

What Is in the Myopathy Literature?

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Abstract

This update begins with the results of a positive trial of intravenous immunoglobulin in dermatomyositis and a study of molecular and morphologic patterns in inclusion body myositis that may explain treatment refractoriness. Single center reports of muscular sarcoidosis and immune-mediated necrotizing myopathy follow. There is also a report of caveolae-associated protein 4 antibodies as a potential biomarker and cause of immune rippling muscle disease. The remainder covers updates on muscular dystrophies as well as congenital and inherited metabolic myopathies with an emphasis on genetic testing. Rare dystrophies, including one involving *ANXA11* mutations and a series on oculopharyngodistal myopathy, are discussed.

Key Words: myopathy, muscular dystrophy, myositis, congenital myopathy

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AUTOIMMUNE MYOPATHIES

Aggarwal and other members of the ProDERM trial group recently reported the positive results of a randomized, placebo-controlled trial of intravenous immune globulin (IVIG) in active dermatomyositis.¹ IVIG treatment was administered every 4 weeks for 16 weeks, and the primary endpoint was change in the total improvement score (TIS), a composition of a core set of 6 measures including manual muscle strength testing, global assessments of disease activity and quality of life, and serum muscle enzymes. The trial permitted concomitant therapy, and 88% of patients were receiving glucocorticoids.

Ninety-five patients underwent randomization: 47 received IVIG and 48 were in the placebo group. Treatment and placebo groups were well balanced. At 16 weeks,

79% in the IVIG group and 44% in the placebo group had an increase in the TIS of at least 20 points ($P < 0.0001$) and 20 was defined as the threshold of at least minimal improvement. There was also improvement in secondary endpoints except for serum creatine kinase levels. Treatment benefits were apparent by 4 weeks. Regarding secondary efficacy endpoints, at least moderate improvement—TIS of 40 or greater—was present in 68% of patients in the IVIG group versus 23% receiving placebo. Major improvement—TIS of 60 or more—was noted in 32% in the IVIG group versus 8% in the placebo group.

Patients who did not have confirmed deterioration while receiving IVIG were allowed to continue into an open-label extension phase that lasted up to 40 weeks. They continued to receive 2 grams per kilogram of IVIG every 4 weeks, or the dose was reduced to 1 gram per kilogram starting at week 28 depending on the treatment response. Sixty-nine patients completed the extension phase.

During the placebo-controlled phase, 5 patients in the placebo group crossed over to receive IVIG. Two of those patients were switched because of confirmed deterioration, and 3 were switched in error. No patients in the IVIG group crossed over to placebo.

Adverse events were more common in the IVIG group in which headache occurred in 42%, pyrexia in 19%, and nausea in 16%. There were 6 thromboembolic events. Because of thromboembolic events, the trial protocol was amended to reduce the maximal infusion rates from 0.12 to 0.04 mL per kilogram per minute. The incidence of thromboembolic events dropped from 1.54 to 0.54 per 100 patient-months after the protocol was amended.

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The authors mention study limitations including a relatively short—16 week—placebo-controlled treatment phase and the exclusion of patients with juvenile, cancer-associated, or amyopathic dermatomyositis. In addition, the primary endpoint was a complicated measure; myositis antibody subsets were not evaluated, and there was a high placebo response rate.¹ Nevertheless, this was a high-quality study that provides additional compelling evidence that IVIG is beneficial in patients with dermatomyositis. Clinicians must continue to consider the risks and to monitor for adverse events including thromboembolism.

Inclusion body myositis (IBM) remains a disease for which we have no substantially effective disease-modifying treatment. Perhaps the degenerative component makes the disorder refractory to immunotherapy, but Kleefield et al recently provided more evidence that there are dysfunctional T cells in IBM, a possible clue to the treatment resistant state.²

These authors studied morphologic and molecular patterns in muscle biopsy specimens associated with diagnoses of IBM and the somewhat controversial subtype of polymyositis (PM) with mitochondrial pathology (PM-Mito), with the latter being considered a probable *forme fruste* of IBM by some. Biopsy specimens labeled PM-Mito lack rimmed vacuoles but have other features seen in IBM. The authors sought to determine if PM-Mito and IBM are part of the same disease spectrum.

