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Review

Genetic test for Mendelian fatigue and muscle weakness syndromes

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Abstract. Several inherited disorders involve chronic fatigue, muscle weakness and pain. These conditions can depend on muscle, nerve, brain, metabolic and mitochondrial defects. A major trigger of muscle weakness and fatigue is exercise. The amount of exercise that triggers symptoms and the frequency of symptoms are highly variable. In this review, the genetic causes and molecular pathways involved in these disorders are discussed along with the diagnostic and treatment options available, with the aim of fostering understanding of the disease and exploring therapeutic options. (www.actabiomedica.it)

Key words: chronic fatigue, muscle weakness, genetic test

Introduction

Several genetic diseases feature conditions like fatigue and muscle weakness accompanied by pain. Examples are collagen synthesis defects and inherited or acquired ion channel and muscle protein myopathies. The prognosis of persons with these abnormalities varies widely: some may have a normal life span with little or no disability, while others may have severely disabling, progressive, life-threatening and ultimately fatal conditions. Muscle weakness can depend on muscle, nerve, brain, metabolic or mitochondrial defects (1).

Myophosphorylase deficiency (McArdle disease)

McArdle disease (myophosphorylase deficiency), also known as glycogen storage disease type V, is a serious disorder of glycogen storage with autosomal recessive inheritance. It is caused by variants in the *PYGM* (muscle associated glycogen phosphorylase) gene, which is involved in the synthesis of myophosphorylase (2). Glycogen phosphorylase catalysis is the first step of glycogenolysis that converts glycogen stored in the liver and muscles to glucose-1-phosphate monomers. McArdle disease is a rare disorder, with an estimated prevalence of 1 per 100,000 to 140,000 persons (2).

The first symptoms appear in early childhood, manifesting as an exercise intolerance with muscle weakness, fatigue and cramps. Other symptoms include a significant increase in creatine kinase, rhabdomyolysis, myoglobinuria and dark urine that can lead to acute kidney failure after exercise. In many patients, relief from fatigue and myalgia is obtained by resting for a few minutes, whereas for severe forms of the disease, onset takes place at an early age with general muscle weakness, hypotonia and advanced respiratory failure (3).

Thus, the *PYGM* variant associated with McArdle disease results in inactivation of the encoded enzyme.

The most frequently reported hotspots are in exons 1 and 17, and almost 50% of patients carry nonsense variants. Almost 147 pathogenic variants and 39 genetic polymorphisms have been reported, the most prevalent of which is 148C>T p.(Arg50*) (4).

The clinical diagnosis of McArdle disease is mostly based on biological and biochemical findings showing a lack of any elevation in blood levels of lactate during the forearm ischemic exercise test, excessive glycogen storage and deficiency of myophosphorylase enzyme activity in muscle biopsy specimens (5).

There is currently no specific therapy for McArdle disease. Most treatment approaches focus on managing symptoms and avoiding intensive physical exercise. Further adjuvant treatment involves well-controlled physical exercise that enhances muscle mitochondrial oxidation capacity and increases glucose intake in proportion to the duration of exercise.

Myoadenylate deaminase deficiency

Myoadenylate deaminase deficiency is a hereditary disorder of muscle energy metabolism, linked to adenosine monophosphate (AMP) deaminase deficiency in skeletal muscle. The main characteristics of the disease include rapid fatigue, myalgia and cramps after exertion. About 1-2% of the Caucasian population carries the genetic defect that causes myoadenylate deaminase deficiency, though only a small proportion show symptoms. At world level, several hundred patients are known to be affected, although the exact prevalence of myoadenylate deaminase deficiency is unknown. Inheritance is mostly autosomal recessive and a majority of patients have a homozygous nonsense variant c.133C>T (p.Gln45*) in the *AMPD1* gene. This nonsense variant inserts a premature stop codon, thus terminating translation of the enzymically active protein (6,7).

Muscle AMP deaminase deficiency has also been reported in patients suffering from other neuromuscular diseases, like Duchenne muscular dystrophy, inflammatory myopathy and hypokalemic periodic paralysis. Severe cases of these disorders often show reduced levels of muscle creatine kinase activity as well as non-collagen protein. Muscle degeneration is more susceptible to AMP deaminase deficiency than to creatine kinase deficiency (8).

