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Review

Muscle Diseases of Metabolic and Endocrine Derivation

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Abstract: Muscle function and pathology are complex subjects; the medical fields involved in their diagnosis and treatment represent rheumatology, physiatry and metabolic disease, among others. While we, rheumatologists, concentrate our efforts predominantly on inflammatory varieties and those associated with medications (e.g., corticosteroid and statin use), we are often the "turn to" gatekeepers for the identification of the diagnostic category represented by a patient's symptomatology. The broad base of rheumatologic training prepares us for the recognition of endocrinologically derived myopathy. This subject and fundamentally biochemically derived myopathies form the basis for this review.

Keywords: myopathy; glycogenosis; lipid storage diseases; adenosine deaminase; endocrine disease

1. Introduction

Primary care physicians often refer individuals for rheumatologic assessment, not only when they suspect a rheumatologic/immunologic cause, but also when they are stymied. Thus, among the cornucopia of presentations, alterations in muscle function represent symptoms and signs which are often referred to our services. Although rheumatologists are fully conversant with rheumatologic diseases and immunologic causes, we are perhaps less familiar with metabolic and endocrine-derived myopathies (unless we have participated in an inter (multi)-disciplinary muscle clinic). The purpose of this manuscript is not to provide contrast with inflammatory myopathies or muscular dystrophies such as limb girdle, myotonic and Becker's, but to fulfill the premise that alternative diagnoses will not be considered unless one is conversant with those alternatives. This manuscript provides a perspective of the character and complexities of metabolic and endocrine-derived myopathies and reminds us that we do not work in isolation, but in collaboration.

Two varieties of contractile fibers are responsible for muscle function [1]. Type I fibers, responsible for sustained muscle activity, utilize long-chain fatty acids as their energy source; Type II fibers are responsible for rapid twitch activities and are supported by the breakdown of glycogen stores. Diseases that affect their relative functions are the subject of this review. Myopathies are typically categorized as congenital (e.g., muscular dystrophy, nemaline, centronuclear, central core, myotonic dystrophy, motor neuron disease), inflammatory/immunologic (e.g., polymyositis, inclusion body disease) and metabolically/endocrinologically derived [2–5]. The latter is reviewed herein, divided into dysfunctions related to carbohydrate, lipid and purine metabolism, endocrine function and mitochondria.

Metabolic myopathies occur because of inefficient or absent enzymes or transport proteins involved in creating adenosine triphosphate (ATP). Their pathophysiology is derived from the interruption of the biochemical cascade involved in assuring availability of energy. Deficiencies may result in substrate accumulation, insufficiency of product availability for other enzymes in the cascade, disrupted feedback loops or compromised transportation.

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Symptoms may include muscle fatigue, weakness (which may be progressive), pain, cramping (electromyographically silent pseudomyotonia), contractures and rhabdomyolysis (presenting as brown urine), often exacerbated by exercise. Occasionally, motor weakness may be fixed, imitating inflammatory or immunologically derived myopathy. Respiratory muscle involvement results in dyspnea, tachypnea or hypernea and inappropriate tachycardia, especially in response to exercise. Exercise may induce the increased adenylate kinase breakdown of purine nucleotides, resulting in hyperuricemia.

The management of individuals with metabolic myopathies is a multidisciplinary effort, in which the rheumatologist comanages with neurologists, physiatrists, metabolic disease specialists, dietitians, genetic counselors and often with cardiologists and pulmonologists.

2. Carbohydrate Metabolism

Glycogen, the major source of quick energy for muscles, is synthesized from glucose-1-phosphate by uridine triphosphate glycogen transferase, phosphorylase A and branching enzyme [6–8].

The physical character of glycogen molecules inhibits phosphorylase B, the effect of which is that the enzyme is unable to cross branching points. Debranching enzyme resolves this challenge, permitting phosphorylase B to release glucose-1-phosphate as per the energy requirements.

Phosphoglucomutase converts glucose-1-phosphate to glucose-6-phosphate, the substrate required for conversion by glucokinase to glucose or by phosphohexose isomerase to fructose-6-phosphate. Fructose-6-phosphate may be metabolized by phosphofructokinase to fructose, which enters into the tricarboxylic acid (TCA) energy production cycle or is further metabolized to pyruvate and lactate.

Acute exercise would be expected to consume glycogen stores, producing metabolic products which accumulate as lactate, since the metabolism of pyruvate as an energy source is the rate-limiting factor in the pathway. Contrasting with the oxygen-dependent TCA cycle, glycogen metabolism (to lactate) can proceed anaerobically.

Disorders of carbohydrate metabolism manifest with the activity-related accumulation of lactate, as measurable by the ischemic exercise test (Table 1) [9]. After obtaining baseline lactate levels, circulation to the test limb is occluded for one minute while it is subjected to vigorous exercise. Lactate levels are then obtained one, three, six and ten minutes after the restoration of blood flow. When glycogen stores are present, an intact glycogen catabolism system permits increased lactate production pathway interruptions, compromising lactate production.

Table 1. Disorders associated with positive ischemic exercise test. Phosphorylase deficiency—McArdle's disease.

Phosphohexoisomerase deficiency
Phosphofructokinase deficiency
Mitochondrial myopathy
Thyrotoxicosis
Alcoholic myopathy, acute
Myasthenia gravis, occasionally
Muscular dystrophy, occasionally
Polymyositis, occasionally

3. Deficiencies in Enzymes Involved in Carbohydrate Metabolism

The following deficiencies are numbered in the order that they were discovered, not in their order in glycogen metabolism [1,4,5].

3.1. Muscle Phosphorylase

A deficiency of muscle phosphorylase, referred to as Type V glycogen storage or McArdle's disease, is autosomal recessive (rarely dominant), affecting 1 in 100,000. It usually presents before age 20 with muscle weakness, stiffness, cramps and hypoglycemia-related seizures [7,10–14]. Predominantly affecting males, an identifiable family history is present in approximately half of affected individuals with this autosomal recessive, occasionally dominant disorder on chromosome band 11q13. Symptomatic episodes initially present as two weeks of weakness, stiffness and aching. The muscles become firm and shortened, with painful cramps resulting from exercise, ischemia and infection. A characteristic observation is the development of a "second wind", which permits more vigorous exercise than the initial effort. This describes the sudden major augmentation of ability to again pursue aerobic exercise after a brief rest.

The phenomenon probably relates to hyperemia and the mobilization of free fatty acids as an energy source. Occasionally, it progresses to a fixed myopathy. Creatine kinase (CPK) levels are generally elevated, especially after exercise, as potassium and serum venous lactate. Episodic myoglobinuria is noted in 55% of cases. The ischemic exercise test is abnormal, associated with blood potassium increases. While electromyography reveals the short polyphasic potential of myopathic disease, electrical silence may be noted at rest or in contracted muscle. Repetitive supramaximal (18/s) nerve stimulation reduces evoked potentials in phosphorylase, in contrast to lack of effect in phosphofructokinase deficiency.

Muscle biopsy generally has a normal appearance on hematoxylin–eosin staining, although necrotic fibers with fatty replacement may be present. (PAS) stain and electron microscopy reveals glycogen blebs and vacuoles.

Diagnosis is confirmed by phosphorylase histochemistry, which is negative in affected individuals. Phosphorylase deficiency responds to therapeutic intervention with glucagon, epinephrine, glucose and insulin.

Regular aerobic moderate intensive exercise may be helpful. Diets high in complex carbohydrates and low in fat (maintaining adequate liver glycogen derivation of glucose) may be helpful, as may low dose (60 g/kg/d) creatine. Higher doses actually exacerbate symptoms.

3.2. Acid Maltase Deficiency

The deficiency of acid maltase, referred to as Type II glycogen storage or Pompe's disease, is an autosomal recessive deficiency of alpha-1-4-glucosidase [15,16]. There are five to ten thousand cases, representing one in forty to fifty thousand life births. Not limited in its distribution to muscles, prognosis is dependent on the extent to which it occurs in the central nervous system, cardiac involvement and the extent of organomegaly. One clue to diagnosis is that the degree of ventilatory insufficiency is often out of proportion to limb weakness. Infantile acid maltase deficiency presents with feeding difficulties, dyspnea, intermittent cyanosis, hypotonia, areflexia, macroglossia, firm rubbery muscles and organomegaly, including cardiomegaly. A lacelike network of glycogen vacuoles is noted (Figure 1). Enzyme replacement is not effective in its treatment.

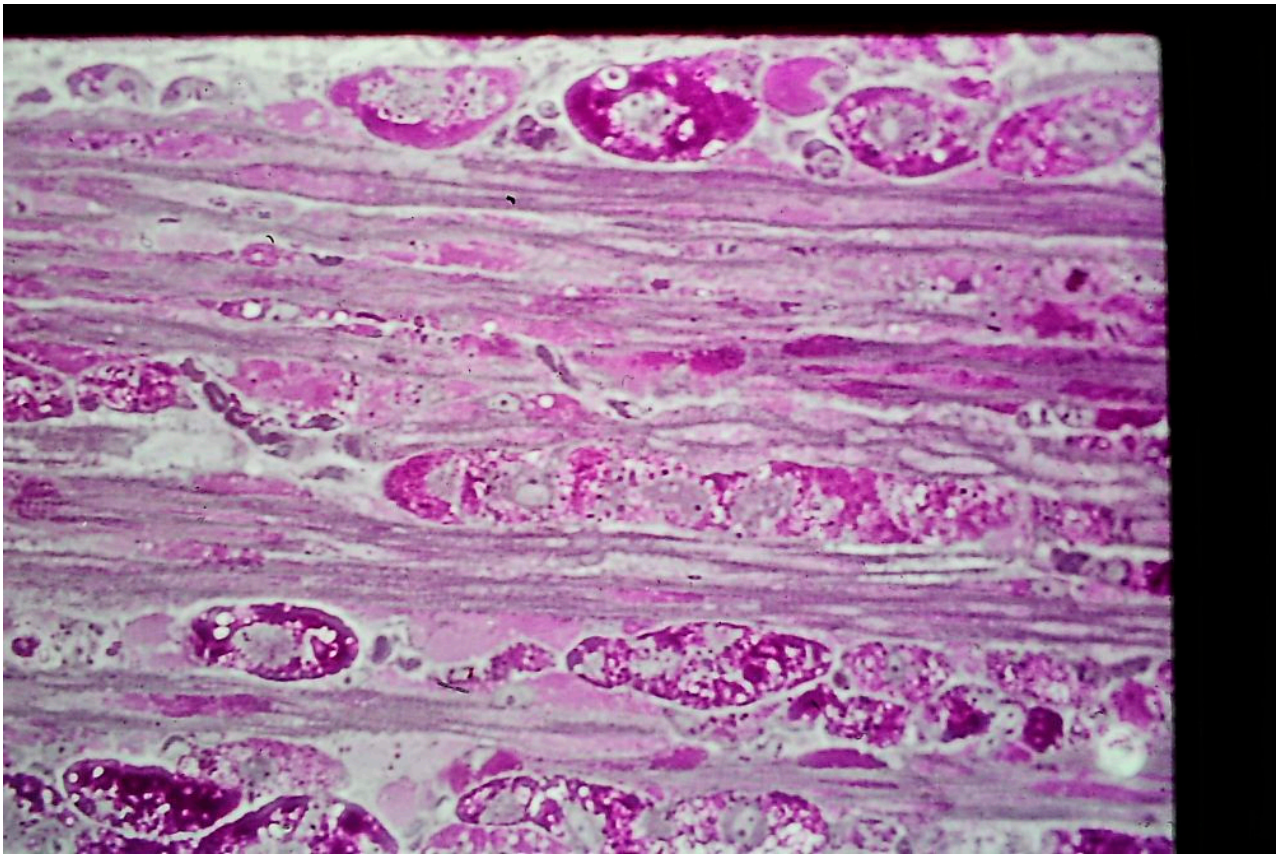


Figure 1. Histologic section of muscle affected by acid maltase deficiency. Periodic acid–Schiff (PAS) stain revealing glycogen granules.

"So-called" benign acid maltase deficiency is also characterized by firm, rubbery muscles and proximal muscle weakness (although muscles remain firm to palpation and depressed deep tendon reflexes). Intercostal muscle weakness results in early respiratory failure. CPK is elevated, but the ischemic exercise test is normal. Electromyography (EMG) reveals insertional activity and positive sharp and bizarre high frequency waves, in addition to the short polyphasic potentials of myopathic disease. Clinically inapparent myotonia (despite myotonic EMG discharges) may be present. The fatty degeneration of paraspinal and hamstring muscles may be noted. Histologic examination reveals a variation in fiber size with basophilia, regenerative hypertrophy, the centralization of sarcolemmal nuclei and zones of myofibrillar degeneration, with acid phosphatase staining. Fiber splitting is common but muscle fiber phagocytosis is rare. Two to sixty micron vacuoles and electron dense particles may be noted in mitochondria. PAS staining reveals glycogen content confirmable by diastase digestion. The measurement of acid maltase activity in muscle tissue or dried blood spots confirms diagnosis.

