Case Study in Neuromuscular Medicine

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Histopathological Abnormalities are Progressive in Myotonic Dystrophy Type 2

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. Myotonic dystrophy type 2 (DM2) is an inherited muscular dystrophy involving a tetranucleotide repeat(CCGT) in the ZNF9 gene.
. Myotonia, weakness, and cataracts are the most common symptoms, although myalgia, diabetes and cardiac abnormalities are also frequently associated with the disease.
. The clinical presentation of DM2 is insidious and its morphological progression remains to be described.
. The disease was first described in 1994 and the molecular analysis were available in 2001.
Reviewed 15 patient charts with ages spanning 31-84 years old.
Reviewed muscle biopsy from 11 patients ranging from age 31-74.
The severity of central nucleation and nuclear pyknosis was manually determined from the H&E slides.
The rates of central nucleation and nuclear pyknosis were expressed as the percentage of total fibers which are abnormal.
The severity of central nucleation was further quantified by finding the average number of nuclei per centrally nucleated fiber.
<table>
<thead>
<tr>
<th>Clinical Finding:</th>
<th>31 year old patient</th>
<th>32-59 years old (n=7)</th>
<th>61-79 years old (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness, primarily hip flexors</td>
<td>Mild</td>
<td>71%</td>
<td>100%</td>
</tr>
<tr>
<td>Clinical myotonia</td>
<td>Present</td>
<td>57%</td>
<td>43%</td>
</tr>
<tr>
<td>EMG demonstrate myotonia</td>
<td>Absent</td>
<td>43%</td>
<td>86%</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>Present</td>
<td>14%</td>
<td>25%</td>
</tr>
<tr>
<td>History of cataracts</td>
<td>Absent</td>
<td>57%</td>
<td>71%</td>
</tr>
<tr>
<td>Pathological Finding:</td>
<td>31 year old patient</td>
<td>49-53 years old (n=3)</td>
<td>69-74 years old (n=7)</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td>Central nucleation</td>
<td>Present</td>
<td>75%</td>
<td>86%</td>
</tr>
<tr>
<td>Nuclear pyknosis</td>
<td>Present</td>
<td>50%</td>
<td>86%</td>
</tr>
<tr>
<td>Fiber size variation</td>
<td>Absent</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>Fiber angulation</td>
<td>Present</td>
<td>50%</td>
<td>71%</td>
</tr>
</tbody>
</table>
Figure 3: The rate of nuclear pyknosis, expressed as the rate of abnormal fibers per total fibers, was highly correlated with age ($r^2=0.69$). The rate of central nucleation was moderately correlated with age ($r^2=0.31$), while the number of nuclei per centrally nucleated fiber showed no correlation with age ($r^2=0.01$).
Figure 2: The 31 year old patient exhibited mild abnormalities including increased central nucleation (A), pyknotic nuclear clumps (B), macrophagocytosis (C), and regenerating fibers (D). 400x.
Conclusions-1

Patients 69 years old and older tended to exhibit a “classic” DM2 histopathology with central nucleation, nuclear pyknosis, fiber size variation and angulation, intermysial fibrosis, and fat replacement. These findings were less prevalent and less severe in patients between 49-53 years old.

One patient presented with mild proximal leg fatigability at age 31. He was subsequently confirmed to have DM2 by genetic test. Muscle biopsy of this patient appeared nearly normal with only rare angulated fibers, myophagocytosis, and scattered central nucleation.
Conclusions-2

. The rate of fibers exhibiting nuclear pyknosis was well correlated with age. and none of the biopsies demonstrated inflammatory infiltration.

. The rate of central nucleation was moderately correlated with age and the rate of nuclei per centrally nucleated fiber did not progress with age.

. None of the biopsies demonstrated inflammatory infiltration.

. The most prevalent clinical findings were EMG myotonia and muscle weakness primarily in the hip flexors. Clinically evident myotonia and cataracts were common, and several patients had histories of cardiac arrhythmias.

. These findings are similar to those reported by Day et al. and Ricker et al. (1995).
Our study shows that morphological abnormalities worsen and become more prevalent with age. While older patients present with findings typically associated with DM2, younger patients may show more subtle changes such as mildly increased levels of central nucleation and nuclear pyknosis. Careful clinical-pathological correlation, particularly in younger patients, may better facilitate diagnosis.
REFERENCES
Fatal Lipid Storage Myopathy: An Atypical Presentation of Late-Onset Multiple Acyl-coenzyme A Dehydrogenase Deficiency (MADD)

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. Lipid storage myopathies (LSM) are rare disorders which display varied clinical presentations.