Histopathology and immunohistochemistry were performed on all 25 IBM and 25 PM-Mito specimens, and quantitative polymerase chain reaction on 41 gene transcripts was performed on 22 IBM and 17 PM-Mito specimens and on 5 healthy controls. Assays focused on interferon (IFN)-mediated inflammation, including IFN-induced guanylate-binding protein (GBP) 6 expression,³ T-cell dysfunction, and transactive response element DNA binding protein-43 (TDP 43)-associated cryptic exons. Known molecular markers of IBM, including killer cell lectin-

like receptor G1 (KLRG1), which is present in terminally differentiated T-cells, were included.⁴ *Of interest to clinicians, molecules expressed by a highly pathogenic T-cell population have been postulated to be potential favorable targets for an IBM therapy.*⁴

Many of the PM-Mito patients lacked significant quadriceps and finger flexor weakness as is typical of IBM. Twenty-eight percent had dysphagia. Two of 6 tested had anti-cN1a antibodies. Most (13 of 14), who were followed, progressed to IBM.

The authors found that histopathologic features overlapped in PM-Mito and IBM. Mononuclear cell expression of IFN-induced GBP6 and T-cell function KLRG1 was higher in IBM than PM-Mito, and both disease states had higher levels than in healthy controls. Other measures of T-cell dysfunction were present in both IBM and PM-Mito with quantitative differences—higher measures in IBM. TDP43-associated cryptic exons (splicing variants that may lead to frameshifts or stop codons or other changes in the resulting mRNA) were present in IBM and PM-Mito with higher values in IBM. As an aside, Britson et al⁵ previously showed that the loss of TDP-43-mediated splicing repression occurred in an IBM xenograft model.

The investigators feel that PM-Mito is an early form of IBM. They concluded that “specific IFN-mediated inflammation plays a key role in both IBM and PM-Mito. GBP6 was identified as a new molecule marker of type II IFN-induced inflammation distinguishing IBM from PM-Mito. Skeletal muscles from both groups harbor dysfunctional T cells of similar type, albeit in different quantity. T-cell senescence exemplified by KLRG1 positivity does not play a significant role in PM-Mito.”²

Greenberg⁶ provided an accompanying editorial that outlines the history of IBM with respect to differentiating it from PM, and he nicely addresses controversies. He also agrees that highly differentiated cytotoxic T cells are resistant to death by apoptosis, and he notes that such T cells are not depleted in vivo by corticosteroids (CS). The notion that

treatment-refractory IBM is associated with this highly differentiated cytotoxic T-cell state has merit. A drug that depletes KLRG1+ T cells is under study.^{7,8}

Although granulomatous inflammation is occasionally encountered in IBM, the most common cause of non-necrotizing granulomas in skeletal muscle is sarcoidosis.⁹ Granulomas in muscle are often asymptomatic in patients with sarcoidosis, but symptomatic muscle involvement occurs in only 0.5%–2.0%.

Ten Dam et al¹⁰ recently performed a single center retrospective cohort study and literature review on muscular sarcoidosis. Case records of adult patients seen between 2015 and 2020 at the Amsterdam University Medical Center, a tertiary referral center for sarcoidosis and inflammatory myopathies, were reviewed. Included patients had a histopathologic diagnosis consistent with sarcoidosis, muscle weakness or myalgias, and histologic or imaging [muscle magnetic resonance imaging (MRI) or fluoro-18-deoxyglucose positron emission tomography] evidence of sarcoid myopathy.

Three hundred and three patients were seen with suspected neurosarcoidosis. Half (153) were diagnosed with neurosarcoidosis, and muscle sarcoid was diagnosed in 12. There were 8 females; median age at onset was 56 years (range, 31–74). Eleven had weakness. It was proximal in all—lower limbs only in 4 and 3 also had distal weakness. Myalgias were present in 7 and were usually generalized. Two also had small fiber neuropathy, and 2 had central nervous system involvement. Most had affected lungs. Creatine kinase levels were increased in 8 of 10 (range, 10–1324 U/L with a median of 382 U/L). Serum angiotensin-converting enzyme was elevated in 8 of 10; soluble interleukin 2 receptor was elevated in all 4 of the 4 evaluated. Two patients had either anti-Jo1 or anti-OJ antibodies, but there were no other features of antisynthetase syndrome.

