Amyloid myopathy
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Introduction

This article includes discussion of amyloid myopathy and muscle disease. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Symptoms of primary systemic amyloidosis include neuropathy, myopathy, and cardiac or renal insufficiency; multiple organ systems are often involved. Amyloidosis can involve both the central nervous system and peripheral nerves. Amyloid myopathy is a rare manifestation of primary systemic amyloidosis. It is less well recognized that amyloid can directly infiltrate and weaken skeletal muscle. Like most other myopathies associated with systemic disorders, it is manifest by proximal limb muscle weakness and increased serum levels of creatine kinase.

Key points

- Amyloid myopathy is one of the uncommon manifestations of systemic amyloidosis.
- The symptoms are usually nonspecific, typically including progressive proximal limb weakness with an increased creatine kinase level, macroglossia, and muscle pseudohypertrophy.
- The diagnosis of amyloid myopathy is usually overlooked, and it is often misdiagnosed as inflammatory myopathy, even when a muscle biopsy is available.
- Amyloid myopathy associated with a plasma cell dyscrasia is a rare cause of muscle hypertrophy. It can be a challenging diagnosis because pathological findings are often elusive.
- When suspecting amyloid myopathy, Congo red staining and either an immunohistochemical assay or immunofluorescence study should be performed.
- Amyloid myopathy should be a consideration in adults with progressive neuromuscular weakness of uncertain cause.
- Recognition of amyloid myopathy is important because clinical symptoms may respond to melphalan and prednisone therapy

Historical note and terminology

The first recognized patient with amyloid-associated muscle involvement was reported by Lubarsch in 1929; both vascular and interstitial deposits were seen in skeletal muscle and heart (Lubarsch 1929). It has now been reported in 3 of the largest series that myopathy is rarely caused by amyloidosis (Gertz and Kyle 1996; Prayson 1998; Spuler et al 1998). Classification of the amyloidosis is based in part on the chemistry of the amyloid fibrils. Amyloidosis accompanying plasma cell dyscrasia is characterized by fibrils containing a component of immunoglobulin light chains. The oval masses may contribute to the muscular hypertrophy and to the formation of nodules within the muscles. These nodules may also contribute to muscle weakness by compression of nearby muscle fibers (Cohen and Rubinow 1984).

Clinical manifestations

Presentation and course

Symptoms of systemic amyloidosis include neuropathy, myopathy, and cardiac or renal insufficiency; there is often multiple-organ involvement. Myopathy is a rare clinical manifestation in primary systemic amyloidosis (Metzler et al 1992; Kyriakides et al 2002). Proximal weakness, muscle stiffness, pseudohypertrophy, and myalgia constitute the principal features.

The initial manifestation may predominantly consist of proximal muscle weakness. Other features due to amyloid
deposition at different sites may develop later (Gertz and Kyle 1996). Pseudohypertrophy, nodular lesions of muscles, and macroglossia are often lacking. This syndrome usually develops in cases with well-recognized generalized amyloidosis (Roke et al 1988).

The mean onset age of amyloid myopathy is 60 years. Ninety percent of patients report proximal weakness. This may be associated with macroglossia and muscle pseudohypertrophy in almost a third of the patients. Macroglossia sometimes precludes closure of the mouth; dysphagia and hoarseness may also occur. Dysphagia is present in 25% of patients (Prayson 1998; Rubin and Hermann 1999; Chapin et al 2005). The clinical importance of macroglossia in a patient with dyspnea and cardiomyopathy is highlighted in a recent case report (Ghosh et al 2013).

The most prominent findings are abnormal firmness and pseudohypertrophy of the musculature and palpable tumors within muscles (Martin et al 1970; Whitaker et al 1977; Ringel and Claman 1982). Muscle weakness caused by amyloid myopathy has also been described in the absence of pseudohypertrophy. The clinical picture then comprises proximal limb weakness with pronounced atrophy. As expected, with any proximal muscle weakness, patients have difficulty raising the arms overhead or climbing stairs (Jennekens and Wokke 1987). Weakness of the neck flexors as well as shoulder and thigh muscles with atrophy is also common (Lange 1970; Whitaker et al 1977; Ringel and Claman 1982).