Also in inherited myoadenylate deaminase deficiency, almost 93% of patients are reported to show exertional myalgia as the predominant symptom. The median age at diagnosis is reported to be 37 years (range 14-76 years), while 79% of patients had their first symptoms in childhood or early adulthood, albeit with limited disease progression (9).

Another non-invasive test option for the clinical diagnosis of myoadenylate deaminase deficiency is the ischemic forearm exercise test which measures increases in plasma levels of lactate and ammonia due to exertion. Since AMP deaminase is regarded as the main enzyme in the synthesis of ammonia in muscles, a decrease in ammonia profile is indicative of enzyme deficiency. Myoadenylate deaminase deficiency is confirmed by direct enzyme assay or histochemical staining of a muscle biopsy specimen (10,11).

There is currently no therapy for inherited symptomatic myoadenylate deaminase deficiency, although oral administration of ribose before and during exercise (not more than 1 g/kg body weight daily or 0.2 g/kg body weight hourly) has been shown to decrease exercise-related symptoms without significant improvement of other symptoms (12).

Carnitine palmitoyl transferase II deficiency

The myopathic form of carnitine palmitoyl transferase II (CPT II) deficiency is an inherited metabolic disorder that affects mitochondrial oxidation of long chain fatty acids. This form of CPTII deficiency is not very severe. Almost 300 cases of CPTII deficiency have been reported, but this prevalence may be underestimated. Age of onset ranges from 1 to 61 years, although 70% of patients are diagnosed in childhood. Prevalence is higher in males, probably because males are more inclined to prolonged exercise. Clinical characteristics include fatigue, muscle pain and repeated attacks of rhabdomyolysis after prolonged exercise. The myopathic form of CPTII deficiency is caused by pathogenic variants in the *CPT2* gene (13).

The carnitine palmitoyl transferase system facilitates long-chain fatty acid transport into the mito-

chondrial matrix. The carnitine palmitoyl transferase system also includes CPT I, which is located in the outer mitochondrial membrane, while CPT II is located in the inner mitochondrial membrane and catalyzes acyl-coenzyme A formation from acylcarnitine by coenzyme A. Although unlike CPT I, CPT II exists in a single isoform across different tissues, there are different CPT II deficiency phenotypes and they have autosomal recessive inheritance (14).

Different forms of the disease include acute multisystemic infantile, milder muscle and lethal neonatal forms, as well as forms with onset in childhood or adulthood. The milder muscle form is usually characterized by attacks of muscle pain induced by exercise, along with myoglobinuria and rhabdomyolysis. Molecular analysis of the *CPT2* gene in patients with the muscle form of the disease revealed a common variant (p.Ser113Leu) in 76% of cases. Although no genotype-phenotype correlation has yet been established (15), significant clues to such correlations in CPT II deficiency include association of certain missense variants with the muscle form and certain other variants with lethal neonatal or the multisystemic infantile form in homozygous state (16).

Moreover, the lethal neonatal form has often been associated with truncating variants in both alleles. Compound heterozygosity of a severe and a mild variant could also be linked to an acute multisystemic infantile form or a mild muscle form. Patients with a truncating variant have complained of weakness during attacks, unlike patients carrying missense variants. These observations reveal that the muscle CPT II deficiency phenotype is basically affected by the underlying variant. Patients with the truncating variant in a single allele may be affected more severely (17). Symptomatic patients having a single heterozygous variant in the *CPT2* gene have, however, been reported and may be cases of some error in the detection of the second variant. In such cases, genetic analysis of the *CPT2* gene should be done more extensively in search of the second mutant allele (18).

Attack intensity seems to vary and exercise is considered the most significant trigger. Other triggering factors may include infections (46%), cold (14%) and low nutrient intake or fasting (18%). Emotional stress, general anesthesia and drugs have also been reported to trigger attacks. There seems to be a slight predominance of male gender among patients (5,19).