Skeletal muscle MRI, performed in 10 patients, showed edema in various degrees involving whole muscles or in a linear or

“tiger man” appearance. Focal nodular edema in fascia or muscle also occurred. Fluoro-18-deoxyglucose positron emission tomography, performed in 6, showed increased uptake in muscles in 5, more often in a linear than nodular pattern. Electrodiagnostic testing (EDx) was performed in only 5 patients. Four had axonal sensorimotor polyneuropathy, and 3 showed signs of myopathy. Nine underwent muscle biopsy including 4 who lacked a previous diagnosis of sarcoidosis. Six showed noncaseating granulomas. Three exhibited endomysial or perimysial inflammation without identified granulomas. Findings of IBM were not seen on careful study.

Median follow-up was 42 months (range, 2–78 years). All received CS. Methotrexate or azathioprine was used in 3. Infliximab was used in 1, and 1 received rituximab, IVIG, and mycophenolate mofetil. At last follow-up, muscular involvement was considered in remission in one, improved in 6, stable in 3, and worse in 2.¹⁰

While highlighting the clinical features and patterns of involvement, this report illustrates the use of more modern diagnostic tools in an “old” disease. Muscle MRI with a “tiger man” appearance and elevated serum soluble interleukin 2 receptor as diagnostic markers are examples. Still, treatment was unfortunately limited. The authors also provided a literature review that emphasized the rare occurrence and disabling nature of the disorder.

Chompoonpong and Liewluck⁹ recently reviewed the topic of non-necrotizing granulomatous inflammation in skeletal muscle biopsy specimens for those who wish to read an update on the entire spectrum of this entity.

Immune-mediated necrotizing myopathy (IMNM) is being increasingly recognized as a cause of autoimmune myopathy, but optimal treatment regimens are uncertain. Pending the results of a positive prospective phase III trial, decision making has been based on experience and retrospective studies. Wang et al recently added their retrospective analysis of treatment and outcome

predictors involving patients diagnosed with IMNM. Enrolled subjects had biopsy specimens that showed a necrotizing myopathy. They were obtained at John Hunter Hospital and Royal Adelaide Hospital between 2012 and 2019. Interpretation was performed at South Australia Pathology.¹¹

Forty-six patients were identified, and 12 were excluded because of inadequate records or alternative diagnoses. Of the 34 included, 18 (53%) were males. Seventy-four percent were older than 60 years of age. Median CK was 6456 U/L. About 80% were taking or had received a statin. 3-hydroxy-3-methylglutaryl-CoA reductase antibodies (Abs) were present in 44%; 18% had signal recognition particle Abs, and 35% were seronegative. Initial treatments were CS alone in 41.2%, CS and IVIG in 26.5%, and CS plus a conventional synthetic disease modifying antirheumatic drug, namely, mycophenolate, methotrexate, or azathioprine in 29.4%.

Analysis of predictors and outcomes was limited by the retrospective design, nonuniform treatments, and relatively small numbers. Earlier introduction of IVIG appeared to be beneficial, especially in those with moderate-severe weakness at baseline. Dysphagia was not evaluated separately. Older age and female sex had a better biochemical response. It was believed that CS treatment alone was often insufficient. Too few patients received individual conventional synthetic disease modifying antirheumatic drugs to allow for analysis of their potential benefit. Intravenous methylprednisolone drove down CK but was not associated with significant improvement in strength. The results of this study are in keeping with our view that early implementation of IVIg should be considered in adult IMNM.¹²

Rippling muscle disease (RMD) is a rare myopathy in which there are wave-like muscle contractions and percussion or stretch-induced muscle mounding that is electrically silent. It can be inherited or autoimmune. Inherited RMD is usually due to pathogenic variants in caveolin-3 (*CAV3*) or, less frequently, cavin-1 (*CAVIN1*). Dubey

et al¹³ recently reported the presence of cavin-4 IgG in the serum of patients with RMD, and this antibody may be a biomarker of immune-mediated rippling muscle disease (iRMD).¹⁴ The authors examined serum from 10 adults who were previously diagnosed with iRMD. Using human proteome phage immunoprecipitation sequencing, they identified an IgG autoantibody against caveolae-associated protein 4 (cavin-4) in 8 of the 10 patients. This antibody was not present in disease or healthy controls. Seven of 8 patients were tested for *CAV3* and *CAVIN1* mutations and were negative.