Muscle claudication is rare but has been recognized in patients with amyloid myopathy. It results from progressive vascular deposition of amyloid and leads to ischemia and obstruction of small vessels. These patients have been misdiagnosed as having giant cell arteritis and inappropriately treated with high dose corticosteroids (Whitaker et al 1977; Schneider et al 1993).

The presence of amyloid myopathy with myeloma and lytic bone disease has been recognized. Santos and colleagues reported a patient with amyloid myopathy associated with multiple myeloma who showed clinical characteristics of pseudomyopathy (Santos et al 2011). Amyloid myopathy involving the diaphragm and resulting in diaphragmatic failure requiring ventilatory support is also well recognized (Streiten et al 1986; Santiago et al 1987; Ashe et al 1992). Amyloidosis may cause adult-onset sensorimotor peripheral neuropathy. Unlike neuropathy secondary to amyloid deposition, myopathy is infrequently described (Trotter et al 1977).

Amyloid myopathy is frequently misdiagnosed as an inflammatory myopathy, especially polymyositis because of similarities in clinical, neurophysiological, and muscle biopsy findings. Both can show similar inflammatory infiltrates on muscle biopsy, especially when only the hematoxylin-eosin stain is used (Mandl et al 2000; Hull et al 2001; Karacostas et al 2005; Das et al 2010). Spuler and colleagues found that routine use of Congo red-stained sections increased the frequency of a diagnosis of amyloid myopathy almost 10-fold.

Failure to recognize amyloid myopathy precludes patients of potentially life-prolonging treatment. Congo red staining and immunohistochemical analysis of tissue could prevent misdiagnosis (Mandl et al 2000). In middle-aged or elderly patients with proximal limb weakness, the diagnosis of amyloid myopathy should be considered (Jennekens and Wokke 1987).

**Prognosis and complications**

Likelihood of survival with this disease remains poor, with a median survival rate of 1 to 2 years. Congestive heart failure and nephrotic syndrome are predominant causes of death. Without early therapy, however, the disease has a dismal prognosis (Kelly 2006). A recently published case report from Ohtsuka and colleagues emphasized the fact that when amyloidosis is suspected and there is evidence of muscle injury, a muscle biopsy should be performed (Ohtsuka et al 2012).

**Clinical vignette**

A 71-year-old woman with a history of primary systemic amyloidosis noted worsening fatigue, claudication, and weakness in her legs more than arms and hands over the past 2 years. Neurologic examination revealed symmetrical proximal limb weakness in lower and upper extremities with preserved tendon reflexes. Examination showed no other abnormalities. EMG study revealed myopathic findings and CK values were borderline elevated. Bone marrow biopsy revealed an IgG kappa monoclonal gammopathy. MRI of the thighs revealed increased T2 signal of subcutaneous fat and tissue between muscle groups with only minimal signal intensity alteration of muscle. Muscle biopsy revealed characteristic apple-green birefringent amyloid deposits surrounding individual muscle fibers in Congo red stained sections. Electron microscopy demonstrated amyloid filaments in close apposition to muscle fibers exhibiting
excessive corrugations of the sarcolemmal membrane. Treatment included prednisone 60 mg daily and cyclophosphamide 150 mg daily with improvement of symptoms.

**Biological basis**

**Etiology and pathogenesis**

Plasma cell dyscrasia or multiple myeloma is associated with amyloid myopathy in the majority of the patients (Fisher and Thomson 1958; Lange 1974; Bruni et al 1977; Dalakas and Cunningham 1986). The mechanisms by which the amyloid deposits weaken the skeletal muscles remain unclear.

The clinical phenotype and muscle histology are well known, but the pathophysiological mechanisms remain poorly understood. Amyloid denotes a waxy, amorphous, and eosinophilic material. Amyloidosis can involve multiple organs, including kidney, heart, skin, joints, peripheral nerve, and skeletal muscle. The most common form of amyloidosis in the United States is termed "light chain amyloidosis," which results from deposition of monoclonal antibody light chains. Of the 3 types of systemic amyloidosis, primary systemic amyloidosis is the type that most often involves skeletal muscle. Amyloid is generally not deposited in muscle in the secondary type (amyloid A protein) and can occasionally be seen in transthyretin (familial) forms of amyloidosis (Kyle and Gertz 1990).

Amyloid is mostly deposited in connective tissue; that is, around the basal lamina of blood vessels, in nodules, or between parenchymal cells. This distribution is seen in nerve, skeletal muscle, and heart muscle (Cohen and Rubinow 1984; Smith and Kyle 1984; Roke et al 1988). The skeletal muscle is also infiltrated as a rule in patients with amyloid polyneuropathy (Engel and Banker 1986). The deposits arise without obvious cause or from monoclonal serum proteins in a plasma cell dyscrasia. The cause of organ damage or skeletal muscle dysfunction in amyloidosis is unclear but is most likely due to the direct toxic effects of amyloid. Other hypotheses include mechanical interference of muscle function by amyloid, ischemic atrophy of muscle caused by accumulation of amyloid in vessels, or amyloid accumulating within or on the sarcolemmal membrane and interfering with electrical conduction along the muscle fiber (Doriguzzi et al 1987; Kelly 2006).

Amyloid deposition has been recognized histopathologically as causing compression atrophy of muscle fibers and ischemic atrophy owing to extreme narrowing of capillaries when muscle pseudohypertrophy is not present (Roke et al 1988). One of the possible pathophysiological mechanisms in amyloid myopathy is mechanical disruption of the sarcolemma by the abutting amyloid fibrils (Kyriakides et al 2002).

The pathological features of progressive amyloid myopathy associated with primary systemic amyloidosis are distinct from the intracellular amyloid deposits characteristic of sporadic inclusion body myositis and inherited inclusion body myopathy (Nadkarni et al 1995). Inclusion body myositis is an inflammatory myopathy characterized pathologically by rimmed vacuoles and the accumulation of amyloid-related proteins (Inamori et al 2012). The frequency of the diagnosis of amyloid myopathy increased 10-fold with the use of fluorescent Congo red stain as a routine procedure in assessing muscle biopsy specimens (Spuler et al 1998). Congo red-stained sections revealed infiltration of blood-vessel walls and endomysium with amyloid protein as well as an unusual pattern of pathologic changes to muscle fibers. Congo red-stained sections of muscle biopsy viewed under fluorescent or polarized optics, and serum or urine protein immunoelectrophoresis, play an important role in the evaluation of myopathy (Chapin et al 2005).

**Prevention**

No clear literature on prevention exists, but early diagnosis is essential for further management.

**Differential diagnosis**

Differential diagnosis for an adult presenting with acquired proximal muscle weakness is broad and includes inflammatory myopathies, drug- and toxin-induced myopathies, infectious myopathies, endocrine myopathies, muscular dystrophies, anterior horn cell disease (progressive muscular atrophy), and the Lambert-Eaton myasthenic syndrome (Chawla 2011).

Differential difficulties exist in diagnosing the disorder, and familial amyloid polyneuropathy directly mimics the disease. Clinically, pseudohypertrophy is easy to recognize, and the differential diagnosis is narrow. The atrophic form of amyloidosis is much harder to recognize as such, and these patients should proceed directly to muscle biopsy for...
confirmation of a diagnosis because amyloidosis is often omitted from the differential diagnosis.

Amyloid myopathy should be included in the differential diagnosis when proximal limb muscle weakness without pseudohypertrophy develops in middle-aged or elderly patients. In such cases, a search for plasma cell dyscrasias should be made (Kelly 2006).

**Diagnostic workup**

Diagnostic tools include analysis of serum and urine, electromyography, imaging, and histological investigation of appropriate tissue.

A monoclonal protein is often found by immunoelectrophoresis of serum and urine. An important clue to the recognition of this disease, particularly when pseudohypertrophy is not present, is the demonstration of a monoclonal gammopathy in serum or urine. Immunoelectrophoresis or immunofixation should be considered mandatory in the evaluation of a patient with a myopathy. Immunoelectrophoresis of serum and urine should be a routine diagnostic test during the evaluation of myopathy of unknown cause.

Skeletal amyloidosis has been evaluated by CT, MRI, technetium-99m methylene diphosphonate, and technetium 99m-pyrophosphate (Jennekens and Wokke 1987; Urban et al 1993; Worsley and Lentle 1993). The MR appearance of amyloid myopathy differs from that of other neuromuscular conditions in the minimal changes found in muscle. The MRI in amyloid myopathy has the striking abnormality with marked reticulation of the subcutaneous fat (Metzler et al 1992). Unique findings on the MRI can alert the clinician to the diagnosis of amyloidosis prior to the muscle biopsy (Hull et al 2001). Quantitative turnover studies can measure the total body burden of amyloid and can show whether amyloid deposits are being mobilized after chemotherapy (Hawkins 1994).

The utility of MRI has significantly increased to target affected muscles for biopsy as well as to assess disease activity (Metzler et al 1992). It has been hypothesized that the high calcium content of amyloid deposits that binds the serum amyloid P component also binds the radionuclide. Scintigraphic studies with radiiodinated serum amyloid P component have been used to evaluate amyloid deposits in vivo. The use of MRI for the evaluation of inflammatory myopathies and neuromuscular disorders has become increasingly common, especially in cases of polymyositis (Adams et al 1995; Hull et al 2001; Mercuri et al 2007).

None of the procedures are diagnostic, and biopsy is still required to confirm the diagnosis. Invasive techniques can be less or more invasive based on the type used. Less invasive techniques include rectal biopsy or subcutaneous fat aspirate. Muscle biopsy is essential in the diagnostic evaluation of possible polymyositis because metabolic abnormalities, muscular dystrophies, drug-induced changes, inclusion-body myopathy, dermatomyositis, and amyloid myopathies can be overlooked.

In one of the series, the prevalence rate of amyloid myopathy in muscle biopsy specimens was low. Most of the muscles showed neurogenic features histologically. All concomitant sural nerve biopsy specimens contained amyloid, and most showed a predominance of axonopathic changes. When suspecting amyloid myopathy, Congo red staining and an immunohistochemistry or immunofluorescence assay should be performed. In middle-aged patients with progressive myopathy or muscle pain of unclear cause, amyloid should be considered with muscle biopsy as the definite test (Adams et al 1995; Prayson 1998; Mercuri et al 2007).

Acquired and hereditary amyloidosis can be definitively distinguished from one another only by immunohistochemical staining or molecular genetic testing (Simmons and Specht 2010).

**Management**

The recognition of amyloid myopathy is important because clinical symptoms may respond to chemotherapy (Smestad et al 2004). Manoli and colleagues recently highlighted the importance of early diagnosis and therapy for this treatable cause of a chronic myopathy with muscle hypertrophy (Manoli et al 2013). Amyloid myopathy may be responsive to chemotherapy with melphalan and prednisone (Sheehan-Dare and Simmons 1987). Given the poor prognosis associated with this disorder, it seems that a trial of chemotherapy would be reasonable in all patients. Melphalan and prednisone treatment for at least 1 year has resulted in increased survival rates. There have also been reports of benefit from high-dose chemotherapy followed by peripheral blood stem cell transplantation (Scola et al 2001).
Special considerations

Pregnancy

Pregnancy is not a major concern as amyloid myopathy primarily affects the middle-aged population.

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**References especially recommended by the author or editor for general reading.**

**ICD and OMIM codes**

**ICD codes**

**ICD-9:**
- Muscle disease or syndrome: 359.9
- Symptomatic inflammatory myopathy in diseases classified elsewhere: 359.6
- Other inflammatory and immune myopathies: 359.79
- Amyloidosis, unspecified: 277.30
- Muscle weakness, generalized: 728.87

**ICD-10:**
- Myopathy, unspecified: G72.9
- Myopathy in diseases classified elsewhere: G73.7
- Other inflammatory and immune myopathies, not elsewhere classified: G72.49
- Amyloidosis, unspecified: E85.9
- Muscle weakness (generalized): M62.81

**OMIM numbers**

Amyloidosis, hereditary, transthyretin-related: #105210

**Profile**

**Age range of presentation**

45-64 years

65+ years

**Sex preponderance**

male>female, >4:1

**Family history**

family history may be obtained

**Heredity**
heredity may be a factor for familial amyloidosis related disorders

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

endocrine myopathies
inflammatory myopathies
paraneoplastic myopathy
infectious myopathies
drug- and toxin-induced myopathies
muscular dystrophies
anterior horn cell disease (progressive muscular atrophy)
Lambert-Eaton myasthenic syndrome
familial amyloid polyneuropathy
critical illness myopathy
metabolic and myopathies with other systemic disorders

**Associated disorders**

Peripheral neuropathy
Systemic amyloidosis

**Other topics to consider**

Dermatomyositis
Distal myopathies
Inclusion-body myositis
Neuromuscular pathology: overview
Primary systemic amyloidosis: neurologic complications