No effective therapy is available for CPT II deficiency, except prevention of attacks through diet and symptomatic treatment for renal complications and myoglobinuria. In dietary therapy, frequent intake of carbohydrates before exercise is recommended along with restricted intake of long-chain fatty acids in favor of medium-chain fatty acids. Recent studies have shown that a carbohydrate-rich diet containing polysaccharides can improve exercise intolerance of patients with muscle CPT II deficiency (20).

Congenital myasthenia syndromes

Congenital myasthenia syndrome is a genetically heterogeneous disorder caused by changes in neuromuscular junctions responsible for transmission of signals between nerves and muscles for the regulation of muscle contraction. Neuromuscular junction defects cause muscle weakness accelerated by exercise from early childhood (21). In Europe the estimated prevalence of congenital myasthenia syndrome is about 1 per 500,000 persons. As far as treatment is concerned, most syndromes are treatable. Some medications may, however, be beneficial for one syndrome but detrimental for another (22).

Congenital myasthenia syndrome features irregular signal transmission at neuromuscular junctions or motor endplates, due to defects in one or more proteins (21,23). The neuromuscular transmission safety margin is lowered by a one or more specific mechanisms. It depends on the difference between the depolarization produced by endplate potential and that needed to activate voltage-gated $Na_v1.4$ channels on the postsynaptic membrane (23).

A general clinical diagnosis of congenital myasthenia syndrome may be based on positive family history, age of onset from birth to childhood, fatigue and weakness influencing eye and other cranial muscles and irregular single-fiber electromyography or decremental electromyography response (24).

Current therapies for congenital myasthenia syndrome usually rely on adrenergic and cholinergic agonists, such as pyridostigmine and 3,4-diaminopyri-

Table 1. Syndromes characterized by fatigue and muscular weakness for which the genetic basis is known. AD = autosomal dominant; AR = autosomal recessive; XLR = X-linked recessive; GSD = glycogen storage disease; MMDD = myopathy due to myoadenylate deaminase deficiency; TAM = tubule aggregate myopathy; ORTHYP = orthostatic hypotension; CMS = congenital myasthenic syndrome

Gene	OMIM# gene	Inheritance	Phenotype	OMIM# phenotype	**Gene function** (https://www.genecards.org/)
PYGM	608455	AR	GSD5 (McArdle disease)	232600	Glycogenolysis
SERPINA6	122500	AD, AR	Corticosteroid-binding globulin deficiency	611489	Transport protein for glucocorticoids and progestins in blood
AMPD1	102770	AR	MMDD	615511	Deamination of AMP to IMP in skeletal muscle. Important role in energy metabolism
AMPD3	102772	AR	Erythrocyte AMP deaminase deficiency	612874	Deamination of AMP to IMP. Important role in energy metabolism
CPT2	600650	AD, AR	Stress-induced myopathic carnitine palmitoyltransferase II deficiency	255110	Long-chain fatty acid oxidation in mitochondria
PHKA1	311870	XLR	GSD9D	300559	Catalysis of phosphorylation of serine of troponin I in skeletal muscle
STIM1	605921	AD	TAM1	160565	Mediation of Ca^{2+} influx after depletion of intracellular Ca^{2+} stores
ORAI1	610277	AD	TAM2	615883	Membrane calcium channel subunit activated by calcium sensor STIM1 when calcium stores are depleted
DBH	609312	AR	ORTHYP1	223360	Catalysis of conversion of dopamine to norepinephrine
CYB561	600019	AR	ORTHYP2	618182	Secretory vesicle-specific electron transport protein
SLC6A2	163970	AD	Orthostatic intolerance	604715	Reuptake of norepinephrine into presynaptic nerve terminals. Regulator of norepinephrine homeostasis
AGRN	103320	AR	CMS8	615120	Central role in formation and maintenance of neuromuscular junctions and postsynaptic differentiation
ALG14	612866	AR	CMS15	616227	Protein N-glycosylation. Dolichol-linked oligosaccharide pathway
SYT2	600104	AD	CMS7	616040	Calcium sensor in vesicle trafficking and exocytosis
PREPL	609557	AR	CMS22	616224	Regulation of synaptic vesicle exocytosis
GFPT1	138292	AR	CMS12	610542	Control of glucose flux into hexosamine pathway. Involved in regulation of availability of precursors for N- and O-linked protein glycosylation. Expression regulation of circadian clock genes
SLC5A7	608761	AR	CMS20	617143	Choline transport from the extracellular space into presynaptic terminals for acetylcholine synthesis
CHRNA1	100690	AD, AR	CMS1A, CMS1B	608930, 601462	Acetylcholine binding/channel gating in acetylcholine receptor

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Gene	**OMIM# gene**	**Inheritance**	**Phenotype**	**OMIM# phenotype**	**Gene function** (https://www.genecards.org/)
CHRND	100720	AD, AR	CMS3A, CMS3B, CMS3C	616321, 616322, 616323	Muscle acetylcholine receptor function
COLQ	603033	AR	CMS5	603034	Anchor of catalytic subunits of asymmetric acetylcholinesterase to synaptic basal lamina
DOK7	610285	AR	CMS10	254300	Postsynaptic differentiation, clustering of acetylcholine receptor in myotubes
ALG2	607905	AR	CMS14	616228	Alpha 1,3 mannosyltransferase
MUSK	601296	AR	CMS9	616325	Clustering of acetylcholine receptors in postsynaptic neuromuscular junction
CHAT	118490	AR	CMS6	254210	Reversible catalysis of synthesis of acetylcholine at cholinergic synapses
SLC18A3	600336	AR	CMS21	617239	Acetylcholine transport into synaptic vesicles
COL13A1	120350	AR	CMS19	616720	Link between muscle fiber and basement membrane. At neuromuscular junctions, role in acetylcholine receptor clustering
LRP4	604270	AR	CMS17	616304	Formation and maintenance of neuromuscular junctions, the synapse between motor neurons and skeletal muscle.
RAPSN	601592	AR	CMS11	616326	Postsynaptic protein required for clustering of nicotinic acetylcholine receptors at neuromuscular junctions
DPAGT1	191350	AR	CMS13	614750	Catalysis of initial step of dolichol-linked oligosaccharide biosynthesis in N-linked protein glycosylation pathway
VAMP1	185880	AR	CMS25	618323	Docking and/or fusion of synaptic vesicles with presynaptic membrane
MYO9A	604875	AR	CMS24	618198	Regulation of neurite branching and motor neuron axon guidance
CHRNE	100725	AD, AR	CMS4A, CMS4B, CMS4C	605809, 616324, 608931	Muscle acetylcholine receptor function
CHRNB1	100710	AD	CMS2A, CMS2C	616313, 616314	Muscle acetylcholine receptor function
SCN4A	603967	AR	CMS16	614198	Muscle fiber excitability, normal muscle contraction and relaxation cycles, and constant muscle strength
SNAP25	600322	AD	CMS18	616330	Important role in synaptic function of specific neuronal systems. Associates with proteins involved in vesicle docking and membrane fusion.
SLC25A1	190315	AR	CMS23	618197	Required for proper neuromuscular junction formation

dine, which are prolonged acetylcholine receptor ion channel blockers. Pyridostigmine acts by inhibiting acetylcholine receptors in the synaptic basal lamina, increasing the number that are activated by a single quantum. On the other hand, 3,4-diaminopyridine increases the number of acetylcholine quanta released by nerve impulses and enhances the amplitude of endplate potentials, increasing the neuromuscular transmission safety margin (21). Likewise, quinidine and fluoxetine are long-term open-channel acetylcholine receptor blockers that inhibit depolarization blockade and acetylcholine receptor desensitization at physiological stimulation rates, also mitigating postsynaptic cation overload, a cause of junctional fold degeneration and endplate geometry alteration (21).

Orthostatic hypotension

Orthostatic or postural hypotension is an extreme drop in blood pressure on standing upright from lying or sitting position. According to the formal definition, a 20 mmHg drop in systolic blood pressure or 10 mmHg in diastolic blood pressure, or both, usually occurs within 3 minutes of the change in position from supine to upright. Symptoms such as dizziness, weakness, obnubilation, fatigue and confusion take place within a few minutes of standing up and rapidly disappear on return to lying position. Some patients also experience syncope, falls or even general convulsions. A heavy meal or exercise may enhance symptoms. Certain studies have proposed that orthostatic intolerance may be linked to chronic fatigue syndrome. A significant form of orthostatic hypotension that usually occurs in early childhood has genetic causes involving rare variants (25).

Classic neurogenic orthostatic hypotension syndrome or orthostatic hypotension-1 is a genetic condition of dopamine β-hydroxylase deficiency, a critical enzyme that converts dopamine into norepinephrine, absence of which leads to sympathetic failure. The syndrome has autosomal recessive inheritance and onset is usually in early childhood or childhood. Major features include low urinary and plasma levels of epinephrine and norepinephrine, together with episodic hypoglycemia. Orthostatic hypotension-1 is linked to pathogenic variants in the *DBH* gene (25,26).

Van den Berg et al. recently reported a new genetic syndrome related to sympathetic failure which they indicated as orthostatic hypotension-2. The syndrome has autosomal recessive inheritance, childhood onset and is characterized by acute orthostatic hypotension with recurring hypoglycemia and reduced plasma levels of epinephrine and norepinephrine; some patients also have renal dysfunction and decreased life expectancy. Different pathogenic variants in the *CYB561* gene have been reported (27).

Postural tachycardia syndrome

Prolonged orthostatic intolerance, sometimes associated with tachycardia but without any blood pressure drop, is mostly referred to as postural tachycardia syndrome. Postural tachycardia syndrome is usually considered a disorder of the autonomic nervous system of unknown etiology that presents with clinical symptoms such as syncope, constant upright tachycardia and increased norepinephrine spillover along with fatigue, dizziness, sleep disturbances, palpitations, confusion and cognitive impairment. An association of postural tachycardia syndrome with pathogenic variants in the *SLC6A2* gene, which encodes a norepinephrine transporter, has been reported (28).

Corticosteroid binding globulin deficiency

Corticosteroid binding globulin or transcortin deficiency is a rare autosomal recessive adrenal disorder featuring decreased corticosteroid binding capacity with normal or decreased plasma concentrations of corticosteroid binding globulin and low total plasma levels of cortisol. The deficiency is usually caused by variants in the *SERPINA6* gene. Patients may experience hypo- or hypertension, chronic pain and fatigue (29).

Muscle phosphorylase kinase deficiency

Muscle phosphorylase kinase deficiency causing muscle glycogenosis is a benign hereditary glycogen

metabolic defect characterized by exercise intolerance. Fewer than 30 cases of this very rare condition have been reported to date. Onset is usually in adolescence or adulthood. Patients may experience cramps, exercise intolerance, myalgia, myoglobinuria and fatigue. Pathogenic variants in the *PHKA1* gene have so far been identified as the main cause of the deficiency and inheritance is usually X-linked (30).

Inherited congenital myopathies

Congenital myopathies are heterogeneous inherited muscle disorders present from birth, although onset may be delayed until infancy or even early childhood. Some of these rare disorders include centronuclear (myotubule) myopathies, central core disease, nemaline myopathy and congenital fiber-type disproportion. All these disorders have specific morphological abnormalities expressed prematurely along with hypotonia, loss of muscle mass, limb weakness and sometimes dysmorphism (31).

Conclusion

Various Mendelian fatigue and muscle weakness syndromes, like mitochondrial and metabolic myopathies and collagen, protein and enzyme defects, involve chronic fatigue, muscle pain and weakness. Exercise is a major trigger of symptoms. The severity of exercise that triggers symptoms and the frequency of symptoms are both highly variable. With the aim of fostering understanding and new therapeutic options, the present review outlined the genes and pathways involved, and the diagnostic techniques and treatment options available for syndromes such as McArdle disease, myoadenylate deaminase deficiency, carnitine palmitoyl transferase II deficiency and congenital myasthenia syndromes.

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