. The muscles of the limbs are more strongly affected than respiratory muscles.

. Multiple acyl-coenzyme A dehydrogenase deficiency (MADD) causing significant respiratory insufficiency (1,2,3).

. In late-onset LSMs, muscle weakness progresses slowly over years; reported fatalities occur due to metabolic crises (4).
A previously healthy 33-year-old woman presented with progressive muscle weakness over 4 months, dyspnea on minimal exertion, and proximal muscle pain. Her weakness was more proximal than distal, including difficulty holding her head up. The patient’s only lifestyle change during this time was starting a weight-loss diet. She had no known family history of myopathy.

Physical exam showed weakness in the proximal limb muscles (3/5 strength in the deltoids, triceps, biceps, and iliopsoas bilaterally) and neck muscles (weakness worse in extensors than flexors), and depressed reflexes in the upper limbs.

Her labs showed creatine kinase of 3600 IU/L, decreased levels of total and free plasma carnitine (8 μmol/L and 7 μmol/L, respectively), and elevated AST (400 IU/L) and ALT (200 IU/L). The patient was started on oral carnitine (4g/day), but without obvious improvement. Within one month, she developed worsening dyspnea and was started on nocturnal BiPAP.
Further labs showed:
Significantly elevated urine organic acids (including glutaric, 2-hydroxyglutaric, 3-hydroxyglutaric, adipic, and suberic acids)

Plasma elevations of short-, medium-, and long-chain acylcarnitines.

One week later, the patient presented in severe respiratory failure, and died within 2 days.

Genetic tests were ordered
Urine Organic Acid Profile

Organic acids

* Normal urine organic acid values are negligible in adults.
Lipid droplets are not membrane-bound and accumulate in parallel rows between myofibrils. Inset: high-power view of lipidology.
The muscle biopsy was crucial for this patient’s diagnosis. The three LSMs known to present with massive lipid storage on muscle biopsy are primary carnitine deficiency (PCD), MADD, and neutral lipid storage myopathy (NLSM) (4,5).

This patient’s biochemical tests showing increases in short-, medium-, and long-chain plasma acylcarnitines, the characteristic urine organic acid profile, and lack of response to oral carnitine therapy are most consistent with MADD.
Late-onset LSMs, in particular adult-onset MADD (type III), present with milder symptoms, whereas those with neonatal or early onset have rapid, fatal progression (6).

Fasting is a known trigger of LSMs, so our patient being on a diet may have set off her symptoms (4).

To our knowledge, this is the first reported case of late-onset MADD with a rapid, fatal progression of symptoms.
Genes known to cause MADD are ETFDH, ETFA, and ETFB.

Patients with MADD who have responded to riboflavin supplementation (riboflavin-responsive MADD, or RR-MADD) were found to have mutations in the ETFDH gene (3,6).

Some patients with RR-MADD show greater improvement if also put on coenzyme Q supplementation (4,5).

Cases of MADD caused by a mutation in ETFA or ETFB have not been shown to respond as well to nutritional supplementation.


Lipid (storage) myopathies

. Disorders of fatty-acid oxidation (FAO)
  Primary carnitine deficiency (PCD)
  CPT2, VLCAD, MTP
  MADD

2. Defects of triglyceride catabolism
  Neutral lipid storage disease with ichthyosis (CGI-58)
  Neutral lipid storage myopathy (PNPLA2)

3. Defects of triglyceride and membrane phospholipid biosynthesis
  Recurrent acute rhabdomyolysis in childhood (LPIN1)
## Muscle morphology

Frequency of lipid storage
- 160/1600 (10%) in Lyon
- 47/9639 (0.5%) in Japan

Genetic defect identified
- few cases, Laforet,
- 9/47 (24%) Ohkuma,

<table>
<thead>
<tr>
<th>Genes</th>
<th>Lipid Storage</th>
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<tr>
<td>CPT2, VLCAD</td>
<td>lipid storage rare</td>
</tr>
<tr>
<td>MADD, PCD, NLSD</td>
<td>always lipid storage</td>
</tr>
<tr>
<td>LPIN1</td>
<td>no lipid storage</td>
</tr>
</tbody>
</table>