Physical training decreases glycogen deposition and increases fat consumption, thus emphasizing the importance of participation in a daily aerobic exercise program. Diets consisting of 25–30% protein, 30–35% carbohydrates and 35–40% fat may be effective, but do contribute to weight gain. Enzyme (Mozyme) replacement therapy with transgenic rabbit-derived recombinant acid α- glucosidase has been effective in the past, as least in the short term (see treatment below).

3.3. Debrancher Enzyme Deficiency

Debrancher enzyme deficiency, also known as Type II glycogenosis or Cori–Forbes disease, is autosomal recessive in one in a hundred thousand individuals. It is localized

on chromosome 1p21 [6,17–19]. Muscle weakness is associated with cardiomyopathy, peripheral neuropathy, hepatomegaly, hypoglycemia and failure to thrive.

3.4. Phosphofructokinase Deficiency

Phosphofructokinase deficiency, also known as Tarui disease or glycogenosis VII, is a familial disorder of childhood (1 in 20–43,000 live births), presenting either as autosomal recessive or x-linked recessive on chromosomal band 1cenq32 [20,21]. It is characterized by exercise intolerance with nausea, pain, stiffness, contractures and rare cramps. Second wind phenomenon is present. CPK levels are elevated at the wrist. Reticulocytosis is invariably present and one-fifth of patients have increased bilirubin levels related to hemolytic anemia. The hemolysis precipitating these alterations often manifests with hemoglobinuria. The ischemic exercise test is abnormal. Electromyogram reveals myopathic potentials with repetitive spikes, but amplitude is unaffected by supramaximal stimulation. Biopsy reveals glycogen accumulation in scattered vacuoles or subsarcolemmal blebs.

3.5. Phosphoglucomutase

Phosphoglucomutase deficiency, also known as Type 14 glycogenosis, interferes with the transfer of the phosphate in α-D-glucose-1-phosphate to the six position [22–24]. The prevalence is less than one in a million. Muscle hypotonia, contractures and cramps are noted. Second wind phenomenon is present. Ischemic exercise test does not affect lactate, but ammonia levels elevate. It is associated with cleft palate, hepatomegaly and short stature. CPK is elevated and myoglobinuria is present. N-glycans are lost. Galactose supplementation improves symptoms.

3.6. Phosphoglycerate Mutase

Phosphoglycerate mutase, also known as Type X glycogenosis, catalyzes the internal transfer of a phosphate group from C-3 to C-2 [25,26]. This rare disorder (less than 50 reported) is autosomal recessive on chromosome 7p12-p13. Deficiency produces cramps and intensive exercise-related weakness which is relieved by rest. Recurrent myoglobinuria results. CPK serum level is elevated; electromyography, normal. The ischemic exercise test is abnormal. Biopsy reveals increased PAS staining, while electron microscopy shows increased glycogen particles between myofibrils and under sarcolemma. Gouty tophi may develop.

3.7. Lactate Dehydrogenase

Lactate dehydrogenase deficiency, with a prevalence of one in a million and also known as glycogenosis XI, is autosomal on chromosome band 11p15.4 and is associated with fatigue and exercise intolerance [27]. Myoglobinuria is present, but muscle strength and ischemic exercise tests are normal. CPK is elevated and hemolytic anemia may be present.

3.8. Phosphoglycerate Kinase

Phosphoglycerate kinase deficiency, also known as glycogenosis IX, is X-linked recessive on chromosome band Xq13 [28] and affects less than 1 in 100,000. The ischemic exercise test and electromyography are normal.

3.9. Brancher Enzyme Deficiency

Brancher enzyme deficiency, also known as adult polyglucosan body disease, glycogenosis IV or Andersen disease is autosomal recessive on chromosome 3p12 [29–32]. The enzyme is responsible for transferring short α1,4-linked glucosyl fragments to glycogen. Manifestations include myopathy, hypotonia, spastic paraparesis cardiomyopathy, progressive

liver fibrosis, neurogenic bladder and peripheral neuropathy. Histology reveals abnormal mitochondria containing polyglucosan inclusions.

3.10. Aldolase Deficiency

Aldolase deficiency, known as glycogenosis Tupe XII, is autosomal recessive on chromosome 16q22-q24 [33], with a population prevalence of one in a hundred thousand. The result is fructose intolerance and liver accumulation with death of liver cells. Weakness, fatigue, exercise intolerance and reduced muscle mass and tone are noted. The breakdown of damaged muscle fibers produces rhabdomyolysis. Hypoglycemia, jaundice and hyperuricemia is a result of this.

4. Defects of Lipid Metabolism

Lipids provide the energy required for sustained (e.g., greater than 40 min) submaximal muscle activity. Short- and medium-chain fatty acids easily transit mitochondrial membranes; long-chain ones do not. Carnitine-binding is required for that process.

Adipose tissues release triglycerides which, along with plasma free fatty acids, cross muscle cell membranes. Once inside the cell, they are esterified by palmityl-CoA synthetase into palmityl CoA. Palmityl CoA is esterified with carnitine by carnitine palmityl transferase I to produce palmityl carnitine, which can cross the mitochondrial membrane. Once across, carnitine palmityl transferase II converts it back to carnitine and palmityl CoA (to which the mitochondrial membrane is impermeable). Symptoms result from sustained (e.g., greater than 40 min) submaximal exercise [34–36].

5. Type I Lipid Storage Disease—Carnitine Deficiency

Carnitine (γ-trimethylamine-β-hydroxybutyrate) deficiency is characterized by a muscle uptake abnormality, with a population prevalence of less than one in a million [37]. Decreased long-chain (greater than 12 carbon) fatty acid oxidation occurs because of an impairment of mitochondrial transport. This may occur as a predominantly muscle disorder or as a systemic disease. Carnitine levels are depressed to 4–30% of normal levels in skeletal muscle, leukocytes, cardiac muscle and Swann cells. Serum carnitine levels are normal except in the systemic form of this disorder, in which the patient develops hepatic encephalopathy. Carnitine deficiency may also occur as a secondary phenomena, reflecting the depression of serum levels during malnutrition, hemodialysis, organic aciduria, Fanconi syndrome, chronic liver disease, the low dietary intake of lysine and methionine and with zidovudine and valproate drug toxicity. Curiously, the cardiac lesion of diphtheria is characterized by a depression of carnitine levels.

Carnitine deficiency is predominantly a disorder that has a childhood onset, with a 10% occurrence if there is a family history of the disease. Type I, involving the heart, liver and kidneys, has been considered fatal. Type II, which predominantly affects the muscle has a benign course. Pregnancy has exacerbating effects on the symptomatology and course.

The patient presents with a slowly progressive proximal muscle weakness. The involvement of the face and pharynx is a clue to diagnosis. Cramps are extremely common, precipitated by exercise and fasting, with high-fat, low-carbohydrate diets. Respiratory muscle involvement may be prominent. Intermittent ataxia may be noted. Almost 90% of patients have elevated CPK levels. The serum lactate/pyruvate rations and triglycerides are elevated and transient ketosis may ensue. The examination of peripheral blood leukocytes reveals lipid droplets in 50% of patients. Electromyography reveals fibrillation and short polyphasic potentials. Histologic examination reveals vacuolar myopathy, predominantly affecting Type I cells (Figure 2). The vacuoles stain with Sudan black, indicating the

presence of lipid droplets. They appear as empty non-membrane lined spaces in electron microscopy. Type II fibers often manifest atrophy. Mitochondrial dense deposits are noted, as are crystalloid inclusion bodies.

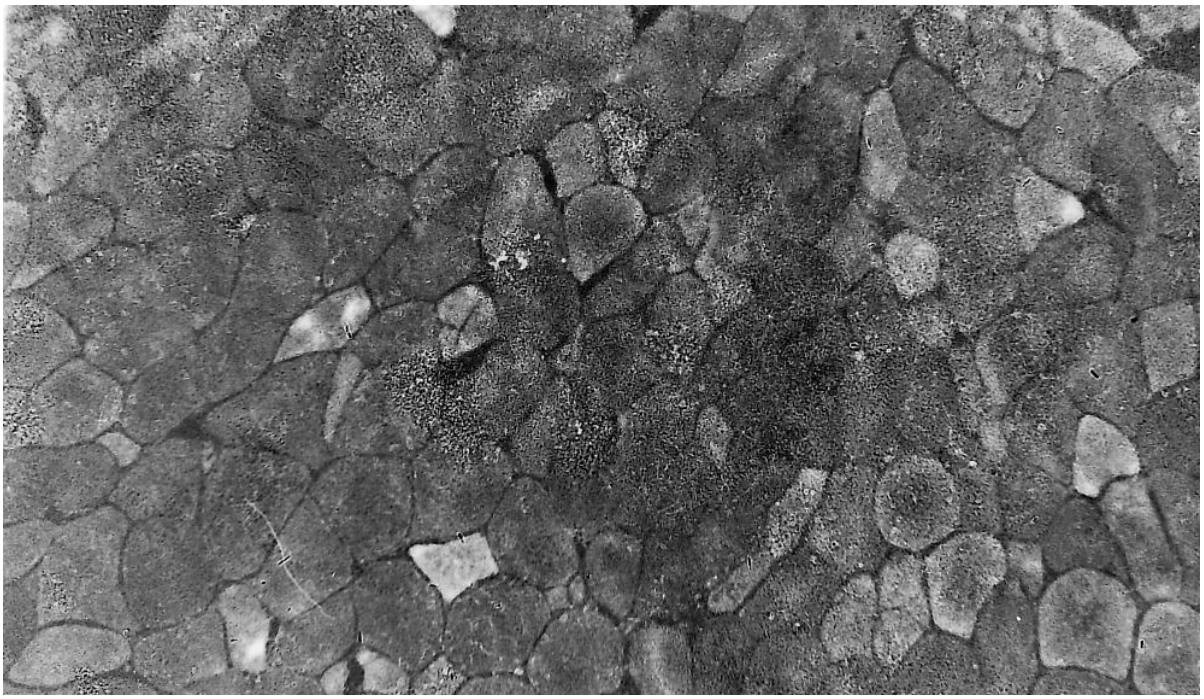


Figure 2. Histologic section of muscle affected by carnitine deficiency. ATPase fiber typing stain reveals Type II fiber atrophy and vacuoles.

Carnitine deficiency is often steroid-responsive. Two to six gram doses of d,l-carnitine daily is effective but can be accompanied by loose stools.

6. Congenital Ichthyosis—Associated Myopathy

Congenital ichthyosis (prevalence = 1 in 200,000; its association with myopathy is unclear) presents with steatorrhea, proximal muscle weakness and elevated CPK [38,39]. The electromyogram is myopathic. Biopsy reveals Type I predominance and Type II atrophy. Lipid accumulation is especially noted in Type I fibers. The defect appears to be one of triglyceride utilization.

7. Carnitine Palmityl Transferase Deficiency

Carnitine palmityl transferase deficiency, classically diagnosed prior to age 30, though rare (300 cases reported), is the most common cause of hereditary recurrent myoglobinuria [40,41]. It is essential in long-chain fatty acid transport to the mitochondria. While brief strenuous exercise is tolerated, prolonged is not. Prolonged exercise, especially when fasting, is especially dangerous. There is no second wind phenomena. Exertion precipitates weakness, swelling, tenderness and tightness of proximal or exerted muscle groups, but usually not cramps. Although cramps are rare, CPK is often elevated and myoglobinuria is uniformly present during symptomatic episodes, but actually absent in 21%. The acute involvement of respiratory muscles is not uncommon. In approximately 50% of patients, attacks may be precipitated by anxiety, infection or fasting prior to exercise.

The neonatal form is associated with microgyria, neuronal heterotopia (neuron collection outside of gray matter), facial dysmorphism and renal cysts, hypoketotic hypoglycemia, hepatomegaly and failure, cardiomegaly, arrythmias, lethargy, seizures and coma.

The ischemic exercise test is normal and does not induce contractures. CPK is abnormal at rest in 20% of patients. In contrast to carnitine deficiency, leukocytes in this disorder appear normal morphologically, although enzyme levels are at 5–30% of normal levels. Triglyceride levels may be elevated. Electromyography is abnormal in 18% of patients between episodes. Muscle biopsy is often normal, although Type I fibers may contain excess small sudanophilic vacuoles if the patient has suffered numerous attacks (Figure 3).

