Pearls & Oy-sters: Hickam's Dictum in Genetic Myopathies

When a Proven Pathogenic Mutation Does Not Explain the Phenotype

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Pearls

- Exercise intolerance is the most common phenotype in McArdle disease. Fixed weakness can be present in advanced ages, mainly affecting the shoulder girdle.
- ANOS patients may present with a wide spectrum phenotype, including limb-girdle dystrophies, distal myopathies, and asymptomatic or mild symptomatic hyperCKemia. A characteristic radiologic pattern, involving the posterior compartment of the thigh, soleus, and medial gastrocnemius muscles in the legs, may assist in the genetic diagnosis of this entity.

Oy-sters

- Consider the coexistence of genetic conditions, particularly among patients with a history of consanguinity.
- Although fixed muscle weakness may be present in patients with McArdle disease, in the majority of cases, it is mild to moderate and associated or preceded by a history of exercise-related symptoms.
- The presence of subsarcolemmal vacuoles that may contain periodic acid–Schiff (PAS)–positive glycogen and the absence of histochemical staining for myophosphorylase are hallmarks of McArdle disease on muscle biopsy. However, severe dystrophic changes are rare and should raise the suspicion of an additional concomitant myopathy.

A 67-year-old woman, born to consanguineous parents, was referred to our Neuromuscular National Reference Center with the diagnosis of McArdle disease made at age 58. She first noticed difficulties in climbing stairs and standing up from a sitting position in her 40s, which progressed over 10 years when she lost independent ambulation. She denied any history of exercise intolerance or episodes of rhabdomyolysis or myoglobinuria. She did not have symptoms of bulbar or extraocular musculature weakness, nor did she report cardiac or respiratory issues.

Initial laboratory tests showed elevated creatine kinase (CK) levels (range 1049–1269 U/L) and normal lactate levels. ECG showed a first-degree atrioventricular block, with a normal echocardiogram. Given the progressive proximal weakness and hyperCKemia, a muscle biopsy was performed and showed subsarcolemmal accumulation of glycogen (PAS-positive vacuoles) and myophosphorylase deficiency, but also striking dystrophic changes (figure). Sanger sequencing of the *PYGM* gene (NM_005609.3) identified the c.13_14del (p.Leu5ValfsTer22) frameshift variant in homozygosity, previously associated with McArdle disease (HGMD accession number: CD066398; ClinVar variation ID: 371064).

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(A) Hematoxylin & eosin (H&E) staining shows changes in fiber size with endomysial fibrosis (*) and fatty replacement (♦). (A, B) H&E staining shows subsarcolemmal vacuoles with excess glycogen storage, determined by periodic acid-Schiff staining (arrowheads). (C, patient; D, control) Histochemical staining reveals the absence of myophosphorylase activity. (E, F) Axial T1-weighted MRI shows extensive muscular fatty infiltration (♦) at pelvic and thigh levels, sparing gracilis (blue arrowhead) and sartorius (black arrowhead) muscles. (G) Axial T1-weighted image at leg level shows a predominant involvement of medial gastrocnemius (black arrows) and soleus muscles (blue arrows), a characteristic radiologic pattern of limb-girdle muscular dystrophy 12.

Neurologic examination revealed symmetric proximal muscular weakness and bilateral calf hypertrophy. Manual muscle strength testing revealed the following Medical Research Council scores: shoulder abduction 4/5, elbow flexion 4-/5, elbow extension 4+/5, distal upper limbs musculature 5/5, hip abduction, adduction, and flexion 2/5, knee flexion and extension 4/5, distal lower limbs musculature 5/5. The patient was not able to rise from a chair and independent ambulation was not possible, requiring bilateral support. The rest of the neurologic examination was unremarkable, and reflexes were normal. A nonischemic exercise forearm test showed a flat curve for both venous lactate and ammonia, probably due to insufficient effort during the test.

After review of clinical and paraclinical features, an overlapping muscle dystrophy was suspected. A muscle MRI was performed (figure), confirming extensive muscular fatty infiltration, which involved almost the whole pelvic and thigh musculature, sparing solely gracilis and sartorius muscles. At the leg level, it showed a predominant involvement of medial gastrocnemius and soleus.

