A Tale of Two Brothers and Some Others

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Case 1: WT
History of Present Illness

- 11 year-old boy who presented to the CMC Neuromuscular clinic at age 6 for muscle weakness and abnormal gait
- Difficulty with walking and poor balance with frequent falls
- Trouble climbing stairs and getting in/out of a vehicle
Birth History

- No pregnancy complications
- 40 weeks gestation via SVD
- Delivery complicated when the umbilical cord was cut before clamping
- BW 3.6 kg
- One week NICU stay
  - Sacral lipoma noted, which led to discovery of a tethered cord
Past Medical & Surgical

- Motor developmental delay
- Neurogenic bladder & bowel
- Scoliosis
- Anosmia
- Feeding difficulties and malabsorption
- Surgical release of tethered cord at 6 months
- Gastrostomy tube placement
Developmental History

- Gross Motor
  - Rolled and Sat at 7 months
  - Crawled at 11 months
  - Walked at 22 months

- Fine Motor - delayed

- Speech/Language - normal

- Social - appropriate
Diagnostic Studies

- CK level: reportedly normal
- Muscle Biopsy
  - Type I myofiber predominance with chronic myopathic alterations
  - Rare denervated fibers
ATPase
NADH-TR
Case 2: HT
History of Present Illness

- 7 year-old boy who was referred to the CMC Neuromuscular clinic at age 2 for muscle weakness
- Daily falls
- Fatigues easily following short periods of activity
Birth History

- 41 weeks gestation via SVD at home
- No pregnancy or delivery complications
- BW 2.95 kg
- Congenital heart defects (ASD & VSD), micropenis, and facial hemangioma
  - Genetics evaluation- diagnosis of partial trisomy 6
Past Medical & Surgical

- Gross motor developmental delay
- GERD
- Failure to thrive with feeding difficulties
- Seizures
- Gastrostomy tube placement
- Orchiopexy
Developmental History

- Gross Motor
  - Rolled at 12 months
  - Sat at 13 months
  - Crawled at 15 months
  - Walked at 19 months

- Fine Motor - normal

- Speech/Language - normal

- Social - appropriate
Diagnostic Studies

- CK level: 83
- EMG/NCS
  - Nerve conduction study was normal
  - EMG showed many low amplitude and short duration motor units in the right upper and lower extremities consistent with diffuse myopathy
Physical Examination
Genetic Changes in WT & HT

- **RYR1**
  - exon 33, c.4711A>G heterozygous, p.Ile1571Val (paternal)
  - exon 67, c.10097G>A heterozygous, p.Arg3366His (paternal)
  - exon 86, c.11798A>G heterozygous, p.Tyr3933Cys (paternal)
  - exon 102, c.14731G>A heterozygous, p.Glu4911Lys (maternal)
Ryanodine Receptor 1 (RYR1)

- AKA: sarcoplasmic reticulum calcium release channel
- 19q13.1
- 106 exon gene encoding skeletal muscle ryanodine receptor
  - Intracellular calcium-release channel essential for excitation-contraction coupling
- Mutations leading to neuromuscular disease
  - Dysregulation of calcium homeostasis
Ryanodine Receptor 1 (RYR1)

- Genetic Testing
  - Single Gene
  - Congenital Myopathy Panel
  - Neuromuscular Panel
  - Whole Exome Sequencing
- Malignant Hyperthermia Risk
RYR1
Background

- Pathogenic mutations in the ryanodine receptor type 1 (RYR1) gene have been well documented as a cause of congenital myopathies. The clinical presentation, genetic changes, and histopathology among this group have been demonstrated to be very heterogenic.
Objective

- To review a group of patients with congenital RYR1-related myopathies in order to aid in future diagnosis.
Methods

- A group of patients in the Neuromuscular Clinic at a tertiary pediatric center with documented RYR1 variants were selected, and their charts were retrospectively reviewed.

- History, physical examinations, laboratory studies, and other diagnostic investigations were accessed.
Results

- 12 patients with RYR1 variants, which were felt likely to be pathogenic or were documented as causative for their disease
- Female = 7, Male = 5 were male
- Age range at the time of review: 3-22 years
- 9 of 10 with permanent weakness had symptoms at birth
  - Remaining patient presented with symptoms at 2 years
- Two other patients had induced weakness secondary to malignant hyperthermia due to anesthesia
  - Both presented at 7 years of age
| PATIENT NUMBER | CURRENT AGE (years) | AGE AT ONSET | GENDER  
|----------------|---------------------|--------------|---------
| 1              | 3                   | Birth        | F       
| 2              | 6                   | Birth        | F       
| 3              | 6                   | Birth        | M       
| 4              | 7                   | Birth        | M       
| 5              | 7                   | Birth        | M       
| 6              | 10                  | 7 years      | F       
| 7              | 11                  | Birth        | M       
| 8              | 11                  | 7 years      | F       
| 9              | 14                  | Birth        | F       
| 10             | 15                  | 2 years      | F       
| 11             | 15                  | Birth        | F       
| 12             | 22                  | Birth        | M       |
Results