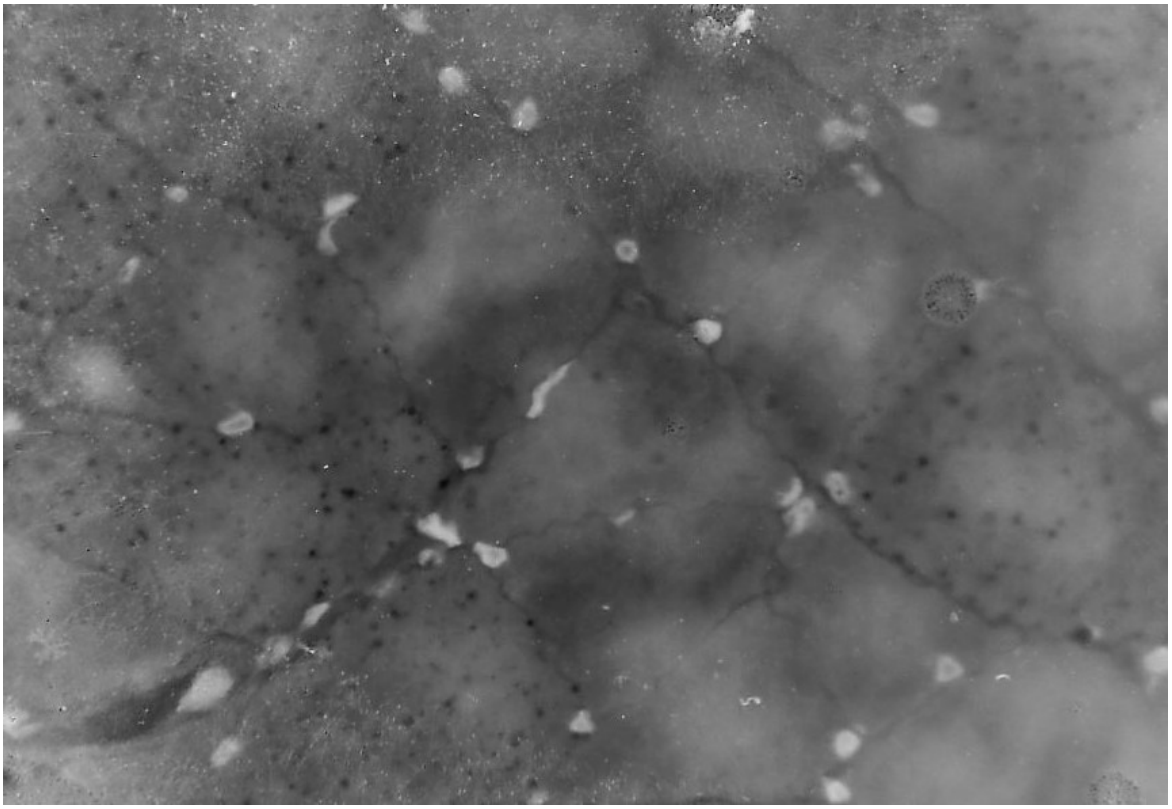


Figure 3. Histologic section of muscle affected by carnitine palmityl transferase deficiency. Note the vacuoles.

Treatment is frequent small meals consisting of a high-carbohydrate, low-fat diet and, of course, the avoidance of prolonged exercises.

8. Disorders of Purine Nuclide Metabolism

Myoadenylate Deaminase Deficiency

Myoadenylate deaminase is important in the muscle cell transformation of adenosine monophosphate (AMP) to adenosine triphosphate (ATP) [42,43]. While a population prevalence of two percent is recognized as homozygous for mutants, many lack clinical symptoms. The disorder is autosomal recessive, with a deficiency in the lysosomal enzyme α- glucosidase responsible for cleaving 1,4- and 1,6-α-glycosidic linkages. Deficiency is associated with weakness, cramping, hypotonia, fasciculations, and stiff, sore muscles that rapidly fatigue. Muscle mass is reduced. CPK may be elevated or normal. The ischemic exercise test is normal, with ammonia elevations proportional to lactate. Electromyography reveals polyphasic potentials with trains of positive waves, but they may be normal. Histology reveals mild Type I atrophy.

9. Endocrine/Metabolic-Related Myopathy

9.1. Thyroid Function-Related Myopathy

Alterations in thyroid function are not uncommonly associated with the perturbation of muscle function [44,45]. Hyperthyroidism may present with muscle involvement. Subclinical myopathy is invariably present. Other forms of muscle disorders noted in patients with hypothyroidism include myasthenia gravis, polymyositis, periodic paralysis and a peculiar proximal muscle myopathy. The latter is often one of the early signs of thyroid disease. Muscle weakness and the fatigability of a localized or generalized nature may progress to actual atrophy. Respiratory muscles may be involved and coarse fascicular twitching may be noted. Although CPK levels remain normal, urinary creatine excretion is increased. Electromyography reveals short polyphasic potentials. Neither sharp waves nor fibrillation potentials are present. Muscle biopsy is often non-specific or normal. Mild fiber atrophy (Type I greater than Type II) may be noted along with variation in fiber size. Mitochondria are swollen and elongated, containing dense granules. Glycogen granules are frequently present.

Myasthenic presentation of hyperthyroidism is an intriguing phenomenon. Five percent of patients with myasthenia gravis develop hyperthyroidism; conversely, one percent of patients with hyperthyroidism develop myasthenia gravis. Although one-fifth have a simultaneous onset of the two phenomena, hyperthyroidism is the first event in almost half of cases.

9.2. Hyperthyroid Periodic Paralysis

Thyrotoxic periodic paralysis, present in 2% of Asians and occurring in 0.2% of others with hyperthyroidism, is characterized by periodic episodes of muscle weakness or paralysis, associated with low potassium and phosphate levels [45]. For one to two days prior to and on the day of an attack, a decrement in the urinary excretion of water, potassium, sodium and chloride is associated with increased serum aldosterone levels. The disorder primarily affects muscles with high concentrations of mitochondria. The attacks are associated with a decrease in calcium transport and sarcolemmal uptake, secondary to the decreased activity of the magnesium–potassium ATPase and decreased muscle levels of creatine and phosphocreatine. Attacks are precipitated by carbohydrate loading, which results in an abnormal increase in insulin and lowers the muscle membrane potential. Sodium loads, cold, insulin and rest after exercise precipitate attacks, while propranolol or a reduction in thyroid stimulation have an attenuating effect. It is thought that the mechanism is thyrotoxic depletion or the improper utilization of high energy stores and uncoupling of oxidative phosphorylation. Hyperthyroid periodic paralysis is discussed further in the text in more detail in the general review of periodic paralysis.

9.3. Hypothyroid Myopathy

Hypothyroid myopathy, present in 30–80% of individuals with hypothyroidism, was at one time referred to as Kocher–Debré–Sèmélaigne syndrome [44,46]. It is characterized by proximal muscle weakness of a localized or generalized nature. Muscle hypertrophy or atrophy may ensue, as may myotonia. Typically, the patient complains of muscle pain and cramps, which are precipitated by rest, exertion or cold weather. The presence of delayed Achilles tendon relaxation during reflex evaluation is suggestive of hypothyroidism. It is, however, not pathognomonic, as delayed relaxation is also noted in hypothermia, pedal edema, diabetes and anorexia nervosa, Parkinsonism, neurosyphilis, sarcoidosis, sprue and pernicious anemia, and is secondary to drugs including procainamide, propranolol, quinidine and reserpine (Table 2).

Table 2. Causes of delayed Achilles tendon relaxation.

Endocrine	hypothyroidism, diabetes mellitus
Metabolic	
Environmental	hypothermia
Physiologic	pedal edema
Psychologic	anorexia nervosa,
Neurologic	Parkinsonism, pernicious anemia (vitamin B12 deficiency)
Infectious	neurosyphilis,
Gastrointestinal	sprue
Medication	procainamide, propranolol, quinidine and reserpine

Another more characteristic phenomena is myoedema, an electrically silent, painless mounding which occurs secondary to percussion. It is short-lived, generally less than one minute's duration. The elevation of CPK is difficult to assess, as this is a common phenomenon in hypothyroidism, occurring secondary to the diminution of renal clearance, decrease in circulating blood volume and decreased CPK catabolism. Urinary creatine levels are, however, normal. Electromyography reveals random muscle firing, fasciculations, fibrillations, positive sharp waves and short polyphasic potentials. Although the mounding phenomena is electrically silent, tapping induces a repetitive potential in one-third of patients. This is not the "dive bomber" type, but more reflects the pattern seen in myotonia congenita or myotonic muscular dystrophy. Minimal alterations are noted on histologic examination. Focal necrosis and Type I atrophy may be present, along with a variation in fiber size and a centralization of sarcolemmal nuclei. Focal subsarcolemmal glycogen accumulation may be noted. Toluidine blue staining may reveal a metachromatic infiltrate.

10. Periodic Paralysis

The term periodic paralysis encompasses four varieties: hypokalemic (prevalence of one in a hundred thousand), hyperkalemic (prevalence one in two hundred thousand), normokalemic (prevalence is less than one in a million) and thyrotoxic periodic paralysis (present in 2% of Asians; 0.2% in others with hyperthyroidism) (Table 3) [45,47–49].

Table 3. Distinguishing among the forms of periodic paralysis.

Characteristic	Hypokalemic	Hyperkalemic	Normokalemic
Potassium level	Decreased	Increased	Normal
Age of onset	2nd decade	1st decade	1st decade
Episode frequency	5–15/yr	1/week	4–12/year
Onset timing	Early AM in sleep	Variable	Early AM In sleep
Episode duration	6–48 h	1 h	2 h–3 weeks
Flaccid paralysis	Severe	Moderate	Severe
Respiration impeded	Often	Rarely	Occasionally
Chvostek sign	Negative	Positive	Negative

Hyper- and normokalemic periodic paralysis are triggered by potassium. Hyperkalemic periodic paralysis is triggered by hunger, whereas the normokalemic form is triggered by alcohol or nervous tension. Hypokalemic is triggered by acetazolamide, carbohydrate ingestion, insulin, epinephrine and thyroid deficiency. All are provoked by rest

after exercise and by cold temperatures. If an attack is precipitated, it will be attenuated in hypo- and hyperkalemic periodic paralysis by reinstituting continuous, mild exercise. Carbohydrate ingestion will further attenuate hyperkalemic, but exacerbate hypokalemic periodic paralysis. The ingestion of sodium chloride will attenuate attacks of normokalemic periodic paralysis.

All three are autosomal dominant, but the hypokalemic form manifests incomplete penetrance in females. Potassium levels during the attacks are in keeping with the nomenclature. Hyper- and normokalemic periodic paralysis have the onset in the first decade of life, whereas hypokalemic begins in the second. The hypokalemic variety is associated with a mortality rate of 10%.

Attacks of hypokalemic periodic paralysis occur predominantly in the early morning hours while the patient is sleeping. They last from 6 to 48 h and occur five to fifteen times a year. Attacks of hyperkalemic periodic paralysis can occur at any time, although they are more frequent during the day. They last approximately one hour and recur at weekly intervals. Normokalemic periodic paralysis episodes are similar in timing to those of hypokalemic periodic paralysis. They last from two hours to three weeks and occur four to twelve times per year. They all present with flaccid paralysis, which is severe in hypo- and normokalemic and moderate in hyperkalemic patients. Respiratory muscles are often affected in hypokalemic periodic paralysis, but only occasionally in normokalemic and rarely in hyperkalemic. Paresthesia may be noted in hyperkalemic and normokalemic periodic paralysis, but is only transiently present at the onset of attacks of the former. Curiously, hyperkalemic periodic paralysis is often associated with a positive Chvostek sign. Pathologic examination reveals vacuolization in all types. The hypokalemic variety, which may progress to a fixed myopathy, is associated with variation fiber size and centralization of sarcolemmal nuclei. Perinuclear PAS positive vacuoles are noted, as is subsarcolemmal glycogen accumulation. Occasional fiber degeneration may be noted.

The importance of distinguishing the various types is highlighted by the disparity of the indicated therapeutic approaches. Hypokalemic periodic paralysis is treated by potassium salts (up to 10 g) and prophylaxis requires five grams of potassium daily. Spironolactone and low-sodium diets have also been prescribed. Hyperkalemic periodic paralysis is treated by calcium gluconate or a combination of glucose and insulin. Prophylaxis requires acetazolamide or chlorothiazide. The treatment of normokalemic periodic paralysis is with sodium chloride; for prophylaxis, treatment is with alpha-fluorohydrocortisone or acetazolamide.

Theare are many similarities between hypokalemic and thyrotoxic periodic paralysis. Both are associated with potassium depletion, provoked by carbohydrate load, rest after exercise, cold, acetazolamide and insulin and attenuated by light continued exercise.

Thyrotoxic periodic paralysis occurs later in life (usually in the fifth decade, versus the second), is provoked by calcium load, not by epinephrine and is attenuated by propranolol or withdrawal or excess thyroid stimulation. The latter clearly distinguishes this entity from hypokalemic periodic paralysis, which is provoked by the withdrawal of thyroid stimulation. The insulin response in hypokalemic periodic paralysis is secondary to driving glucose intracellularly, while that of thyrotoxic periodic paralysis is secondary to driving potassium intracellularly.

11. Corticosteroid Excess

Corticosteroid excess, whether exogenous or endogenous (e.g., Cushing's syndrome), is not uncommonly associated with the occurrence of a myopathy [50,51]. The prevalence of pituitary-derived corticosteroid excess is between one and three cases per million each year; for iatrogenic, the occurrence is between forty and seventy. It typically has its onset 3 to

20 months after the onset of the hypercorticoid state. The iatrogenic variety is more common with fluorinated steroids or those that have a long half life. The myopathy may be directly related to steroid therapy or indirectly related to steroid-induced kaluresis, resulting in hypokalemic myopathy. The former variety presents as proximal myopathy. The CPK levels are minimally elevated, but urinary creatine is increased. Electromyography reveals short polyphasic, but no fibrillation, potentials. Biopsy reveals Type IIβ fiber atrophy. The variation in mitochondrial size and glycogen/lipid accumulation may be noted. Although the disorder will usually respond to the withdrawal of excess steroid stimulation, the response may take months or even a year. Dilantin may be helpful.

12. Parathormone

12.1. Hyperparathyroidism

Approximately 24% of hyperparathyroidism patients (one to seven cases per thousand) have proximal myopathy, characterized by fatigability, weakness and/or atrophy, often associated with effort-induced pain and cramps [44,52]. There is a characteristic decrease in strength with each muscle contracture. The tongue may even be involved, resulting in fasciculations and slurred speech. Clues to the diagnosis may be found in their stiff, slow, cautious, wide-based gait, decreased arm swing and decreased muscle tone. Although considered a proximal myopathy, the patients also have difficulty walking on their toes or heels. CPK levels are normal and urinary creatine is increased. Electromyography reveals both the short polyphasic potentials of myopathic disease and long, high amplitude potentials of neuropathic disease. The fibrillation potentials are absent. Maximal effort results in a decreased number of motor unit potentials. Histologic examination is usually normal or demonstrates non-specific myopathic alterations, including a scattered atrophy of both Type I and Type II fibers. The deposition of calcium in mitochondria may be noted, secondary to associated vitamin D deficiency.

12.2. Hypoparathroidism

While the overproduction of parathormone can result in myopathy, so too can underproduction (prevalence is thirty-seven per hundred thousand). Hypoparathyroid myopathy presents with stiffness and cramping, predominantly affecting the distal musculature, but also affecting the facial and neck flexor muscles [44,53]. Hyperventilation appears to precipitate attacks. CPK is elevated during attacks, perhaps secondary to tetany. Electromyography may be normal or reveal a tendency toward polyphasic potentials. Occasional fibrillation potentials may be noted. Biopsy reveals fiber necrosis with a centralization of sarcolemmal nuclei. Ring fibers may be noted, secondary to para-mitochondrial inclusions.

13. Vitamin D Deficiency and Hypophosphatemia

Vitamin D deficiency-induced osteomalacia, with a population prevalence as high as 20%, may be associated with muscle disease, either as a manifestation of nutrient deficiency, such as calcium, magnesium or phosphate, or as a secondary phenomenon, because of pain-induced disuse atrophy or associated hyperparathyroidism [54,55]. Magnesium deficiency interferes with the action of parathormone, producing a functional hormone deficiency.

Hypophosphatemia, present in five percent of the US population, may produce significant muscle pathology [56,57]. Acute myopathy is associated with marked hypophosphatemia, general weakness, muscle pain and rhabdomyolysis. The latter manifests as myoglobinuria, associated with elevation of CPK and aldolase levels. The myopathy of chronic hypophosphatemia occurs with moderate hypophosphatemia, proximal muscle weakness and difficulty walking. Rhabdomyolysis is noted by its absence, and CPK and

aldolase levels are normal. In keeping with the usual association of osteomalacia, serum alkaline phosphatase levels are elevated.

14. Carcinoid Syndrome

Carcinoid syndrome, present in one to two cases per hundred thousand, has been associated with proximal muscle weakness, wasting and cramps [58,59]. Electromyograms are typically myopathic. Biopsy reveals Type I predominance and Type II atrophy, with variation in fiber size and the centralization of sarcolemmal nuclei.

15. Acromegaly

Forty-one percent of patients with acromegaly (population prevalence 30–100 per 100,000) develop proximal muscle weakness, eight to twenty-one weeks after disease onset [60–62]. CPK is elevated and the electromyogram reveals myopathic potentials. Biopsy reveals a patchy myopathy, with the hypertrophy of both Type I and Type II fibers and glycogen accumulation.

16. Amyloidosis

Amyloidosis (prevalence one in a hundred thousand) is classically associated with a pseudohypertrophy of skeletal muscle, resulting in the so-called "shoulder pad" sign [63,64]. The interstitial deposition of amyloid surrounding muscle fibers also causes tongue enlargement. Progressive weakness and fatigue are often associated with distal muscle weakness. The clinical evaluation of muscle function reveals a slowed rate of contraction and relaxation.

17. Hypermetabolic States

Hypermetabolic states may be associated with myopathic disease [65].

Luft's Syndrome

One form of non-thyroidal hypermetabolism is referred to as Luft's syndrome, with less than ten cases reported. It presents as fever, heat intolerance, profuse sweating, tachypnea and dyspnea at rest, polydipsia, polyphagia and weakness. It generally manifests in childhood with an elevation of the metabolic rate to 150–270% of the normal level. Erythrocyte mass and blood volume are increased. Deep tendon reflexes are decreased. Histologic examination reveals an increase in oxidative enzymes, abundant capillaries and mitochondrial alterations. The latter includes aggregation, an alteration in shape to a pleo- or megaconial configuration, poor calcium retention and osmiophilic inclusions.

18. Mitochondrial Myopathy

Exercise intolerance with easy fatiguability (disproportionate to muscle weakness) suggests mitochondrial myopathy [66–74]. Rather than a second wind phenomena, afflicted individuals can resume activity after a short rest. Muscle heaviness or burning occurs, but no stiffness or cramps. Lactate is elevated at rest, increasing with activity. CPK may be normal. Biopsy reveals ragged red fibers by the modified Gomori trichome stain and cytochrome c oxidase (COX)-deficient fibers [75,76]. However, ragged fiber increases are age dependent, normally present after age 30. Similarly, COX-negative fibers occur in less than two percent of patients prior to age 50 and less than five percent following this age [77]. Decreased high energy phosphate (e.g., ATP, phosphocreatine) may be noted on ^{31}phosphate nuclear magnetic resonance spectroscopy. Mitochondrial encephalomyopathy lactic acidosis produces stroke-like episodes, with myoclonus, epilepsy and ataxia. Other symptoms include cognitive impairment, dementia, transient ischemic attacks, epilepsy, hearing loss, ophthalmoplegia, cardiac conduction defects, gastrointestinal dysmotility

with associated diarrhea, cramps and bloating. A partial list of mitochondrial myopathies conveys the complexity of the issue beyond the purpose/scope of this review.

Multiple "varieties" of mitochondrial myopathy have been identified [75] with prevalence ranging from 1 per 21 to 100 thousand [78,79]. Curiously, the rate was 0.5% in a small study of neonatal cord blood samples for ten of the most common mitochondrial DNA mutations [80], though this was not necessarily clinically relevant.

However, there appears to be no specific clinically available treatment at this time for most [74]. Management is predominantly symptomatic, involving physical and occupational therapy, respiratory support, seizure prevention, cardiac stabilizing and the use of assistive devices.

19. Megaconial Mitochondrial Myopathy

Megaconial mitochondrial myopathy, with a prevalence of less than one in a million, is characterized by giant mitochondria, excess lysosomal concentration and proximal muscle weakness. This pathologic picture may also be noted in patients with progressive or Kearns–Sayre ophthalmoplegia. Pigmentary retinopathy is associated with ataxia and cardiac conduction block. Pleoconial mitochondrial myopathy is characterized by increased number of mitochondria, hypotonia and salt craving. Mitochondrial inclusions are also noted. This pathologic picture may also be seen in hypokalemic myopathy, muscular dystrophy, myotonic dystrophy and familial ophthalmoplegia.

20. Multiple acyl-CoA Dehydrogenation and CoQ_{10} Deficiency

Multiple acyl-CoA dehydrogenation deficiency, known as glutaric aciduria Type II, is an autosomal recessive mutation involving the electron transfer flavoprotein or its dehydrogenase, with a population prevalence of 1 in 250,000 [81–84]. The result is abnormal amino acid, fatty acid and choline metabolism. Progressive muscle weakness is associated with easy fatiguability and weakness. CPK and lactate are elevated. Lipid droplets accumulate, predominant in Type I fibers. It may respond to riboflavin or CoQ_{10} supplementation. Responsible mutations affect para-hydroxybenzoate polyprenyltransferase, decaprenyl-diphosphate synthase subunits 1 and 2, aarF domain containing kinase 3, ubiquinone biosynthesis protein COQ9, ubiquinone biosynthesis protein COQ4 homolog, mitochondrial 5-demethoxyubiquinone hydroxylase and coenzyme Q5, methyltransferase.

21. Barth Syndrome

Barth syndrome, with a prevalence of three per million, is a male disorder involving lipid deposition in myelin sheaths and methylglutaconic aciduria [84]. The result is fatigue, muscle weakness and hypotonia. Responsible mutations affect production of taffizin, the protein responsible for the remodeling of immature cardiolipin to its mature state.

22. Chronic Progressive External Ophthalmoplegia (CPEO or PEO)

As the name states, general body weakness and exercise intolerance are associated with the progressive loss of eye mobility [84] in this disorder, afflicting 1 in 100,000 individuals. Reported mutations include the DNA polymerase subunit gamma, adenine nucleotide translocator 1, ribonuclease H1, twinkle mtDNA helicase, thymidine kinase 2, DNA polymerase subunit gamma-2, deoxyguanosine kinase, DNA topoisomerase 3-alpha and ribonucleotide-diphosphate reductase subunit M2 B.

23. Kearns–Sayre Syndrome (KSS)

Kearns–Sayre, affecting one to three people per hundred thousand, is characterized by its first or second decade onset of cognitive impairment, ataxia, ophthalmopareis, ptosis, "salt and pepper" retinal pigmentation, cardiac conduction block, hearing loss, elevated cerebral fluid protein levels and the development of diabetes [84]. Non-ocular muscle weakness is mild. It may result from deletion or duplication of a mitochondrial transfer DNA segment. Histology reveals ragged red fibers (Gomori trichome or Succinate dehydrogenase stain) and deficient cytochrome c oxidase. Mutations in the mitochondrially encoded transfer RNA leucine 1 (UUA/G) also known as MT-TL1 is responsible.

24. Pearson Syndrome

Pearson syndrome, with prevalence of one per million, starts with sideroblastic anemia and pancreatic disease [85] and subsequently progresses to Kearns–Sayre syndrome.

25. Leigh Syndrome or MILS

Leigh syndrome, with prevalence of 1 in 40,000, usually starts within the first two years of life and rapidly progresses. Symptoms include irritability, appetite loss, vomiting, continuous crying, seizures, loss of neck muscle control going on to lack of muscle tone and generalized weakness; lactic acidosis compromises respiratory and renal function.

26. Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP)

NARP, with a prevalence of one to nine per hundred thousand, results in a loss of vision, dementia, seizures and developmental delay. The mtDNA mutation is linked to MILS.

27. Mitochondrial DNA Depletion Syndromes (MDDS)

Starting in infancy, respiratory muscle weakness is prominent in mitochondrial DNA depletion syndromes (which have a prevalence of less than one per million), associated with brain abnormalities and development of progressive liver disease. Alpers progressive infantile poliodystrophy is a variant in which spasticity, dementia, seizures and vision loss are prominent. Responsible mutations affect mitochondrial genome maintenance exonuclease 1, mitochondrial dicarboxylate carrier, thymidine kinase 2, DNA polymerase subunit gamma, mitochondrial 2-oxodicarboxylate carrier, succinyl-CoA ligase subunits alpha and beta, twinkle mtDNA helicase, mitochondrial transcription factor A, mitochondrial acylglycerol kinase, 21S rRNA (uridine2791-2′-O)-methyltransferase, adenine nucleotide translocator 1, dynamin-like 120 kDa protein and

28. Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes (MELAS)

The MELAS syndrome, with a prevalence of one to sixteen per hundred thousand, consists of mitochondrial encephalomyopathy, lactic acid and stroke-like episodes (more like transitory ischemic events with temporary compromised speech, hearing and vision) and occurs in the first four decades of life as dementia and seizures, in addition to those symptoms mentioned in its title, and may be associated with diabetes, deafness and headaches [84,86]. Curiously, brain lesions do not match watershed regions, apparently because the pathology is at the level of endothelial and smooth muscle cells of arterioles and capillaries [87]. Pathogenic blood presentation confirms diagnosis, often related to a 3243A>G $tRNA^{Leu(UUR)}$ mutation. Reported mutations include various amino acid transfer RNAs and NADH-ubiquinone oxidoreductase.

29. Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE)

MNGIE, with a prevalence of one to nine per million, combines prominent gastrointestinal symptoms (e.g., diarrhea, vomiting) with progressive external ophthalmoplegia and peripheral sensory and motor neuropathy [84]. Responsible mutations affect thymidine phosphorylase, ribonucleotide-diphosphate reductase subunit M2 B, DNA polymerase subunit gamma and DNA ligase III.

30. Myoclonus Epilepsy with Ragged Red Fibers (MERRF)

MERRF, with a prevalence of less than one per hundred thousand, consists of myoclonus epilepsy with ragged red fibers and presents in the second decade of life with myoclonus, muscle weakness ataxia and seizures. Similar to most mitochondrial disorders, short stature and hearing loss may occur. Eighty percent have a m.8344A?G $tRNA^{Lys}$ mutation; reported mutations include various amino acid transfer RNAs.

31. Thymidine Kinase Elated Mitochondrial DNA Depletion Syndrome

Thymidine kinase 2 (TK2) recycles nucleotides, permitting the repair of errors in mitochondrial DNA (mtDNA) sequencing and allowing the generation of new mtDNA [84]. Defects in less than one per hundred thousand result in nucleotide shortages and thus compromises mitochondrial function. It presents as muscle weakness, increased serum CPK and lactate, and is associated with ragged red muscle fibers, necrosis with regeneration and fat replacement [88,89].

32. Adenylosuccinate Synthetase 1 Myopathy

Adenylosuccinate synthetase is responsible for purine metabolism, catalyzing the conversion of inosine monophosphate to guanosine diphosphate. The downregulation of all three purine nucleotide genes is a result of this [90]. Defects affecting less than one in a million result in skeletal (with prominent facial muscle involvement) and cardiac muscle pathology (ventricular hypertrophy) and reduced vital capacity [91]. Fatigability, dysphagia and ptosis are noted. The fatty infiltration of lower extremity muscles is prominent. CPK, uric acid and calcium are elevated and histologic findings include rimmed vacuoles [92], intracellular lipid vacuoles, glycogen aggregates, nemaline bodies necrosis and myocyte phagocytosis [91].

33. Multisystem Diseases Associated with Myopathy

Neutral lipid storage disease (Chanarin–Dorfman syndrome) is the result of Abhydrolase Domain Containing 5 and Lysophosphatidic Acid Acyltransferase (ABHD5) deficiency, with less than 150 reported cases. Thus, the first stage in fatty acid activation, adipose triglyceride lipase, is compromised, with resultant triglyceride accumulation in some individuals with icthyosis [93]. It produces organomegaly, hepatic failure, cirrhosis, cataracts, ectropion and sensorineural deafness. Muscle involvement occurs late in the disease.

This contrasts with abnormalities of the patatin-like phospholipase domain containing 2 (PNPLA2) gene which is not associated with ichthyosis [94]. It is associated with cardiomyopathy and exercise, fasting and the infection-induction of muscle weakness.

Lipin-1 (phosphatidic acid phosphatase) deficiency is a steroid-responsive but very rare cause of fever-induced rhabdomyolysis [95]. Second only in prevalence to lipid oxidation disorders, it can only be diagnosed with exome sequencing [96].

34. Workup

The workup for metabolic myopathies includes an evaluation of medical and family history and the examination of cognitive skills, muscle strength and endurance, reflexes and vision. Laboratory assessment includes CBC, reticulocyte count, liver and kidney function CPK, myoglobin, lactic acid and pyruvate in serum and urine. However, lactate elevations occur with other inborn errors of metabolism, thiamine deficiency, ischemia and exposure to toxins [97,98], and both lactate and pyruvate levels are elevated if a tourniquet is used during collection or if the sample is not transported on ice [99]. Similarly, there are a multitude of causes of myoglobin elevations, but persistence at rest requires workup for inflammatory and metabolic myopathies, although thrombotic, thyroid and infectious diseases must also be considered [100,101]. However, there are several caveats: Muscle regeneration (e.g., from injury) involves the release of a fetal isoenzyme which produces false positive phosphorylase assays [102].

Serum may also be assed for elevated alanine, acylcarnitine, serum and urine 3-methulgluticonic acid. Spinal fluid lactic acid may be assessed, as well as amino acids and 5-methyltetrahydrofolate. Additionally indicated are a forearm exercise test (now often replaced by a simple hand-grip test), a measuring response to lactate and ammonia [103] and electromyography and muscle biopsy with special stains (Gomori trichrome, nicotinamide adenine nucleotide dehydrogenase, cytochrome C oxidase, succinate dehydrogenase (for ragged blue fibers), periodic acid Schiff and oil red O) which are provided/assessed by a neuropathologist experienced with muscle pathology. The issue is slightly more complicated, since ragged red fibers may also occur with aging [74]. MR spectroscopy, brain scans, electroencephalograms (in presence of seizures) and electrocardiograms are often pursued. Genetic testing is an essential component.

Muscle phosphorylase deficiency (McArdle's disease) is associated with chromosome 11 myophosphorylase gene mutations and may be identified by Arg50 sequencing, although next generation sequencing may be required [104]. There are caveats: Myoadenylate deaminase deficiency is often compensated by other pathways, so its notation of variants does not necessarily represent a clinical disorder [105].

35. Potential Treatments

Prevention is key with newborn screening, similar to that in routinely performed diagnoses (e.g., for aminoacidopathies and thyroid disease). However, false positives are common, especially with carnitine [74]. Targeted diets (e.g., riboflavin and other vitamins (e.g., vitamin B6) with or without CoQ10 and ll-carnitine) and exercise training programs are under consideration, as well as the possibilities of enzyme and gene replacement [74,100,106–108]. The former (rhGGA, Myuozyme, Lumizyme) has been applied to Type II glycogen storage disease (alpha-1-4-glucosidase deficiency), also known as Pompe's disease [109–111], which is typically proved by adeno-associated mediated gene vectors. However, gene size is problematic [112]. A *Bacillus subtilis* gene with a similar function to that for human glycogen debranching enzyme shows promise in mice, but did not completely correct the muscle deficits [113]. Replacement nucleosides are administered for thiamine kinase (TK2) deficiency [88]. Biweekly enzyme replacement therapy tends to lose effectiveness over time [74], an anti-drug antibody effect [112], suggesting that the needed intervention is actually gene replacement.

Manifestations may be improved in McArdle's disease by pre-exercise sucrose loading [114] and corticosteroids may be beneficial (in reducing rhabdomyolysis) in lipin-1 deficiency [115]. Bezafibrate and triheptanoin been considered in the management of lipid-related myopathies [74,116]. Diet-resistant hyperuricemia is treated with allopurinol; angiotensin-receptor blockers, for albuminuria; and thiazide diuretics, for hypercal-

cemia [112]. Liver transplants have been considered [112]. Given the increased susceptibility of individuals with metabolic myopathies to symptom manifestations, the use of vitamin D and thyroid optimization is considered, as is the avoidance of the use of statins [106].

36. Future Expectations

Next generation sequencing is a major advance, but does not address the issue of repeated sequences and regions with variable GC content [117]; and, of course, the presence of an abnormal gene does not necessarily identify that it has pathologic effects. The exploration of genetic contributions in individuals with severely elevated CPK levels reveals abnormalities in less than 50% [118]. The introduction of RNA sequencing and whole genome sequencing is on the horizon [74,119].

37. Summary

This review concentrates on the muscle pathology of metabolic/endocrine derivation and the characteristics that facilitate the ability to distinguish among them (Tables 4 and 5).

Table 4. Comparative symptomatology of metabolic/endocrine myopathies, according to available information.

Dysfunction/Sign	Cramps	Tone	Second Wind	CPK	Respiratory	Ischemic Exercise Test	Myoglobinuria
Muscle phosphorylase	Present	Firm/Shortened	Present	Elevated	Striking	Abnormal	Episodic
Acid maltase	Present	Hypotonia/Rubbery	Present		Present	Normal	Present
Phosphofructokinase	Present	Contractures	Rare	Elevated		Abnormal	
Phosphoglucomutase	Present	Hypotonia	Present	Elevated		Normal **	Present
Phosphoglycerate mutase	Present			Elevated		Abnormal	Present
Lactate dehydrogenase	Present			Elevated		Normal	Present
Phosphoglycerate kinase	Present		Absent			Normal	Present
Aldolase	Present						Present
Carnitine deficiency	Present			Elevated	Prominent		
Carnitine palmityl transferase	Present		Absent	Occasional	Present	Normal	Present
Myoadenylate deaminase	Present	Hypotonia/Fasiculations	Present	Variable		Normal	
Hyperthyroidism	Rare	Fascicular twitching		Normal	Variable		
Hypothyroidism	Present	Myotonia/Myoedema	Present	Elevated			
Hypercorticalism				Slight			
Hyperparathyroidism	Present			Elevated			
Hypophosphatemia, acute				Elevated			Present
Hypophosphatemia, chronic				Normal			Normal
Carcinoid syndrome	Present						
Acromegaly				Elevated			
Mitochondrial	Absent	Heaviness/Burning	Absent *				
acyl-CoA dehydrogenation				Elevated			

* may resume activity after a short rest. ** lactate is not affected, but ammonia levels rise.

Table 5. Major metabolic/endocrine-derived myopathy considerations when identified symptoms and signs are noted.

Exercise intolerance	
Phosphofructokinase	childhood–adolescence onset
Phosphoglycerate mutase	childhood–early adult onset
Lactate dehydrogenase	in utero to adult onset
Phosphoglycerate kinase	birth or early infancy onset
Aldolase	childhood onset
Carnitine palmityl transferase	infancy to late adult onset
	only after prolonged exercise
Hypokalemic periodic paralysis	second decade onset
Second wind	
Muscle phosphorylase	onset usually before age 20
Debrancher enzyme	infancy to 50s onset
Phosphofructokinase	childhood–adolescence onset
Muscle weakness	
Muscle phosphorylase	onset usually before age 20
Acid maltase	infancy to middle age onset
Debrancher muscle	infancy to late middle age onset
Phosphoglycerate kinase	birth or early infancy onset
Aldolase	childhood onset
Carnitine	first 3 years of life onset; secondary—any age
Ichthyosis-associated myopathy	adolescent to adult onset
Carnitine palmityl transferase	infancy to late adult onset
Myoadenylate deaminase	infancy to late adult onset
Periodic paralysis	
Hypokalemic, normokalemic	first decade of life
Hypothyroid	early to mid adult onset
Hyperkalemic	childhood to adolescence onset
Thyroid disease	
Hyperthyroid	early to mid-adult onset
Hypothyroid	first decade of life onset
Corticosteroid	all ages
Hyperparathyroidism	middle age to late adult onset
Hypoparathyroidism	any age, but especially childhood
Hypophosphatemia	infancy to early childhood onset
Carcinoid	second to third decades of life onset
Acromegaly	third to fourth decades of life onset
Amyloidosis	middle age to late adult onset
Mitochondrial myopathy	any age, but especially childhood and adolescence
Cramps	
Muscle phosphorylase	usually <20
Phosphofructokinase	childhood–adolescence onset
Phosphoglucomutase	childhood–early adult onset
Carnitine	first 3 years of life onset; secondary, any age
Myoadenylate deaminase	infancy to late adult onset
Hypothyroid	first decade of life onset
Hyperparathyroid	middle age to late adult onset
Hypoparathyroid	infancy to early childhood onset
Carcinoid	second and third decades of life onset

Table 5. *Cont.*

Hypotonia	
Acid maltase	infancy to middle age onset
Phosphoglucomutase	childhood–early adult onset
Brancher enzyme	in utero to adult onset
Aldolase	childhood onset
Myoadenylate deaminase	infancy to late adult onset
Hypothyroid	first decade of life onset
Carcinoid	second and third decades of life onset
Muscle hypertrophy	
Acid maltase	infancy to middle age onset
Muscle phosphorylase	usually <20
Mitochondrial	any age, but especially childhood and adolescence
Amyloidosis	middle age to late adult onset
Myoedema	
Hypothyroid	first decade of life onset
Face and/or neck involvement	
Carnitine	first 3 years of life onset
Carnitine palmityl transferase	infancy to late adult onset
Hypoparathyroidism	first decade of life onset
Mitochondrial adenylosuccinate synthetase 1	first decade of life onset
CPK elevation	
Muscle phosphorylase	usually <20—especially after exercise, with lactate and potassium
Acid maltase	infancy to middle age onset
Phosphofructokinase	childhood-adolescence onset
Phosphoglycerate mutase	childhood-early adult onset
Lactate dehydrogenase	in utero to adult onset
Phosphoglycerate kinase	birth or early infancy onset
Carnitine	second and third decades of life onset
Ichthyosis-associated myopathy	adolescent to adult onset
Carnitine palmityl transferase	infancy to late adult onset
Myoadenylate deaminase	infancy to late adult onset
Thyroid disease	childhood to adult onset
paradoxical	elevated routinely in hypothyroidism, but not those with muscle disease
Hypoparathyroidism	first decade of life onset
Acromegaly	third to fourth decades of life onset
Myoglobinuria	
Muscle phosphorylase	usually <20
Phosphofructokinase	childhood-adolescence onset
Phosphoglycerate mutase	childhood-early adult onset
Lactate dehydrogenase	in utero to adult onset
Phosphoglycerate kinase	birth or early infancy onset
Aldolase	childhood onset
Carnitine palmityl transferase	infancy to late adult onset—absent in 21%
Hypophosphatemia	infancy to early childhood onset

Table 5. *Cont.*

Prominent respiratory symptoms	
Acid maltase	infancy to middle age onset
Carnitine	second and third decades of life onset
Carnitine palmityl transferase	infancy to late adult onset
Periodic paralysis	
Hypokalemic, normokalemic	first decade of life
Hypothyroid	early to mid adult onset
Hyperkalemic	childhood to adolescence onset
Thyroid disease	childhood to adult onset
Hemolytic anemia	
Phosphofructokinase	childhood-adolescence onset
Phosphoglycerate kinase	childhood-adolescence onset
Lactate dehydrogenase	in utero to adult onset

Of course, this is only one portion of the trifecta; the others are represented by congenital and inflammatory/immunologic disorders [120]. The differential considerations between them and the disorders of metabolic/endocrine derivation are beyond the purpose/scope of this review. Dysfunction related to carbohydrate, lipid and purine metabolism, endocrine function and mitochondria are distinguished (Table 4), but more analyses are needed. We, as rheumatologists, are attuned to the nuances of those diagnostic categories, the existence of which are known to us, under the mantra "if not us, who will?". This review reminds us of the complexity of the diagnostic considerations to which we are exposed. The findings that suggest the possibility of a metabolic myopathy include exercise intolerance (noting response to high intensity or prolonged exercise, especially when a second wind phenomena is present), muscle cramps, contractures (whether fixed or transient) and/or hypertrophy, ptosis, ophthalmoplegia, pigmenturia, rhabdomyolysis and, of course, family history. It is not a matter of "if we can manage metabolic myopathies", but rather "if we should" [121] do this, instead of identifying their presence and referring the diagnosis of the specific variety and their management to those colleagues who specialize in these fields.

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References

1. Landon, D.N. Skeletal muscle–normal morphology, development and innervation. In *Skeletal Muscle Pathology*; Mastaglia, F.L., Walton, J., Eds.; Churchill Livingston: Edinburgh, Scotland, 1982; pp. 1–87.
2. Cullen, M.J.; Mastaglia, F.L. Pathological reactions of skeletal muscle. In *Skeletal Muscle Pathology*; Mastaglia, F.L., Walton, J., Eds.; Churchill Livingston: Edinburgh, Scotland, 1982; pp. 88–139.
3. Bogdanovich, S.; Gardner, B.B.; McNally, E.M. Abnormal muscle pathology and physiology. In *Cardioskeletal Myopathies in Children and Young Adults*; Jefferies, J.L., Blaxall, B.C., Robbins, J., Towbin, J.A., Eds.; Academic Press: Cambridge, MA, USA, 2017; pp. 65–82.
4. D'Amico, A.; Bertini, E. Metabolic neuropathies and myopathies. *Handb. Clin. Neurol.* **2013**, *113*, 1437–1455. [PubMed]
5. DiMauro, S.; Garone, C.; Naini, A. Metabolic myopathies. *Curr. Rheumatol. Rep.* **2010**, *12*, 386–393. [CrossRef] [PubMed]
6. Bruno, C.; van Diggelen, O.P.; Cassandrini, D.; Gimpelev, M.; Giuffrè, B.; Donati, M.A.; Introvini, P.; Alegria, A.; Assereto, S.; Morandi, L.; et al. Clinical and genetic heterogeneity of branching enzyme deficiency (glycogenosis type IV). *Neurology* **2004**, *63*, 1053–1058. [CrossRef] [PubMed]
7. Ørngreen, M.C.; Schelhaas, J.H.; Jeppesen, T.D.; Akman, H.O.; Wevers, R.A.; Andersen, S.T.; ter Laak, H.R.; van Diggelen, O.P.; DiMauro, S.; Vissing, J. Is muscle glycogenolysis impaired in X-linked phosphorylase b kinase deficiency? *Neurology* **2008**, *70*, 1876–1882. [CrossRef]

8. Toscano, A.; Musumeci, O. Tarui disease and distal glycogenoses: Clinical and genetic update. *Acta Myol.* **2007**, *26*, 105–107.
9. Al-Khatib, A.; Dulaney, E.; Katirji, B. Ischemic forearm exercise test. In *Neuromuscular Disorders in Clinical Practice*; Katriji, B., Ed.; Butterworth-Heinemann: Boston, MA, USA, 2002; pp. 74–79.
10. Andersen, S.T.; Vissing, J. Carbohydrate- and protein-rich diets in McArdle disease: Effects on exercise capacity. *J. Neurol. Neurosurg. Psychiatry* **2008**, *79*, 1359–1363. [CrossRef]
11. Haller, R.G. Treatment of McArdle disease. *Arch. Neurol.* **2000**, *57*, 923–924. [CrossRef]
12. Haller, R.G.; Wyrick, P.; Taivassalo, T.; Vissing, J. Aerobic conditioning: An effective therapy in McArdle's disease. *Ann. Neurol.* **2006**, *59*, 922–928. [CrossRef]
13. Quinlivan, R.M.; Beynon, R.J. Pharmacological and nutritional treatment trials in McArdle disease. *Acta Myol.* **2007**, *26*, 58–60.
14. Reason, S.L.; Voermans, N.; Lucia, A.; Vissing, J.; Quinlivan, R.; Bhai, S.; Wakelin, A. Development of Continuum of Care for McArdle disease: A practical tool for clinicians and patients. *Neuromusc. Disorders* **2023**, *33*, 575–579. [CrossRef]
15. Amato, A.A. Acid maltase deficiency and related myopathies. *Neurol. Clin.* **2000**, *18*, 151–165. [CrossRef] [PubMed]
16. Kishnani, P.S.; Corzo, D.; Nicolino, M.; Byrne, B.; Mandel, H.; Hwu, W.L.; Leslie, N.; Levine, J.; Spencer, C.; McDonald, M.; et al. Recombinant human acid [alpha]-glucosidase: Major clinical benefits in infantile-onset Pompe disease. *Neurology* **2007**, *68*, 99–109. [CrossRef]
17. Bembi, B.; Cerini, E.; Danesino, C.; Donati, M.A.; Gasperini, D.; Morandi, L.; Musumeci, O.; Parenti, G.; Ravaglia, S.; Seidita, F.; et al. Diagnosis of glycogenosis type II. *Neurology* **2008**, *71* (Suppl. S2), S4–S36. [CrossRef]
18. Sadeh, M.; Yosovich, K.; Dabby, R. Glycogen debrancher enzyme deficiency myopathy. *J. Clin. Neuromusc. Dis.* **2012**, *2*, 224–227. [CrossRef]
19. Shen, J.; Bao, Y.; Liu, H.M.; Lee, P.; Leonard, J.V.; Chen, Y.T. Mutations in exon 3 of the glycogen debranching enzyme gene are associated with glycogen storage disease type III that is differentially expressed in liver and muscle. *J. Clin. Investig.* **1996**, *98*, 352–357. [CrossRef] [PubMed]
20. Al-Samkari, H. Mitapivat for phosphofructokinase deficiency. *Am. J. Hematol.* **2024**, *99*, 2045–2046. [CrossRef]
21. Nakajima, H.; Raben, N.; Hamaguchi, T.; Yamasaki, T. Phosphofructokinase deficiency; past, present and future. *Curr. Mol. Med.* **2002**, *2*, 197–212. [CrossRef] [PubMed]
22. Preisler, N.; Cohen, J.; Vissing, C.R.; Madsen, K.L.; Heinicke, K.; Sharp, L.J.; Phillips, L.; Romain, N.; Park, S.U.; Newby, M.; et al. Impaired glycogen breakdown and synthesis in phosphoglucomutase 1 deficiency. *Mol. Genet. Metab.* **2017**, *122*, 117–121. [CrossRef]
23. Stojkovic, T.; Vissing, J.; Petit, F.; Piraud, M.; Orngreen, M.C.; Andersen, B.; Claeys, K.G.; Wary, C.; Hogrel, J.Y.; Laforêt, P. Muscle glycogenosis due to phosphoglucomutase 1 deficiency. *N. Engl. J. Med.* **2009**, *23*, 425–427. [CrossRef]
24. Tegtmeyer, L.C.; Rust, S.; van Scherpenzeel, M.; Ng, B.G.; Losfeld, M.-E.; Timal, S.; Raymond, K.; He, P.; Ichikawa, M.; Veltman, J.; et al. Multiple phenotypes in phosphoglucomutase 1 deficiency. *N. Engl. J. Med.* **2014**, *370*, 533–542. [CrossRef]
25. Noel, N.; Flanagan, J.M.; Ramirez Bajo, M.J.; Kalko, S.G.; del Mar Mañú, M.; Garcia Fuster, J.L.; Perez de la Ossa, P.; Carreras, P.; Beutler, E.; Vives Corrons, J.L. Two new phosphoglycerate kinase mutation associated with chronic haemolytic anaemia and neurological dysfunction in two patients from Spain. *J. Haematol.* **2006**, *132*, 523–529. [CrossRef] [PubMed]
26. Vissing, J.; Quistorff, B.; Haller, R.G. Effect of fuels on exercise capacity in muscle phosphoglycerate mutase deficiency. *Arch. Neurol.* **2005**, *62*, 1440–1443. [CrossRef] [PubMed]
27. Chen, Z.; Bordieanu, B.; Kesavan, R.; Lesner, N.P.; Venigalla, S.; Shelton, S.D.; Deberardinis, R.J.; Mishra, P. Lactate metabolism is essential in early-onset mitochondrial myopathy. *Sci. Adv.* **2023**, *9*, eadd3216. [CrossRef] [PubMed]
28. Liu, H.; Wang, X.; Shen, P.; Ni, Y.; Han, X. The basic functions of phosphoglycerate kinase 1 and its roles in cancer and other diseases. *Eur. J. Pharmacol.* **2022**, *920*, 174835. [CrossRef]
29. Goebel, H.H.; Shin, Y.S.; Gullotta, F.; Yokota, T.; Alroy, J.; Voit, T.; Haller, P.; Schulz, A. Adult polyglucosan body myopathy. *J. Neuropathol. Exp. Neurol.* **1992**, *51*, 24–35. [CrossRef]
30. Koch, R.; Soler-Alfonso, C.; Kiely, B.; Riudavets, M.; Arakaki, N.; Mesa, L.; Sevlever, G.; Goebel, H.; Di Mauro, S. A path forward for patients with glycogen branching enzyme deficiency: Consensus on diagnosing and managing glycogen storage disease type IV. *Genetics Med.* **2023**, *1* (Suppl. S1), 100114. [CrossRef]
31. Paradas, C.; Akman, O.H.; Ionete, C.; Lau, H.; Riskind, P.N.; Jones, D.E.; Smith, T.W.; Hirano, M.; Dimauro, S. Branching enzyme deficiency: Expanding the clinical spectrum. *Neurology* **2014**, *2* (Suppl. S10), P6–P108. [CrossRef]
32. Tran, P.L.; Park, E.-J.; Hong, J.-S.; Lee, C.K.; Kang, T.; Park, J.T. Mechanism of action of three different glycogen branching enzymes and their effect on bread quality. *Int. J. Biol. Macromol.* **2024**, *256 Pt 2*, 128471. [CrossRef]
33. Simons, N.; Debray, F.-G.; Schaper, N.C.; Schaper, N.C.; Kooi, M.E.; Feskens, E.J.; Hollak, C.E.; Lindeboom, L.; Koek, G.J.; Bons, J.A.; et al. Patients with aldolase b deficiency are characterized by increased intrahepatic triglyceride content. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 5056–5064. [CrossRef]
34. Bruno, C.; Dimauro, S. Lipid storage myopathies. *Curr. Opin. Neurol.* **2008**, *21*, 601–606. [CrossRef]