Of the 8 patients harboring cavin-4 Abs, 6 were male and the median age was 60 years (range, 18–76). Muscle rippling initially occurred in the lower limbs or all limbs in 5 of 8, and there was mild proximal weakness in 3. Diffuse rippling followed. Most patients had fatigue. All had percussion-induced muscle rippling. Plasma CK levels were elevated in all except 1 patient (range, 132–2625 U/L). Four of 8 patients also had acetylcholine receptor-binding antibodies, and a decrement on repetitive stimulation was present in 2. Cancer screening was performed in 6 patients, and breast carcinoma was detected in 1. Muscle biopsies were performed in 7 patients. Immunohistochemical reactivity for cavin-4 was assessed in 6 specimens, and all 6 exhibited a mosaic sarcolemmal staining pattern. The authors also demonstrated a presumed secondary loss of caveolin-3 in their patients' muscle biopsy specimens.

Various immunotherapies were provided, and 3 patients had complete resolution of symptoms. One had mild improvement, and 2 had no change. Treatments included IVIG, prednisone, methylprednisolone, azathioprine, and plasma exchange.

Cavin-4 has a role in structural and functional maturation of T tubules according to animal models. Antibodies to cavin-4 may disrupt the excitation-contraction system. The conclusion is that cavin-4 IgG may be a serological and pathogenic biomarker for iRMD, a potentially treatable autoimmune myopathy.¹³

HYPERCKEMIA
AND RHABDOMYOLYSIS

Being faced with a patient with hyperCKemia without symptoms or with minor symptoms and no weakness can be frustrating since the likelihood of finding a cause has been relatively low and finding one with clinical implications is even lower. Thus, one must carefully consider the utility of EDx, muscle biopsy, biochemical studies, and genetic testing in this setting. In adults, the diagnostic yield of EDx and muscle biopsy ranges from 8% to 55%.^{14–16} A diagnosis is more likely in children.¹⁵ As more comprehensive genetic testing becomes available, it would seem likely that the diagnostic yield will increase and genetic testing will be used first line, especially in children.

Wong et al performed a retrospective chart review of patients aged 16 years or less who were seen from 2005 to 2017 at the Children's Hospital of Westmead, Australia.¹⁷ Selected individuals had CK levels of greater than 200 U/L on at least 2 occasions and did not have weakness, family history of muscle disease or hyperCKemia, or medications known to cause hyperCKemia. Forty-three families (47 individuals) from a clinic population of 597 were identified. Leg pain or cramps occurred in 8. Two had toe waking, and 1 had large calves. Three had episodes of rhabdomyolysis.

The authors performed multiplex ligation probe amplification of the dystrophin gene and used massively parallel sequencing panels that increased coverage to 317 genes during the project. Whole exome sequencing was performed on 2 families, and single gene Sanger sequencing was rarely performed.

Only 9 individuals underwent muscle biopsy as practice was shifting toward genetic testing. In one, phosphorylase reactivity was absent; a *PYGM* mutation was confirmed. In one, immunohistochemical reactivity for alpha-sarcoglycan was reduced; a pathogenic variant in *SGCA* was later found. Genetic diagnoses were made in 3 with nondiagnostic muscle biopsies.