Non specific causes of lipid accumulation:
- Drug toxicity, inflammatory disease, mitochondrial disease
Laboratory analysis

Serum CK
- FAO, LPIN1: in attacks ↑, but may be normal in remission
- PNPLA2 defect: always ↑

Urinary organic acids
- ↑ Glutaric acid (GA II) in MADD
- Non-specific changes in other FAO

Free and total carnitine
- Frequently ↓ in FAO defects, ↓ ↓ in primary carnitine deficiency

Plasma/blood acylcarnitine profile
- Most sensitive analysis to differentiate FAO disorders
- Trigger: metabolic stress (prolonged fasting)
- PNPLA2, LPIN1 defects: no abnormality!!!
Treatment

Oral riboflavin (100-400mg/day) in MADD if recovery is incomplete + CoQ10 500-1000 mg/day

Dietary treatments
- High carbohydrate diet → may help to prevent exacerbation during exercise
- Avoid fasting!
- Acute episodes: i.v. glucose

Carnitine supplementation → in primary carnitine deficiency
But has controversial effect in other FAO diseases

Medium chain triglycerides (MTC) in defects of long chain fatty acids has controversial effect in adult patients
Hypokalemic Periodic Paralysis: An Atypical Presentation of a Rare Disease

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Hypokalemic periodic paralysis (HOPP) is a channelopathy that most commonly presents in adolescence and young adulthood with episodes of paralysis in association with transient hypokalemia. As these patients age, the frequency of their attacks decreases but some go on to develop progressive muscle weakness. We present an atypical case of an older male who experienced several years of progressive muscle weakness before having his first documented episode of hypokalemic paralysis.
HPI: A 62 year old male with a history of progressive muscle weakness with previous diagnosis of inclusion body myositis was admitted to the hospital after sustaining bilateral patellar and tibial fractures during a fall. He was subsequently taken to the operating room where these injuries were repaired. Shortly thereafter, the patient began to experience bilateral numbness and weakness in his hands which progressed to the point where he could not grip his hands. He also noted slurred speech and dysphagia. The patient was found to have a markedly low potassium ([K+]: 1.5 mEq/L; nl: 3.5-5.0). Upon correction of his potassium levels, the patient’s symptoms abated.
PMH: Fifteen years prior to this hospitalization the patient began to experience progressive muscle weakness predominantly in the lower extremities. He was eventually sent for a quadriceps muscle biopsy which showed features mimicking inclusion body myositis.

FH: Two nephews with hypokalemic periodic paralysis.

Labs: Previously, [K+] had always been normal on routine labs.
Subsequent course: While in the hospital, the patient was seen by the same nephrologist that managed the patient’s nephews with hypokalemic periodic paralysis. The nephrologist raised the possibility that hypokalemic periodic paralysis might be the etiology of both the patient’s progressive weakness and recent paralytic episode. Review of the slides from the previous biopsy and subsequent genetic testing confirmed A R528H mutation in the CACN1AS gene, which was consistent with the diagnosis of hypokalemic periodic paralysis.
Two distinct forms of muscle symptomatology exist, a transient paralysis and a fixed myopathy.

The fixed myopathy has been termed the myopathic form of the disease and occurs with the typical paralysis in a minority of cases. More rarely, the myopathic form can occur alone without any paralytic symptoms.
.The less typical patients with permanent muscle weakness (i.e. the myopathic form) show the usual histologic features of single or multiple vacuoles.

. Relatively young patients with more typical paralytic symptoms often have normal muscle histology.

Most cases of hypokalemic paralysis can be attributed to defects in the genes which encode for skeletal muscle voltage gated ion channels. One recent study reported that 90% of their cases were due to mutations in the arginine residues of the S segments in these channels.
Hypokalemic periodic paralysis is an uncommon disease, the diagnostic challenge is further amplified when there is an atypical presentation of such a condition.

This case suggests that large amounts of membranous material are more pronounced in the older patients with permanent weakness which is similar to those of inclusion body myositis. Careful search for intracytoplasmic vacuoles and tubular aggregates will be helpful to elucidate the diagnosis.
REFERENCES: