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ABSTRACT

Myopathy or muscle dysfunction is a group of disorders caused by numerous hereditary or acquired factors affecting structural or metabolic integrity of the muscle. Myopathies can be identified and categorized based on clinical features, laboratory, electrophysiological and biopsy findings with genetic testing. Extensive evaluation is imperative to identifying treatable and reversible causes for muscle weakness. This article reviews clinical features, testing and treatment for muscle disorders and provides a basic frame work for a clinical approach to myopathies.

Key Words: Myopathy, hereditary, muscle weakness

INTRODUCTION

The term myopathy refers to muscle dysfunction caused by numerous hereditary or acquired factors affecting structural or metabolic integrity of the muscle. Weakness can be the presenting feature for various central and peripheral nervous system disorders and can be localized to muscles based on specific clinical features, laboratory, electrophysiology and biopsy findings. Primary muscle disorders include acquired immune mediated myopathies, congenital myopathies caused by genetic defects in the contractile apparatus of muscle, muscular dystrophies caused by defects in muscle membrane or supporting proteins and metabolic myopathies caused by defects in mitochondrial, glycogen or lipid metabolism. Secondary muscle dysfunction can be a part of a generalized systemic disorder and toxic effects of drugs or chemicals.

CLINICAL FEATURES

A detailed clinical history and examination is the corner stone to make the correct diagnosis of a muscle disorder. Patients typically present with muscle weakness. Age of onset, distribution, additional symptoms, temporal evolution and triggers of weakness along with family history will help narrow down the diagnosis.

AGE OF ONSET

Infantile onset muscular disorders usually present with generalized hypotonia, feeding difficulties with or without respiratory weakness, facial and extraocular muscle weakness or delayed motor milestones. Nevertheless, the most common reason for infantile hypotonia is a disorder of the central nervous system. 1Neuromuscular disorders presenting in infancy include hereditary and metabolic neuropathies, spinal muscular atrophy, congenital or transient acquired myasthenic syndromes, congenital muscular dystrophy and congenital myopathies. Limb girdle muscular dystrophies (LGMD), metabolic myopathies and immune mediated myopathies like dermatomyositis can present from childhood to the adult age group, polymyositis mostly in adults and inclusion body myositis (IBM) in the elderly.

DISTRIBUTION OF WEAKNESS

The most common presentation of myopathy is with proximal symmetricusually painless muscle weakness. Patients can complain of difficulty standing up from sitting/squatting position and climbing stairs because of proximal lower extremity weakness, while proximal upper extremity weakness presents with difficulty with overhead activities for example combing hair, reaching for cupboards[2,3].

Rare myopathies present with distal extremity weakness manifesting in the hands as difficulty with opening jars or turning keys (e.gMyotonic Dystrophy Type 1, Welandar muscular dystrophy and in the legs with foot drop or difficulty with plantar flexion (e.g Miyoshi, Nonanka, Laing's distal myopathies)4,5. Weakness of facial, ocular and rarely of bulbar muscles can be seen in certain congenital and mitochondrial myopathies andoculopharyngeal muscular dystrophy(OPMD), while regional weakness is seen in disorders like fascioscapulohumeral muscular dystrophy6,7,8,9

(FSHD).

ADDITIONAL SYMPTOMS

Additional features include myalgias, fatigue, atrophy, cramps,myotonia, exercise intolerance, rhabdomyolysis and contractures. Myalgia, fatigue and cramps are non specific symptoms which can be seen in other non neurological disorders.If present in a myopathy, myalgia with muscle tenderness can be seen in inflammatoryand certain metabolic myopathies[2,10].

Muscular cramps with reversible muscle weakness, exercise intolerance and rarely rhabdomyolysis can be seen in metabolic myopathies due to defects in glycogen, lipid or mitochondrial metabolism11,12. Patients can sometimes present with recurrent episodes of rhabdomyolysis or extensive muscle breakdown, which if not treated properly with supportive care can lead to renal failure.