Genetic variants that explained hyperCKemia were found in 25 of 34 (74%) tested. Of these, there were pathogenic/presumed pathogenic variants in 19 neuromuscular disease genes [*DMD* in-frame deletions in 11; in *FKRP*, *RYR1*, *DYSF*, *SGCA*, *CAV3*, *POMT1*, *POMT2*, *MICU1* (codes for Mitochondrial Calcium Uptake 1)] one each. There were pathogenic/presumed pathogenic variants in 4 metabolic myopathy genes (*PYGM* in 4 individuals from 3 families); *CPT2* in 2 individuals from 1 family; *GAA* and *LPIN1* (encodes a magnesium-ion-dependent phosphatidic acid phosphohydrolase enzyme involved in triglyceride synthesis) in one each. *DMD* mutations were a common cause of hyperCKemia in males. Those with higher peak CK levels that normalized were more likely to have metabolic myopathies. Of the 18 patients who remained undiagnosed, 9 did not have genetic testing and 2 had negative *DMD* testing alone. Seven were negative after extensive testing.

Importantly, positive genetic testing has familial implications and confirms a diagnosis. Treatment is available for Pompe disease and some types of dystrophinopathy. *RYR1* mutations raise the possibility of malignant hyperthermia in the family as well as in the index patient.

The authors show that there is a high yield to their genetic approach in children with hyperCKemia without weakness. The yield is still likely to be lower in adults who do not have such a high proportion of *DMD* mutations. It should also be noted that many of the children had symptoms (pain and cramps) and features of neuromuscular disease such as toe walking and large calves. The yield would likely be lower in asymptomatic hyperCKemia without any of these clinical features.

Rhabdomyolysis was seen in a few of the patients reported by Wong et al.¹⁴ Advances in the genetics of rhabdomyolysis was recently presented by Cabrera-Serrano and Ravenscroft.¹⁷ This diagnosis is used very loosely by many clinicians and really should be reserved for those with CK levels above 5

times the upper limit of normal, myoglobinuria, and typically symptoms of muscle pain, swelling, and possibly weakness. There is often a trigger such as exercise, infection, drug, or toxin.

Historically, McArdle disease and carnitine palmitoyl transferase deficiency were the best known genetic causes of rhabdomyolysis, and then, mitochondrial disease and some dystrophies made the list. The list has grown substantially. Regarding dystrophies, it started with dystrophinopathy and now includes *ANO5*, *CAV3*, *FKRP*, *SGCA*, and *GMPPB*.¹⁷

Recessive mutations in *LPIN1*, as seen in a patient in the study by Wong et al,¹⁴ have more recently been found to be a common cause of childhood-onset and severe rhabdomyolysis in the setting of catabolic stress. For example, Kahraman et al¹⁸ reported a 5-year-old with fatal rhabdomyolysis with ventricular tachycardia and a 7-year-old with severe rhabdomyolysis, supraventricular tachycardia, and compartment syndrome. *LPIN1* deficiency causes mitochondrial dysfunction by impeding clearance of damaged mitochondrial DNA. Complications of severe rhabdomyolysis may include ventricular arrhythmias and compartment syndrome as well as acute renal failure.

Mitochondrial dysfunction and rhabdomyolysis also occur with pathogenic variants in *TANGO2* (transport and Golgi organization 2 homolog). Patients may have cardiac arrhythmias and intellectual delay. Fatty acid oxidation may be defective. Dysfunctional assembly of iron-sulfur clusters, which are synthesized in mitochondria and are involved in electron transport and DNA repair, can also cause myopathy with rhabdomyolysis. Mutations in *FDX2* (ferredoxin 2) have these effects.¹⁷

Other novel causes of rhabdomyolysis include variants in *MLIP*, muscle lamin A/C interacting protein, in which recurrent myalgias are common, and *OBSC* which likely causes loss of function of the muscle protein obscurin and disturbances in sarcoplasmic reticulum calcium release. In addition to asymptomatic hyperCKemia as noted above, variants in *RYR1* and their effect on

sarcoplasmic reticulum lead to a spectrum of muscle disturbances that include rhabdomyolysis.¹⁷

MUSCULAR DYSTROPHIES AND CONGENITAL MYOPATHIES

Genetic testing has also greatly enhanced diagnosis of hereditary myopathies with limb-girdle weakness. In the largest study of 1001 undiagnosed patients with limb-girdle weakness that was published in 2020 and used exome sequencing, pathogenic variants were found in 52% of patients across 87 genes. Pathogenic variants in *CAPN3*, *DYSF*, *ANO5*, *DMD*, *RYR1*, *TTN*, *COL6A2*, and *SGCA* accounted for 27.1% of the cohort.¹⁹ Many of the patients included had some previous evaluations.