Subsequently, next-generation sequencing of a targeted panel of 202 genes related to muscular disorders was performed, and an additional homozygous pathogenic mutation was identified in the *ANOS* gene (NM_213599.2: c.191dup, p.Asn64Lysfs*15), associated with limb-girdle muscular dystrophy 12 (LGMDR12),¹ formally called LGMD2L. The patient was finally diagnosed with double genetic trouble, harboring proven pathogenic mutations homozygosity in 2 different genes. The latter is probably the main cause that explains the clinical phenotype.

Discussion

Approximately 1,875 protein-coding genes are known to be linked to autosomal recessive disorders, according to the Clinical Genomic Database of the National Human Genome Research Institute.² It has been estimated that every individual is a carrier of more than 20 of these disorders or traits.³ The probability of sharing carrier status for a rare autosomal recessive disease is considerably higher for related couples than for unrelated individuals. In this report, the patient, born to consanguineous parents, was found to have 2 recessive conditions, which we briefly review.

McArdle disease is the most common glycogen storage disease. It is an autosomal recessive condition caused by mutations in the myophosphorylase gene (*PYGM*) that encodes the skeletal muscle-specific isoform of phosphorylase and leads to blocked muscle glycogenolysis. Age at onset is frequently in the first decade of life, but the diagnosis is often delayed, and many patients are diagnosed after early adulthood.^{4,5} The usual presentation is exercise intolerance that consists of premature muscle fatigue, contractures, pain, and episodes of myoglobinuria, triggered by short intense exercise or by dynamic aerobic exercises involving large muscle mass (e.g., stair-climbing, running, or walking very fast). A characteristic feature of the condition is the so-called second wind phenomenon, considered pathognomonic for the disease. It is described by patients as relief of symptoms triggered by the onset of exertion, which appears about 10 minutes after starting the exercise, and allows them to resume physical activity. Persistent hyperCKemia is present in the majority of patients.⁵

Recessive mutations in the *ANOS* gene are associated with muscular diseases named anoctaminopathies. Patients may present with proximal or distal fixed weakness or isolated persistent hyperCKemia.⁶ Calf hypertrophy is a relatively common sign of this condition.⁷ Muscle MRI may reveal typical signs, with preferential involvement of adductor and gastrocnemius muscles.⁸

In the case we report, the patient was initially diagnosed with McArdle disease based on the evidence of myophosphorylase deficiency in the muscle biopsy, which prompted the performance of a targeted *PYGM* genetic analysis. A muscle biopsy was performed prior to a forearm exercise test because the reported symptoms did not suggest a metabolic muscle disorder. Fixed muscle weakness occurs in approximately 20%–30% of affected individuals with McArdle disease, but it is normally preceded by a history of exercise-related symptoms. It is more likely to involve proximal muscles and is more common in individuals of advanced age.^{4,9} In the literature, there are only a few reports of patients diagnosed in later adulthood with a phenotype of fixed weakness as the sole clinical manifestation.¹⁰ The cause of the fixed weakness in McArdle disease and its phenotype heterogeneity remains unclear.⁴ To date, no genotype–phenotype correlation has been described.^{5,9}

Regarding complementary tests, muscle pathology may show some degenerating or necrotic fibers, accompanied by regeneration, but the most consistent finding is PAS-positive subsarcolemmal vacuoles. The presence, in this case, of intense dystrophic changes in the muscle biopsy led, therefore, to the suspicion of another concomitant myopathy. Muscle MRI showed extensive fatty infiltration. Little is known about radiologic features in McArdle disease, and there are sporadic studies reporting fatty degeneration involving proximal muscles in patients with fixed weakness or advanced age.⁹ Therefore, it was necessary to rule out an associated limb-girdle muscular dystrophy in this case. A genetic analysis confirmed a concomitant anoctaminopathy, which better correlates with the patient's clinical picture.

We highlight the importance of carefully evaluating the entire clinical picture. The clinical features should outweigh the complementary tests to guide the definitive diagnosis. It is also important to remember that the coexistence of genetic conditions is possible, particularly among patients with a history of consanguinity. If complementary findings, including genetic results, do not explain the patient's clinical manifestations, the investigation should continue until it leads to a proper answer.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Aurelio Hernández-Lain, PhD	Department of Pathology (Neuropathology), Hospital Universitario 12 de Octubre, Madrid, Spain	Preparation of images and interpretation of neuropathologic studies
Cristina Domínguez-González, PhD	Neuromuscular Disorders Unit, Department of Neurology, Hospital Universitario 12 de Octubre, Madrid, Spain	History and examination of patient, critical revision of the manuscript for important intellectual content

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