35. Sadeh, M.; Dory, A.; Lev, D.; Yosovich, K.; Dabby, R. Riboflavin-responsive lipid-storage myopathy in elderly patients. *J. Neurol. Sci.* **2024**, *456*, 122808. [CrossRef] [PubMed]
36. Tan, H.; Zhong, Y.; Liu, Z.; Wei, L. Lipid storage myopathy due to late-onset multiple Acyl-CoA dehydrogenase deficiency with novel mutations in ETFDH: A case report. *Front. Neurol.* **2022**, *13*, 991060. [CrossRef]
37. Longo, N.; Amat di San Filippo, C.; Pasquali, M. Disorders of carnitine transport and the carnitine cycle. *Am. J. Med. Genet. C Semin. Med. Genet.* **2006**, *142*, 77–85. [CrossRef] [PubMed]
38. Rizzo, W.B.; Jenkens, S.M.; Boucher, P. Recognition and diagnosis of neuro-ichthyotic syndromes. *Semin. Neurol.* **2012**, *32*, 75–84. [CrossRef]
39. Fischer, J.; Hotz, A.; Komlosi, K. Syndromic ichthyoses. *Med. Genet.* **2023**, *35*, 23–32. [CrossRef]
40. Britton, C.H.; Schultz, R.A.; Zhang, B.; Esser, V.; Foster, D.W.; McGarry, J.D. Human liver mitochondrial carnitine palmitoyltransferase I: Characterization of its cDNA and chromosomal localization and partial analysis of the gene. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 1984–1988. [CrossRef]
41. Deschauer, M.; Wieser, T.; Zierz, S. Muscle carnitine palmityltransferase II deficiency: Clinical and molecular genetic features and diagnostic aspects. *Arch. Neurol.* **2005**, *62*, 37–41. [CrossRef]
42. Elston, T.; Wang, H.; Oster, G. Energy transduction in ATP synthase. *Nature* **1998**, *391*, 510–513. [CrossRef]
43. Mercelis, R.; Martin, J.J.; de Barsy, T.; Van den Berghe, G. Myoadenylate deaminase deficiency: Absence of correlation with exercise intolerance in 452 muscle biopsies. *J. Neurol.* **1987**, *234*, 385–389. [CrossRef]
44. Shah, D.N.; Chorya, H.P.; Ramesh, N.N.; Gnanasekaram, S.; Patel, N.; Sethi, Y.; Kaka, N. Myopathies of endocrine origin: A review for physicians. *Dis.-A-Mon.* **2024**, *70*, 101628. [CrossRef]
45. Tadisina, S.; Asad, R.; Varakantam, A.; Weide, L.; Drees, B. Thyrotoxic periodic paralysis as an ongoing diagnostic challenge: A case report and literature review. *Cureus* **2023**, *15*, e46272. [CrossRef] [PubMed]
46. Arezoumand, A.; Nazari, S.; Jazi, K.; Bagherzade, M.; Riahi, M.M.; AkbariMehr, M.; Kanganee, N.; Masoumi, M. An atypical presentation of hypothyroidism with extremely exaggerated functional impairment. *Clin. Case Rep.* **2023**, *11*, e7708. [CrossRef] [PubMed]
47. Holm-Yildiz, S.; Krag, T.; Witting, N.; Pedersen, B.S.; Dysgaard, T.; Sloth, L.; Pedersen, J.; Kjær, R.; Kannuberg, L.; Dahlqvist, J.; et al. Hypokalemic periodic paralysis: A 3-year follow-up study. *J. Neurol.* **2023**, *270*, 6057–6063. [CrossRef] [PubMed]
48. Schulte, K.; Sheedy, M.; Feustel, K.; Scherbak, D. Newly Diagnosed Hypokalemic Periodic Paralysis Triggered by COVID-19. *Cureus* **2023**, *15*, e47906. [CrossRef]
49. Vivek, A.; Sengar, P.; Chaurasia, R.N.; Pathak, A.; Kumar, A.; Singh, V.K. Hyperkalemic Periodic Paralysis in Twenty-Two Family Members Over Four Generations. *Ann. Indian Acad. Neurol.* **2023**, *26*, 595–597. [CrossRef]
50. Coutinho, A.; Fonseca, N.; Novo, I.; Faria, L.; Iglesias, V. Corticosteroid-induced myopathy. *Cureus* **2023**, *15*, 49548. [CrossRef]
51. Haran, M.; Schattner, A.; Kozak, N.; Mate, A.; Berrebi, A.; Shvidel, L. Acute steroid myopathy: A highly overlooked entity. *Quart. J. Med.* **2018**, *111*, 307–311. [CrossRef]
52. Kochman, M. Primary hyperparathyroidism: Clinical manifestations, diagnosis and evaluation according to the Fifth International Workshop guidelines. *Reumatologia* **2023**, *61*, 256–263. [CrossRef]
53. Babu, T.A.; Hashim, A.; Neyaz, Z.; Mani, V.E.; Jain, N.; Bhatia, E.; Mishra, A.; Sahoo, S.K. Nonsurgical hypoparathyroidism is associated with skeletal muscle dysfunction and restrictive lung disease. *Eur. J. Endocrinol.* **2023**, *189*, 141–148. [CrossRef]
54. Girgis, C.M. Vitamin D deficiency and myopathy. In *Nutrition and Skeletal Muscle*; Walrand, S., Ed.; Academic Press: Cambridge, MA, USA, 2019; pp. 409–418. [CrossRef]
55. Rajkumar, V. Vitamin d deficiency presenting as proximal myopathy: An overlooked diagnosis—A case series and review of the literature. *Eur. Med. J.* **2022**, *21*, 248. [CrossRef]
56. Ito, N.; Hidaka, N.; Kato, H. The pathophysiology of hypophosphatemia. *Best Pract. Res. Clin. Endocrinol. Metab.* **2024**, *38*, 101851. [CrossRef]
57. Puente-Ruiz, N.; Docio, P.; García Unzueta, M.T.; Lavín, B.A.; Maiztegi, A.; Vega, A.I.; Piedra, M.; Riancho-Zarrabeitia, L.; Mateos, F.; Gonzalez-Lamuño, D.; et al. Uncovering genetic causes of hypophosphatemia. *J. Intern. Med.* **2023**, *293*, 753–762. [CrossRef] [PubMed]
58. Swash, M.; Fox, K.P.; Davidson, A.R. Carcinoid myopathy: Serotonin-induced muscle weakness in man? *Arch. Neurol.* **1975**, *32*, 572–574. [CrossRef] [PubMed]
59. Vitale, G.; Carra, S.; Alessi, Y.; Campolo, F.; Pandozzi, C.; Zanata, I.; Colao, A.; Faggiano, A. On Behalf Of The Nike Group. Carcinoid syndrome: Preclinical models and future therapeutic strategies. *Int. J. Mol. Sci.* **2023**, *24*, 3610. [CrossRef]
60. Daniel, C.P.; Wagner, M.J.; Borne, G.E.; Borne, G.E.; Plaisance, C.J.; Ahmadzadeh, S.; Aquino, A.; Shekoohi, S.; Kaye, A.M.; Cornett, E.M.; et al. Acromegaly: Pathophysiological considerations and treatment options including the evolving role of oral somatostatin analogs. *Pathophysiology* **2023**, *30*, 377–388. [CrossRef] [PubMed]
61. McInnis, R.L.; Rjoob, H.; Ohorodnyk, P.; Fraser, J.A.; Van Uum, H.H.; Bursztyn, L.L. Extraocular muscle enlargement in acromegaly. *J. Neuro-Ophthalmol* **2023**, *43*, 547–552. [CrossRef]

62. McNab, T.L.; Khandwala, H.M. Acromegaly as an endocrine form of myopathy: Case report and review of literature. *Endocr. Pract.* **2005**, *11*, 18–22. [CrossRef]
63. Parthiban, G.P.; Wilson, J.; Nesheiwat, J. Amyloid myopathy: A cunning masquerader. *Cureus* **2023**, *15*, e39576. [CrossRef]
64. Ungericht, M.; Wanschitz, J.; Kroiss, A.S.; Röcken, C.; Schuetz, T.; Messner, M.; Zaruba, M.M.; Loescher, W.N.; Poelzl, G. Amyloid myopathy: Expanding the clinical spectrum of transthyretin amyloidosis—case report and literature review. *J. Nuclear Cardiol.* **2023**, *30*, 1420–1426. [CrossRef]
65. Ganetzky, R.D.; Markhard, A.L.; Yee, I.; Clever, D.; Cahill, A.; Shah, H.; Grabarek, Z.; To, T.-L.; Mootha, V.K. Congenital hypermetabolism and uncoupled oxidative phosphorylation. *N. Engl. J. Med.* **2022**, *387*, 1395–1403. [CrossRef]
66. Bergamini, C.; Bonora, E.; Moruzzi, N. Mitochondrial bioenergetics impairments in genetic and metabolic diseases. *Front. Physiol.* **2023**, *14*, 1228926. [CrossRef] [PubMed]
67. Gonzalez-Chapa, J.A.; Macêdo, M.B.; Lood, C. The emerging role of mitochondrial dysfunction in the pathogenesis of idiopathic inflammatory myopathies. *Rambam Maimonides Med. J.* **2023**, *14*, e0006. [CrossRef]
68. Rowland, L.P.; Blake, D.M.; Hirano, M.; Di Mauro, S.; Schon, E.A.; Hays, A.P.; Devivo, D.C. Clinical syndromes associated with ragged red fibers. *Rev. Neurol.* **1991**, *147*, 467–473.
69. Sproule, D.M.; Kaufmann, P. Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes: Basic concepts, clinical phenotype, and therapeutic management of MELAS syndrome. *Ann. N. Y. Acad. Sci.* **2008**, *1142*, 133–158. [CrossRef] [PubMed]
70. Montano, V.; Gruosso, F.; Simoncini, C.; Siciliano, G.; Mancuso, M. Clinical features of mtDNA-related syndromes in adulthood. *Arch. Biochem. Biophys.* **2021**, *697*, 108689. [CrossRef] [PubMed]
71. Andreu, A.L.; Hanna, M.G.; Reichmann, H.; Bruno, C.; Penn, A.S.; Tanji, K.; Pallotti, F.; Iwata, S.; Bonilla, E.; Lach, B. Exercise intolerance due to mutations in the cytochrome b gene of mitochondrial DNA. *N. Engl. J. Med.* **1999**, *341*, 1037–1044. [CrossRef]
72. McFarland, R.; Taylor, R.W.; Chinnery, P.F.; Howell, N.; Turnbull, D.M. A novel sporadic mutation in cytochrome c oxidase subunit II as a cause of rhabdomyolysis. *Neuromusc. Disord.* **2004**, *14*, 162–166. [CrossRef]
73. Simon, L.; Jolley, S.E.; Molina, P.E. Alcoholic myopathy: Pathophysiologic mechanisms and clinical implications. *Alcohol Res.* **2017**, *38*, 207–217.
74. Urtizberea, J.A.; Severa, G.; Malfatti, E. Metabolic myopathies in the era of next-generation sequencing. *Genes* **2023**, *14*, 954. [CrossRef]
75. Tobon, A. Metabolic myopathies. *Continuum* **2013**, *19*, 1571–1597. [CrossRef]
76. Noury, J.B.; Zagnoli, F.; Petit, F.; Marcorelles, P.; Rannou, F. Exercise efficiency impairment in metabolic myopathies. *Sci. Rep.* **2020**, *10*, 8765. [CrossRef] [PubMed]
77. Bernier, F.P.; Boneh, A.; Dennett, X.; Chow, C.W.; Cleary, M.A.; Thorburn, D.R. Diagnostic criteria for respiratory chain disorders in adults and children. *Neurology* **2002**, *59*, 1406–1411. [CrossRef] [PubMed]
78. Gorman, G.S.; Schaefer, A.M.; Ng, Y.; Gomez, N.; Blakely, E.L.; Alston, C.L.; Feeney, C.; Horvath, R.; Yu-Wai-Man, P.; Chinnery, P.F. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann. Neurol.* **2015**, *77*, 753. [CrossRef] [PubMed]
79. Skladal, D.; Halliday, J.; Thorburn, D.R. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. *Brain* **2003**, *126*, 1905–1912. [CrossRef]
80. Elliott, H.R.; Samuels, D.C.; Eden, J.A.; Relton, C.L.; Chinnery, P.F. Pathogenic mitochondrial DNA mutations are common in the general population. *Am. J. Hum. Genet.* **2008**, *83*, 254–260. [CrossRef]
81. Smelt, A.H.; Poorthuis, B.J.; Onkenhout, W.; Scholte, H.R.; Andresen, B.S.; van Duinen, D.G.; Gregersen, N.; Wintzen, A.R. Very long chain acyl-coenzyme A dehydrogenase deficiency with adult onset. *Ann. Neurol.* **1998**, *43*, 540–544. [CrossRef]
82. Gempel, K.; Topaloglu, H.; Talim, B.; Schneiderat, P.; Schoser, B.G.; Hans, V.H.; Pálmafy, B.; Kale, G.; Tokatli, A.; Quinzii, C.; et al. The myopathic form of coenzyme Q10 deficiency is caused by mutations in the electron-transferring-flavoprotein dehydrogenase (ETFDH) gene. *Brain* **2007**, *130*, 2037–2044. [CrossRef]
83. Horvath, R.; Schneiderat, P.; Schoser, B.G.; Gempel, K.; Neuen-Jacob, E.; Plöger, H.; Müller-Höcker, J.; Pongratz, D.E.; Naini, A.; DiMauro, S.; et al. Coenzyme Q10 deficiency and isolated myopathy. *Neurology* **2006**, *66*, 253–255. [CrossRef]
84. OMIM® An Online Catalog of Human Genes and Genetic Disorders. Available online: www.omim.org (accessed on 6 February 2025).
85. DiMauro, S.; Hirano, M. Mitochondrial DNA Deletion Syndromes. GeneReviews. Available online: www.ncbi.nlm.nih.gov/books/NBK1203/ (accessed on 30 January 2025).
86. Lee, H.N.; Eom, S.; Kim, S.H.; Kang, H.-C.; Lee, S.L.; Kim, H.D.; Lee, Y.M. Epilepsy Characteristics and Clinical Outcome in Patients With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS). *Pediatr. Neurol.* **2016**, *64*, 59–65. [CrossRef]
87. Gilchrist, J.M.; Sikirica, M.; Stopa, E.; Shanske, S. Adult-onset MELAS. Evidence for involvement of neurons as well as cerebral vasculature in strokelike episodes. *Stroke* **1996**, *27*, 1420–1423. [CrossRef]