In comparison, Krenn et al²⁰ recently reported an Austrian study that evaluated patients with limb-girdle weakness irrespective of previous genetic or clinical approaches, and they included patients with diagnoses such as facioscapulohumeral muscular dystrophy and spinal muscular atrophy. Therefore, the study was not entirely limited to limb-girdle muscular dystrophy (LGMD), but mostly uncovered LGMD diagnoses. Subjects throughout Austria were recruited by neurologists and neuromuscular centers for adults with unexplained limb-girdle weakness and an elevated CK or myopathic abnormalities on muscle histology, EMG, or MRI. Those with limb-girdle weakness and a previous genetic diagnosis of LGMD were also eligible. Genetic studies were performed in different laboratories using heterogeneous techniques that included single gene studies and next-generation sequencing (NGS), and data were pooled.

One hundred twenty-one patients were enrolled. Females accounted for 52%. The mean age at onset was 28.8 years (± 17.7 years SD). About a third had scapular winging. Cardiomyopathy occurred in 11.7%, and 10.7% had respiratory insufficiency.

Using their approach, which simulates how many clinical practices are evolving,

pathogenic or likely pathogenic variants were found in 27 different genes from 75 of 121 patients for a 62% yield. Next-generation sequencing established the diagnosis in 77.3%, whereas single gene testing did in 22.7%. Of those diagnosed by NGS, single-gene analysis had been negative in 31%. Single gene testing was used when muscle histopathology or clinical phenotypes suggested a specific entity or if a known causative variant was present in the family. Diagnoses were made earlier after onset with NGS compared with single-gene studies (mean 8.9 vs. 17.8 years).

The most common diagnoses were in the 32.2% of myopathies with variants in *CAPN3* (n = 9), *FKRP* (n = 9), *ANO5* (n = 8), *DYSF* (n = 8), and *SGCA* (n = 5). In patients with disease onset after age 18 years, *ANO5* was most common and *DYSF* followed. These 2 disorders had the highest CK levels. With earlier onset, *CAPN3* was the most commonly mutated gene followed by *FKRP* and *SGCA*. Three patients (*LMNA*, *DES*, and *RBCK1*—with polyglucosan body myopathy) had undergone heart transplantation, and 5 required noninvasive ventilation (2 with *CPN3* and 1 each with *FKRP*, *SGCA*, and unknown cause). Overall, the yield was higher with younger age of onset, CK > 10-fold elevated, and myopathic EMG findings.²⁰

This study is useful in providing a view of a nationwide population of hereditary limb-girdle syndromes with respect to the more common entities and factors that correlate with a higher yield of a molecular diagnosis. The yield should continue to improve as NGS becomes more available and extensive. However, most available NGS panels or exome sequencing remain non-diagnostic in some settings including repeat expansions and intronic mutations.

Of course, exome sequencing has been extremely useful in identifying new disease-causing mutations and in defining the spectrum of phenotypic variability. A recent example of the latter comes from Johari et al.²¹ They found that mutations in *ANXA11* cause an autosomal dominant muscular

dystrophy with scapuloperoneal weakness and rimmed vacuoles containing Annexin A11 inclusions. Annexin 11, which is encoded by *ANXA11*, is a member of a family of phospholipid-binding proteins involved in calcium signaling, vesicle trafficking, and apoptosis. Mutations in *ANXA11* have been associated with amyotrophic lateral sclerosis and multisystem proteinopathy.^{22,23}

To make the above discovery, Johari et al.²¹ performed exome sequencing and deep phenotyping on 7 affected patients from 4 Greek families with autosomal dominant muscle disease. Onset of weakness was in the third to fifth decades in shoulder abduction with slow progression to involve proximal upper and lower and then distal lower extremity weakness. Scapular winging was present, and ptosis occurred in the majority. Cognitive function was normal. MRI showed fatty replacement of the adductor magnus and lower leg muscles.