Atrophy of muscles can be seen in any disorder of the motor unit, affecting the anterior horn cell, motor nerves or muscle13. Pattern of atrophy or hypertrophy is important, for example prominent quadriceps and finger flexor atrophy is seen in IBM, scapular and forearm muscle atrophy with deltoid sparing in FSHD9and anterior or posterior tibial atrophy in distal myopathies5. Calf hypertrophyis prominent in Duchenne muscular dystrophy (DMD)LGMD 2 C-Fand infiltrative myopathies[14,15,16.]

Myotonia refers to the failure of a muscle to relax after forceful voluntary contraction. Clinically this can present with failure to open one's hand after a hand shake or clasping an object or in infants with difficulty in opening their eyes after crying. Clinical and/or diffuse electrophysiological myotonia is seen in myotonic dystrophy (Type 1 and 2)4 channelopathies17(myotoniacongenita, paramyotoniacongenita,hyperkalemic periodic paralysis) and some vacuolar myopathies.Early contractures are seen in certain congenital muscular dystrophies/myopathies(e.gEmery Dreifuss muscular dystrophy, Ulrich and Bethlem myopathy)[18].

TEMPORAL EVOLUTION

Temporal evolution of symptoms should be sought after. Immune mediated myopathies such as polymyositis and dermatomyositis tend to have an insidious onset with progressive weakness if untreated as opposed to inclusion body myositis and muscular dystrophies which manifests over years with weakness in a specific distribution. Symptoms can be monophasic versus episodic. Periodic paralysis, certain metabolic and mitochondrial myopathies can present with exercise or stress induced muscular symptoms.[19,20]

SYSTEMIC EVALUATION

All patients with a suspected myopathy should have a complete review of systems. An assessment of cardiac and respiratory function is important as these muscles can be commonly affected in muscular dystrophies and certain immune mediated, metabolic and mitochondrial myopathies. 21Systemic illness can result in signs and symptoms of muscle dysfunction21. Endocrinopathy, metabolic abnormalities, infection, critical illness, organ transplantation, autoimmune conditions, malignancy, medications (e.g statins, colchicine) and toxinexposure need to be considered[21,23].

FAMILY HISTORY

Patients with LGMDs and congenital myopathies can have affected family members. Mitochondrial myopathies can be maternally inherited or develop secondary to denovo mutations. A history of consanguineous marriage should make one consider an autosomal recessive disorder.

LABORATORY EVALUATION

BLOOD TESTS

Serum creatinine kinase (CK) is one of the most important tools in the diagnosis of a myopathy24. CK is elevated in most myopathies. It can be markedly elevated (up to 10 or 100 times the normal) in certain muscular dystrophies such as DMD and rhabdomyolysis. On the other hand it can be normal or even low in long standing muscle disorders due to muscle loss and fibrosis. Sustained elevation of CK levels in the setting of recent onset of muscle weakness is a good marker of primary muscle degradation.

Elevated CK levels should be interpreted with caution. Non myopathic causes such as motor neuron disease, spinal muscular atrophy, post polio syndrome and neuropathies can result in elevated CK levels. Non neurological factors can also affect CK levels such as race and sex of the patient, medications, trauma and endocrine disorders to name a few(24). A CK level should always be performed prior to electrophysiological testing as the needle electrode examination itself canresult in transient elevation in CK levels. Aldolase level, though frequently checked, is less

sensitive and more of a marker for chronic muscle degeneration.In addition to CK, serum electrolytes and thyroid function tests along with autoimmune serologies for immune mediated myopathies should be considered.

When a metabolic myopathy is under consideration; tiered blood testing should be performed including glucose, lactate, pyruvate, lactate dehydrogenase, uric acid, carnitine, ketones, ammonia, liver transaminases, creatinine and acylcarnitineswith urinary levels of myoglobin, ketones, organic/dicarboxylic acids, andacylglycines[11].