88. Domínguez-González, C.; Madruga-Garrido, M.; Mavillard, F.; Garone, C.; Aguirre-Rodríguez, F.J.; Donati, M.A.; Kleinsteuber, K.; Martí, I.; Martín-Hernández, E.; Morealejo-Aycinena, J.P.; et al. Deoxynucleoside Therapy for Thymidine Kinase 2–Deficient Myopathy. *Ann. Neurol.* **2019**, *86*, 293–303. [CrossRef] [PubMed]
89. Domínguez-González, C.; Hernández-Laín, A.; Rivas, E.; Hernández-Voth, A.; Catalán, J.S.; Fernández-Torrón, R.; Fuiza-Luces, C.; García, J.G.; Morís, G.; Olivé, M.; et al. Late-onset thymidine kinase 2 deficiency: A review of 18 cases. *Orphanet J. Rare Dis.* **2019**, *14*, 100. [CrossRef] [PubMed]
90. Park, H.J.; Hong, J.M.; Lee, J.H.; Shin, H.Y.; Kim, S.M.; Park, K.D.; Lee, J.H.; Choi, Y.C. Comparative transcriptome analysis of skeletal muscle in ADSSL1 myopathy. *Neuromuscul. Disord.* **2019**, *29*, 274–281. [CrossRef]
91. Rybalka, E.; Park, H.J.; Nalini, A.; Baskar, D.; Polavarapu, K.; Durmus, H.; Xia, Y.; Wan, L.; Shieh, P.B.; Moghadaszadeh, B. Current insights in ultra-rare adenylosuccinate synthetase 1 myopathy–meeting report of the First Clinical and Scientific Conference. 3 June 2024, National Centre for Advancing Translational Science, Rockville, Maryland, the United States of America. *Orphanet J. Rare Dis.* **2024**, *19*, 438. [CrossRef] [PubMed]
92. Park, H.J.; Lee, J.E.; Choi, G.S.; Koo, H.; Han, S.J.; Yoo, J.H.; Choi, Y.C.; Park, K.D. Electron Microscopy Pathology of ADSSL1 Myopathy. *J. Clin. Neurol.* **2017**, *13*, 105–106. [CrossRef]
93. Cakmak, E.; Bagci, G. Chanarin-Dorfman Syndrome: A comprehensive review. *Liver Int.* **2021**, *41*, 905–914. [CrossRef]
94. Tian, Y.; Wang, S.; Wang, F.; Yi, L.; Dong, M.; Huang, X. Late onset of neutral lipid storage disease due to a rare PNPLA2 mutation in a patient with myopathy and cardiomyopathy. *Chin. Med. J.* **2022**, *135*, 2389–2391. [CrossRef]
95. Zeharia, A.; Shaag, A.; Houtkooper, R.H.; Hindi, T.; de Lonlay, P.; Erez, G.; Hubert, L.; Saada, A.; de Keyzer, Y.; Eshel, G.; et al. Mutations in LPIN1 Cause Recurrent Acute Myoglobinuria in Childhood. *Am. J. Hum. Genet.* **2008**, *83*, 489–494. [CrossRef]
96. Tuchmann-Durand, C.; Roda, C.; Renard, P.; Mortamet, G.; Bérat, C.; Altenburger, L.; de Larauz, M.H.; Thevenet, E.; Cottart, C.; Moulin, F.; et al. Systemic corticosteroids for the treatment of acute episodes of rhabdomyolysis in lipin-1-deficient patients. *J. Inherit. Metab. Dis.* **2023**, *2023. 46*, 649–661. [CrossRef]
97. Mitochondrial Medicine Society's Committee on Diagnosis; Haas, R.H.; Parikh, S.; Falk, M.J.; Saneto, R.P.; Wolf, N.I.; Darin, N.; Wong, L.-J.; Cohen, B.H.; Naviaux, R.K. The indepth evaluation of suspected mitochondrial disease. *Mol. Genet. Metab.* **2008**, *94*, 16–37. [CrossRef]
98. Tarnopolsky, M.; Stevens, L.; MacDonald, J.R.; Rodriguez, C.; Mahoney, D.; Rush, J.; Maguire, J. Diagnostic utility of a modified forearm ischemic exercise test and technical issues relevant to exercise testing. *Muscle Nerve* **2003**, *27*, 359–366. [CrossRef] [PubMed]
99. Parikh, S.; Goldstein, A.; Koenig, M.K.; Scaglia, F.; Enns, G.M.; Saneto, R.; Anselm, I.; Cohen, B.H.; Falk, M.J.; Greene, C.; et al. Diagnosis and management of mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. *Genet. Med.* **2015**, *17*, 689–701. [CrossRef] [PubMed]
100. Nascimento, J.; Pinho, R.; de Castro, A.P.; Vieira, N.B. McArdle's disease: A differential diagnosis of metabolic myopathies. *Cureus* **2024**, *16*(9), e70000. [CrossRef] [PubMed]
101. Giannoglou, G.D.; Chatzizisis, Y.S.; Misirli, G. The syndrome of rhabdomyolysis: Pathophysiology and diagnosis. *Eur. J. Intern. Med.* **2007**, *18*, 90–100. [CrossRef]
102. Wortman, R.L.; DiMauro, S. Differentiating idiopathic inflammatory myopathies from metabolic myopathies. *Rheum. Dis. Clin. N. Am.* **2002**, *28*, 759–778.103. [CrossRef]
103. Hogrel, J.-Y.; Laforet, P.; Ben Yaou, R.; Chevrot, M.; Eymard, B.; Lombes, A. A non-ischemic forearm exercise test for the screening of patients with exercise intolerance. *Neurology* **2001**, *56*, 1733–1738. [CrossRef]
104. Toscano, A.; Barca, E.; Musumeci, O. Update on diagnostics of metabolic myopathies. *Curr. Opin.* **2017**, *30*, 553–562. [CrossRef]
105. Tarnopolsky, M.A.; Parise, G.; Gibala, M.J.; Graham, T.E.; Rush, J.W. Myoadenylate deaminase deficiency does not affect muscle anaplerosis during exhaustive exercise in humans. *J. Physiol.* **2001**, *533*, 881–889. [CrossRef]
106. Tarnopolsky, M.A. Metabolic Myopathies. *Contin. Lifelong Learn. Neurol.* **2016**, *22*, 1829–1851. [CrossRef]
107. Parikh, S.; The Mitochondrial Medicine Society; Saneto, R.; Falk, M.J.; Anselm, I.; Cohen, B.H.; Haas, R. A modern approach to the treatment of mitochondrial disease. *Curr. Treat. Options Neurol.* **2009**, *11*, 414–430. [CrossRef]
108. Camp, K.M.; Krotoski, D.; Parisi, M.A.; Gwinn, K.A.; Cohen, B.H.; Cox, C.S.; Enns, G.M.; Falk, M.J.; Goldstein, A.C.; GopalSrivastava, R.; et al. Nutritional interventions in primary mitochondrial disorders: Developing an evidence base. *Mol. Genet. Metab.* **2016**, *119*, 187–206. [CrossRef] [PubMed]
109. Guémy, C.; Laforêt, P. The new horizons for treatment of Late-Onset Pompe Disease (LOPD). *Rev. Neurol.* **2023**, *179*, 81–89. [CrossRef] [PubMed]
110. Byrne, B.; Bratkovic, D.; Díaz-Manera, J.; Laforêt, P.; Mozaffar, T.; van der Ploeg, A.; Roberts, M.; Schoser, B.; Toscano, A.; Jiang, H.; et al. Cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo in late-onset Pompe disease (LOPD): PROPEL study subgroup analyses. *Mol. Genet. Metab.* **2022**, *135*, S27–S28. [CrossRef]

111. Kishnani, P.S.; Nicolino, M.; Voit, T.; Rogers, R.C.; Tsai, A.C.-H.; Waterson, J.; Herman, G.E.; Amalfitano, A.; Thurberg, B.L.; Richards, S.; et al. Chinese hamster ovary cell-derived recombinant human acid alpha-glucosidase in infantileonset Pompe disease. *J. Pediatr.* **2006**, *149*, 89–97. [CrossRef] [PubMed]
112. Kishnani, P.S.; Sun, B.; Koeber, D.D. Gene therapy for glycogen storage diseases. *Hum. Molec. Genet.* **2019**, *28*, R31–R41. [CrossRef]
113. Lim, J.-A.; Choi, S.J.; Gao, F.; Kishnani, P.S.; Baodong, S. A novel gene therapy approach for GSD III using an AAV vector encoding a bacterial glucogen debranching enzyme. *Molec. Ther. Methods Clin. Develop.* **2020**, *18*, 240–249. [CrossRef]
114. Vissing, J.; Haller, R.G. The Effect of Oral Sucrose on Exercise Tolerance in Patients with McArdle's Disease. *N. Engl. J. Med.* **2003**, *349*, 2503–2509. [CrossRef]
115. Barp, A.; Bellance, R.; Malfatti, E.; Rigal, O.; Acquaviva-Bourdain, C.; Laforet, P. Late Onset Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) Myopathy Misdiagnosed as Polymyositis. *Am. J. Clin. Oncol.* **2019**, *26*, e125–e127.
116. Ørngreen, M.C.; Madsen, K.L.; Preisler, N.; Andersen, G.; Vissing, J.; Laforêt, P. Bezafibrate in skeletal muscle fatty acid oxidation disorders: A randomized clinical trial. *Neurology* **2014**, *82*, 607–613. [CrossRef]
117. Ng, K.W.; Chin, H.-L.; Chin, A.X.; Goh, D.L.-M. Using gene panels in the diagnosis of neuromuscular disorders: A mini-review. *Front. Neurol.* **2022**, *13*, 997551. [CrossRef]
118. Gemelli, C.; Traverso, M.; Trevisan, L.; Fabbri, S.; Scarsi, E.; Carlini, B.; Prada, V.; Mongini, T.; Ruggiero, L.; Patrone, S.; et al. An integrated approach to the evaluation of patients with asymptomatic or minimally symptomatic hyperCKemia. *Muscle Nerve* **2022**, *65*, 96–104. [CrossRef] [PubMed]
119. Zhong, H.; Sian, V.; Johari, M.; Katayama, S.; Oghabian, A.; Jonson, P.H.; Hackman, P.; Savarese, M.; Udd, B. Revealing myopathy spectrum: Integrating transcriptional and clinical feature of human skeletal muscles with varying health conditions. *Commun. Biol.* **2024**, *7*, 438. [CrossRef] [PubMed]
120. Lilleker, J.B.; Keh, Y.S.; Roncareoli, F.; Sharma, R.; Roberts, M. Metabolic myopathies: A practical approach. *Pract. Neurol.* **2018**, *18*, 14–26. [CrossRef] [PubMed]
121. Rothschild, B.M. Are we rheumatologists or just internists who also care for patients with rheumatologically-related challenges? *Arthritis Care Res.* 2024, in press.

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