CK levels ranged 300–1000 U/L in 6 of 7 and were normal in the other patient. EDx was performed in 3 with myopathic findings in 2 and mixed findings in 1. Genetic testing for facioscapulohumeral dystrophy was obtained due to scapuloperoneal and some facial weakness, and it was negative. Muscle histopathology showed chronic myopathic changes with rimmed vacuoles some of which immunoreacted with desmin, myotilin, and Annexin A11. Electron microscopy showed autophagic vacuoles and myofibrillar alterations.

Exome sequencing showed only 1 *ANXA11* variant in exon 3 in the prion-like domain (c.118 G > T:p.D40Y) that segregated with the phenotype in all 4 families. It was not present in healthy family members or in public genome aggregation databases. It is felt to be a founder mutation from the Greek archipelago. Although the pathogenic mechanism is unknown, this study clearly shows that the phenotypic spectrum of *ANXA11* mutations includes an adult-onset autosomal dominant scapuloperoneal myopathy with rimmed vacuoles.²¹

Another rare muscular dystrophy is oculopharyngodistal myopathy (OPDM). It

was first described clinically in Japanese families 4 decades ago,²⁴ and over the last several years, 3 genetic causes were identified, and a fourth mutation was discovered in 2022. Most cases are from Japan and China.²⁵ Manifestations of the OPDM phenotype are ocular (ptosis often with ophthalmoplegia), pharyngeal, facial, and distal weakness with an AD mode of inheritance. Proximal weakness is rare, and central nervous system involvement occurs only in OPDM3. Occasionally, weakness is asymmetric. Patients with oculopharyngeal muscular dystrophy (OPMD) have similar features except that facial weakness is usually not a major finding, and, when present, limb weakness is usually proximal rather than distal. OPMD is caused by expansions in polyadenylate-binding protein nuclear 1.

One cause of OPDM is a repeat expansion in low-density lipoprotein receptor-related protein 12. It is designated OPDM1 and was first reported in 2019.²⁶ OPDM1 is mostly seen in Japan. Shimizu et al more recently reported clinicopathologic findings of 7 patients with OPDM1.²⁷ They were from 5 different families seen at the University of Tokyo Hospital. Inheritance was AD in 3, and 2 were considered sporadic. Age of onset ranged from 20 to 45 years. First symptoms were in the limbs with grip weakness (2), distal leg weakness (3), and proximal leg weakness in 1. One was not documented. Oculopharyngeal symptoms started 3–25 years later and were subtle in some. Ptosis was common, but ophthalmoparesis was clear cut in only 1 patient and subtle in 2. Axial/neck weakness was seen in 6, and fatty infiltration was seen in the rectus abdominis by computed tomography (5 of 5 imaged). Dysphagia, nasal voice, and dysphagia were common.

Serum CK levels ranged from 223 to 1018 U/L (laboratory normal 59–248). EDx showed decreased motor amplitudes recorded from atrophic muscles. Fibrillation potentials were present in distal muscles. Myotonic discharges were present in 2 patients. Motor unit potential morphology was variable.

Chronic myopathy with rimmed vacuoles and p62 reactive aggregates were seen in biopsy specimens from 4 patients, especially those taken from the tibialis anterior. The number of lipoprotein receptor-related protein 12 repeats ranged from 76 to 630 (normal 13–45). This study shows that in addition to the typical phenotype, OPDM1 patients may have prominent axial as well as distal weakness with only later onset of oculopharyngeal weakness that can be subtle.²⁷

OPDM2 is due to pathogenic variants in GAIP/RGS19-interacting protein *GIPC1*, and OPDM3 is due to variants in notch 2 N-terminal-like C (*NOTCH2NLC*).²⁵ So far, the phenotypes are similar except OPDM3 may include CNS features of neuronal intranuclear inclusion disease.²⁶ Expansions of CGG repeats in the untranslated region of the associated genes are seen in all types of OPDM.