ELECTROPHYSIOLOGY

Nerve conduction studies (NCS) and electromyogram (EMG) protocols should be geared not only to aid in the diagnosis of a myopathy but also for the exclusion of other neuromuscular disorders such as motor neuron disease, neuromuscular junction disorders or neuropathyEMG can guide the physician as to which muscle to biopsy25. It is important to note that normal electrodiagnostic studies do not exclude the diagnosis of a myopathy and should be interpreted with the clinical picture and laboratory evaluation.

NCS is usually normal but in a long standing myopathy, may demonstrate diffuse reduction in amplitude of compound motor action potentials with normal sensory responses. EMG characteristically shows early recruitment of short duration, low amplitude, polyphasic motor units. More chronic myopathic processes like IBM can manifest with mixed large and small motor unit potentials26. The distribution of myopathic units on needle electrode examination can also add to the differential diagnosis, as in IBM where predominant electrophysiological changes may be seen in quadriceps and finger flexor muscles.Spontaneous discharges such as positive sharp waves and fibrillations are a marker of an underlying necrotizing myopathy while diffuse myotonia can be seen in vacuolar myopathies,myotonic dystrophies and channelopathies such as myotoniacongenita, paramyotoniacongenita and hyperkalemic periodic paralysis.When the latter threediagnoses are under consideration, more detailed short and long exercise testing should be performed[27].

ISCHEMIC FOREARM EXERCISE TEST

This test is useful in patients with exercise intolerance due to an underlying metabolic myopathy11. Baseline lactate, pyruvate and ammonia levels are measured from a line placed in anantecubital vein. A blood pressure cuff is inflated above the IV access followed by exercise of the hand with opening and closing of the fist. Post exercise levels of lactate, pyruvate and ammonia are measured. In a normal patient, the lactate and ammonia levels increase by three to four fold of normal. In disorders of glycogen metabolism there is no rise of lactate levels with normal rise in ammonia levels. In myoadenylatedeaminase deficiency, there is normal rise in lactate levels with no rise in ammonia levels.

MUSCLE BIOPSY

Histology, biochemical staining,immunostaining and electron microscopy of a muscle specimen can aid in the diagnosis of both acquired and hereditary myopathies, although for the latter, the availability of genetic testing may eliminate the need for a biopsy. The muscle to be biopsied should be chosen carefully as the weakest muscle may just show end stage changes not sufficient for a diagnosis while the strongest muscle may be normal.

Various myopathies have pathognomic findings on biopsy. Polymyositis manifests as diffuse inflammatory infiltrate with necrotic and regenerating fibers2,10. In dermatomyositis the classic finding is of perifascicular atrophy along with inflammatory infiltrate{{199 Amato,A.A. 1997; 184 Dalakas,M.C. 1991}}. IBM shows necrotic fibers, inflammatory infiltrate with characteristic basophilic rimmed vacuoles2,28. Primary inflammatory myopathies are differentiated from muscular dystrophies, which may also demonstrate significant inflammation, by the invasion of non necrotic fibers by inflammatory cells11,12. Metabolic storage diseases stain variably with enzyme staininge.g lipid storage diseases show muscle that is strongly Oil Red O positive while glycogen storage disorders have vacuoles which stain intensely with periodic acid Schiff (PAS) and acid phosphatase. Specific enzyme detection in fibroblasts or muscle tissue can help with the definitive diagnosis. Mitochondrial myopathies may show red rod like inclusions on Gomoritrichrome staining (ragged red fibers) or intense subsarcolemmal staining on succinate dehydrogenase (SDH) and Nicotinamide adenine dinucleotide dehydrogenase (NADH) staining (ragged blue fibers) with cyclooxygenase (COX) negative fibers. Staining with Congo red and Sulfated alcian blue can demonstrate amyloid deposition in muscle or bloovessels.

