◆ Nonsense
□ Deletion
■ Insertion
△ Duplication
* Splice Site

MmD
CCD
Core Myopathy
CNM/CNM-like
CFTD
RRM
KDS
Congenital Myopathy/MH
AR MD
Core/Rod Disease
Does my specific mutation matter?

• Initial evidence suggests that having two or more mutations, with one reducing the ability of the RyR1 protein to be made, is associated with a more severe phenotype than missense changes alone

• Some mutations may be associated with specific phenotypes
  – Evidence for this with malignant hyperthermia
  – Do certain mutations predispose to other symptoms, like rhabdomyolysis, or other clinical features, like ophthalmoparesis?
  – This is a subject of ongoing research
Pathologic heterogeneity

- RYR1 mutations associated with a range of different muscle biopsy findings, including:
  - Central core disease
  - Minicore myopathy
  - Centronuclear myopathy
  - Congenital fiber type disproportion
  - Core rod myopathy (or rod myopathy only)
  - Non specific myopathy
  - Muscular dystrophy

- There is some association between type and location of mutation and histopathology
- The association between histopathology and clinical presentation is not clear
- Note: mutations in other genes can cause the same histopathologic findings
  - So someone with central core disease may not have an RYR1 related myopathy

- Muscle biopsy patterns and their relation to RYR1 myopathy will be reviewed by Kim Amburgey at 9:30
The changing picture of RYR1 mutations

Pre-2003

Circa 2013

CCD 68%

MmD 23%

CNM 7%

CMD

CFTD

Pre-2003

Circa 2013
Non-core myopathies comprise a larger than expected percentage of all recessive RYR1 related myopathies.

- Congenital Myopathy/MH: 1.9%
- AR MD: 0.9%
- Core/Rod Disease: 1.9%
- MmD, 17%
- CNM/CNM-like, 23.6%
- CCD, 11.3%
- Atypical Core Myopathy: 20.8%
- RRM: 11.3%
- CFTD: 7.5%
- KDS: 3.8%
- n=106
I have an RYR1 mutation, does it matter what my biopsy looks like?

• In general, muscle biopsies are used for diagnosis and not for prognosis or management
• The reason(s) why patients with RYR1 mutations have different muscle biopsy findings are poorly understood
• At present, the relationship between biopsy pattern and clinical severity and/or prognosis is not clear
• The significance of the different changes is also not well understood?
  – In other words, does it matter if I have CCD or minicore myopathy or centronuclear myopathy?
Genetic heterogeneity and CM histopathologic subtypes

Centronuclear Myopathy
- MTM1, DNM2, RYR1
- SPEG, BIN1, SPEG

Nemaline Myopathy
- ACTA1, NEB, TPM2, CFL2
- TPM3, TNNT1, LMOD3
- KLHL40, KLHL41, KBTBD13

Core Myopathy
- CCD: RYR1, MYH7
- MmD/other: RYR1, SEPN1
- ACTA1, TTN, MYH7
- CCDC78, MEGF10

Congenital Fiber Type Disproportion
- ACTA1, TPM3, RYR1
- SEPN1, TPM2
I have central core disease, doesn’t that mean I have RYR1 myopathy?

- 90% of all CCD caused by mutations in RYR1
- If you have CCD but have not had genetic testing, you likely have an RYR1 mutation
- However, there are other genetic causes of CCD
  - MYH7, TTN, etc
- It is therefore important to have genetic testing even if your muscle biopsy is highly suggestive of RYR1 mutation
Clinical heterogeneity

• There are many many different clinical presentations associated with RYR1 mutations
• These include:
  – Weakness and disability from birth (i.e. congenital muscle disease)
    • This can range in severity
  – Weakness starting in childhood
  – Weakness presenting in adulthood
  – Dynamic presentations
    • Exertional rhabdomyolysis
    • Exercise related myalgias
    • Heat intolerance and heat stroke
    • Malignant hyperthermia
    • Patients can have both static and dynamic symptoms
Having recessive RYR1 myopathy is associated with an increased clinical severity.
Should I get genetic testing?

• Many reasons to pursue genetic testing and an confirmed genetic diagnosis
  – End of the diagnostic odyssey, aids with prognosis and care management, helps with family planning
  – May influence availability to future gene specific or mutation based therapies
• Remember, by definition, to have an RYR1 myopathy you need to have an RYR1 mutation
My doctors have looked every way possible, but not found a mutation. What should I do?

- Consult (can be virtually) with a congenital myopathy diagnostic expert
  - This is to ensure that all avenues have been pursued

- Consider participation in research studies looking into causes of “unsolved” muscle diseases (ex: Alan Beggs, Carsten Bonnemann, and myself)
I have a RYR1 variant of unknown significance, what does that mean???

- Variants of unknown significance are changes in the DNA sequence where the consequence of the change is not well understood.
- Variants of unknown significance may, in fact, be the mutation that causes diseases.
- Variants of unknown significance may instead have little or no association to the muscle condition.
- Additional methods are needed to evaluate such variants to prove that they are either true mutations or else benign (i.e., non-disease associated).
So I (or my family member) has an RYR1 myopathy, what can I/we do?
Consensus Statement on Standard of Care for Congenital Myopathies

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A few clinical points

- Scoliosis and skeletal complications (joint contractures, hip dysplasia) are common
- Heart involvement is rare
- Need to look out for breathing problems, and these can manifest only at night
  - Nocturnal hypoventilation and sleep apnea are relatively common, particularly in recessive RYR1
  - Sleep studies are important for diagnosing these problems
  - Respiratory issues in RYR1 will be reviewed tomorrow by Dr. Hank Mayer
- Pain and fatigue are often under-recognized aspects of the condition
I have an RYR1 mutation, am I definitely at risk for malignant hyperthermia?

• It is estimated that 30% of patients with RYR1 myopathy are at risk for MH
  – This has not been rigorously determined
  – Conversely >70% of individuals who have had an MH reaction or are MHS have an RYR1 mutation
• Some RYR1 mutations are proven to be associated with MH
• No mutations have been definitively proven to NOT be associated with MH
• Some patients with primary MH or MH susceptibility also can have other muscle symptoms
• Note: MH and related dynamic symptoms will be discussed further tomorrow by Dr. Jerry Parness and Dr. Ron Litman
What about treatment considerations?

• “Secondary” management strategies are very important
  – Physiotherapy, good pulmonary care, orthopedic intervention when necessary

• No approved drug therapies at this time

• Dantrolene is the standard of care for MH reactions
  – It may also help with myalgias and other dynamic symptoms in individuals with certain RYR1 mutations
  – However, it may worsen muscle strength in individuals with certain other RYR1 mutations

• Oral salbutamol has been looked at in a pilot study of core myopathy
  – Improved muscle strength in a small group of patients
  – Awaits more widespread testing and study

• Mestinon has been tried in RYR1 myopathy patients with features of myasthenia
  – How applicable this therapy may be to other RYR1 patients has not been tested
What about research to identify develop new therapies?

• New treatment approaches are being actively developed
  – Dr. Alan Beggs will review research strategies and RYR1 at 11:30am

• N-acetylcysteine is the “furthest alone”, as it is being tested in clinical trial
  – Dr Katy Meilleur will talk about NAC at 1:00 today

• Other approaches, such as RyCal treatment, are showing promising pre-clinical data
  – Dr Andy Marks will talk about RyCals at 11:00am
Thanks!