A fourth type of OPDM was reported in 2022. Yu et al²⁸ and then more recently, Zeng et al²⁹ reported their discoveries that OPDM4 is caused by CGG repeat expansions in *RILPL1* which encodes Rab-interacting lysosomal protein-like 1. Yu et al reported 11 Chinese individuals with the mean age of onset of 23.8 ± 6.23 years. All had typical clinical and histopathologic features of OPDM. Distal weakness was usually a later feature. One had tremor.²⁸ They noted that *RILP1* mRNA formed RNA foci and sequestered RNA-binding protein *MBLN1* as is seen in myotonic dystrophy type 1 and consistent with a toxic gain of function.²⁸

Zeng et al investigated 6 patients from 2 genetically undiagnosed Chinese Han families with OPDM. Age of onset was 19.3 ± 8.0 years with a range of 10–30 years. Most had typical clinical features. Four presented with ptosis, and 2 had distal limb onset. Other features included external ophthalmoplegia and a nasal dysarthric speech. CK levels ranged from 165 to 758 U/L. Electrodiagnostic studies, performed on 3 patients, showed low amplitude motor responses in the lower extremities and short duration motor unit potentials on needle examination. Muscle MRI showed fatty deposition in many distal

and proximal as well as cranial muscles. Muscle biopsy performed in 2 patients showed chronic myopathic changes with rimmed vacuoles and p62 positive inclusions in nuclei and vacuoles. Abnormal RNA foci were also seen. Ultrastructural studies showed filamentous intranuclear inclusions.

Extensive genetic studies mapped the disease locus to 12q24.3. The authors then found GGC repeat expansions in the promoter region of *RILP1*. The length of the expansion did not correlate with the age of onset. Some patients with very long repeats were asymptomatic, and this occurrence was felt to be due to hypermethylation of the promoter region which suppressed expression of *RILP1* protein.

The rate of discovery in this field of OPDM has been amazing. OPDM4 seems to have a slightly earlier age of onset than the other conditions. The 4 subtypes are otherwise very similar regarding clinical and histopathologic features and the commonality of repeat expansions and a suggested toxic gain of function. To date, these discoveries have been made on populations in China and Japan, but clinicians need to keep on the lookout for these disorders in other regions and in other ethnic groups.

It is important to realize that neurologists also encounter adult patients with undiagnosed congenital myopathies. Pinto et al³⁰ recently provided us with their observations of this occurrence. They performed a retrospective observational cohort study in a Portuguese University hospital. Medical records from an adult neuromuscular outpatient clinic were reviewed for patients with proven or suspected genetic myopathy during 2021. Patients diagnosed with a congenital myopathy were included and then divided by age of onset into pediatric-onset and adult-onset groups. All patients had a diagnosis of congenital myopathy by either detection of a gene-causing variant or muscle biopsy showing histopathologic features of a congenital myopathy such as centronuclear, central core, multimincore, nemaline rod, or congenital fiber-type disproportion.

The authors identified 137 patients as having genetic myopathy, and 19 (14%) were determined to have a congenital myopathy. Seventy-four percent were female. Age at symptom onset ranged from 2 to 50 years, and age of diagnosis ranged from 9 to 66 years. Genetic confirmation was made in all. By far, the most common mutations were *RYR1* (16 patients or 84%). Two patients had variants in *TTN*, and 1 had a variant in *MHY7*. Five were diagnosed at a pediatric age, and 14 were diagnosed in adulthood.

Muscle biopsies had been performed in 5 patients with *RYR1* mutations. Central core pathology was seen in one of them who had an autosomal dominant (AD) inheritance pattern. Congenital fiber-type disproportion histopathology was seen in 2 in an autosomal recessive pattern. One patient had findings of centronuclear myopathy, and 1 had core-like features; both had an autosomal recessive pattern. The patient with the *TTN* mutation had pathology consistent with centronuclear myopathy, and the other one had core-like features.

Eleven of the 14, who were diagnosed as adults, had symptoms since childhood, and 9 had a family history of myopathy. Median onset of symptom onset was 4 years, and median age of diagnosis was 37 years. The 5 diagnosed in childhood had *RYR1* mutations and symptom onset between birth and 10 years. The authors point out that diagnostic delay in adulthood may have been due to a mild presentation, slow course, atypical muscle histology, and a lack of awareness of adult onset of congenital myopathy. It will be interesting to see how the spectrum of adult diagnosed congenital myopathy evolves as more centers perform genetic testing routinely and become more aware of such patients.

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