GENETIC TESTING

Although not widely available, genetic testing is an important tool to come to a definitive diagnosis, especially in our society where the prevalence of hereditary neuromuscular disorders is likely to be higher than the

western world due to the higher prevalence of consanguinity. In some cases, where the clinical suspicion is high, diag nostic genetic testing can be performed without the need for a muscle biopsy for example genetic testing for the dystrophin gene in DMD4. Disorders such as myotonic dystrophy, most LGMDs, 9FSHD, 8OPMD, congenital muscular dystrophies and certain congenitaland mitochondrial myopathies can be diagnosed with genetic testing.

TREATMENT

Treatable causes should be addressed which includes discontinuing offending drugs, toxins or treating systemic, metabolic and endocrine abnormalities.

Patients with immune mediated myopathies (except for IBM) usually respond to immunotherapy3,10,29. First line treatment should include high dose steroids, either an intravenous short course or oral steroids (1.5-2mg/kg/day) with a slow taper over months. Adjustments of medications should be made based on the clinical picture and not on the basis of CK levels or EMG changes. If patients symptoms return during steroid taper or if they are unable to tolerate high dose steroids, they may be candidates for steroid sparing agents such as azathioprone, methotrexate, myophenolatemofetil, cyclophosphamide, cyclosporine or tacrolimuskeeping in mind that all the latter agents can take up to several months to reach their full immunosuppressive benefit.

In patients with rapidly progressive weakness due to an inflammatory myopathy, who do not respond to or are unable to tolerate/take steroids, intravenous immunoglobulin can be administered along with starting a second line agent as in small clinical trials, patients with inflammatory myopathies have shown benefit with IVIG treatment. 29,30Response of immune myopathies to plasma exchange is controversial and should best be reserved as a last resort.

IBM is generally considered to be refractory to most known immunosuppressive and immunomodulating agents. The risks and costs of treatment without evidence of clear benefit should be taken in to consideration when evaluating patients with IBM for treatment.

Treatment of muscular dystrophies is largely supportive32-34. Patients with DMD show some improvement in function and delay in disease progression with steroids. A dose of 0.75mg/kg/d has been shown to be most beneficial.Creatine monohydrate (5-10g/d)has shown some benefit in muscular; however management in the latter group remains largely supportive with physical therapy, appropriate orthotics and walking aids35. Cardiac and respiratory monitoring is crucial, as the incidence of cardiac involvement is increasing due to better survival secondary to advances in treatment of the underlying muscle disorder. Remarkable advancement has been made in the field of gene therapy for muscular dystrophies and hopefully can be offered to patients in the near future[36].

Of the metabolic myopathies, extensive research is underway for enzyme replacement therapies.Acid maltase deficiency (Pompe's disease) is a good example of a successful response to enzyme replacement37. Patients with metabolic myopathies need adjustment of their dietary intake depending on the underlying enzyme deficiency7,38. For mitochondrial myopathies; there is conflicting evidence for benefit with creatine, Co-enzyme Q or vitamin E supplementation. Exercise training shows improvement in enhancing the oxidative capacity in mitochondrial disorders while not showing clear benefit in other muscular disorders.At times patients can only be offered symptomatic management. Patients with prominent muscle cramps may benefit from treatment with quinine sulfate; however this is no longer a FDA approved indication due to potential toxicity. Other medications for muscular cramps include Vitamin B complex, Naftidrofuryl, and calcium channel blockerswith off label use of gabapentin, phenytoin, carbamezapine, magnesium, calcium and botulinum toxin. Myotonia in myotonic dystrophies and periodic paralysis can be treated with drugs like mexilitine, phenytoin and carbamazepine[37,40].

CONCLUSION

Myopathies can be diagnosed appropriately with accurate clinical history and physical examination, laboratory investigations, electrophysiological testing and muscle biopsy geared not only to diagnose primary muscle disorders but to exclude central nervous system, anterior horn cell, peripheral nerve, neuromuscular junction disorders and other systemic diseases. The aim is to correctly identify treatable causes of muscle dysfunction as these are reversible with appropriate treatment.

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