- Notable clinical findings in those with permanent weakness
  - Respiratory weakness, ptosis, and ophthalmoparesis
- 7 novel variants were seen in 5 of the total patients
- Biopsies were performed in 9 of the 10 patients with the congenital myopathy clinical presentation
  - 8 showed definite myopathic changes, including 3 with central nuclei and 2 with central cores.
<table>
<thead>
<tr>
<th>PATIENT NUMBER</th>
<th>CARDIAC DYSFUNCTION</th>
<th>RESPIRATORY WEAKNESS</th>
<th>PTOSIS</th>
<th>OPHTHALMOPARESIS</th>
<th>OTHER FACIAL WEAKNESS</th>
<th>EXTREMITY WEAKNESS</th>
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<tr>
<td>1</td>
<td>Unknown, did not follow-up</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes, but secondary to other genetic congenital heart defect</td>
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<tr>
<td>7</td>
<td>No, per parent's report, not seen at CMC</td>
<td>No</td>
<td>Yes, not at rest but fatigable</td>
<td>No</td>
<td>Yes</td>
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<td>9</td>
<td>No (evaluated at outside facility)</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>PATIENT NUMBER</td>
<td>CK LEVEL</td>
<td>EMG/NCS</td>
<td>PATHOLOGY</td>
<td>GENETIC CHANGE</td>
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</table>
| 1              | 226        | Non-irritative myopathic process affecting upper and lower extremities | Neonatal myopathy process associated with central nuclei and marked myofiber atrophy | ***1. exon 33, c.4816C>A heterozygous, p.Arg1606Ser  
***2. exon 91, c.12978delC heterozygous, p.Glu4327Argfs*14  
(Both variants undocumented as of test report 6/17/14.)  
*** undocumented variant |
| 2              | 84         | Non-irritative myopathic process affecting upper and lower extremities | Congenital myopathy with centrally-located nuclei and focal myofibrillar disarray | 1. exon 41, c.6721C>T heterozygous, p.Arg2241*  
***2. junction of exon 91 & intron 91, c.13437+1G>A heterozygous, (abnormal exon splicing)  
*** undocumented variant |
| 3              | 107        | Non-irritative myopathic process affecting upper and lower extremities | Moderate fiber size variability, type I myofiber predominance, and mild chronic myopathic changes | 1. c.2122G>A heterozygous, p.D708N  
2. c.14818G>A heterozygous, p.A4940T  
3. c.7523G>A heterozygous, p.Arg2508His |
| 4              | 834-1321   | Not done                     | Non-specific morphologic and ultrastructural changes:  
Morphologic features include moderate fiber size variability, several esterase-positive denervated fibers, central sarcoplasmic pallor in several fibers on oxidative stains, and several fibers with bluish acid phosphatase reactivity; Ultrastructural exam with several atrophic fibers with slightly expanded Z-lines in continuity with usual sarcomeric architecture; Central pallor and Z-line expansion may represent early core and nemaline rod expansion respectively | exon 47, c.7523G>A heterozygous, p.Arg2508His |
| 5              | 83         | Diffuse myopathy affecting upper and lower extremities | Not done                                                                  | 1. exon 33, c.4711A>G heterozygous, p.Ile1571Val (paternal)  
2. exon 67, c.10097G>A heterozygous, p.Arg3366His (paternal)  
3. exon 86, c.11798A>G heterozygous, p.Tyr3933Cys (paternal)  
4. exon 102, c.14731G>A heterozygous, p.Glu4911Lys (maternal) |
| 6              | 247-567    | Not done                     | Not done                                                                  | ***1. c.7755delC heterozygous, p.Val2586Cysfs*160 (expected to be pathogenic)  
***2. c.6726C>G heterozygous, p.Ile224Met (VUS) |
<table>
<thead>
<tr>
<th>PATIENT NUMBER</th>
<th>CK LEVEL</th>
<th>EMG/NCS</th>
<th>PATHOLOGY</th>
<th>GENETIC CHANGE</th>
</tr>
</thead>
</table>
| 7              | ? | Not done | Type I myofiber predominance with chronic myopathic alterations; rare denervated fibers--> nonspecific but likely congenital myopathy | 1. exon 33, c.4711A>G heterozygous, p.Ile1571Val (paternal)  
2. exon 67, c.10097G>A heterozygous, p.Arg3366His (paternal)  
3. exon 86, c.11798A>G heterozygous, p.Tyr3933Cys (paternal)  
4. exon 102, c.14731G>A heterozygous, p.Glu4911Lys (maternal) |
| 8              | 4426-98,570 3/8-12/13 *during admission | Not done | Not done | exon 28, c.4071C>T homozygous, p.Pro1357Pro (VUS) |
| 9              | ? | Not done | Central cores (performed at outside facility; could not find report) | exon 101, c.14581C>T heterozygous, p.Arg4861Cys |
| 10             | 72 2/6/15 | Normal | Slight myopathic changes with early multi-minicore formation | exon 29, c.4178A>G heterozygous, p.Lys1393Arg |
***2. exon 101, c.14623A>G heterozygous, p.Met4875Val |
| 12             | 44 2002 or earlier | Not done | Centronuclear myopathy | ***exon 91, c.13324G>T heterozygous, p.Asp4442Tyr (This VUS had not been reported as of test report 1/27/14 but in region where other variants have been documented as pathogenic.) |
Limitations

- Patients must be manually placed on the specific disease/disorder list in the EMR
- Additional patients with RYR1 variants who also have variants in other genes which can cause congenital myopathies, namely titin (TTN)
- Lack of centralized genomic database to know if undocumented variants are truly novel
Conclusions

- This study adds to the body of growing information regarding congenital RYR1-related myopathies.
- In those with ophthalmoparesis on exam, all had central nuclei documented on muscle biopsy.
- Genetic heterogeneity was seen in keeping with previously reported series, including 7 undocumented variants.
References


- LOVD (Leiden Open Variation Database), http://www.lovd.nl/3.0/home.

