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Mini Review

Transthyretin Amyloid Myopathy: A Diagnostic Approach

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Abstract

This review will focus on clinical findings, diagnostic approaches and treatment strategies of transthyretin (ATTR) amyloid myopathy (AM). Cardiomyopathy and peripheral neuropathy are well-recognised manifestations of ATTR amyloidosis and may be accompanied by musculoskeletal pathologies. Amyloid deposition in the skeletal musculature results in AM. As ATTR AM may precede the onset of cardiomyopathy or peripheral neuropathy by several years, increasing the awareness of its presence is crucial. This is not least because disease-modifying therapies for ATTR amyloidosis are most effective when started early in the disease course. ATTR amyloid deposition in the skeletal musculature is common. Key manifestation is the symmetric proximal weakness of upper and lower extremities. Inconclusive laboratory and neurophysiological features often lead to misdiagnosis. 99mTc-DPD scintigraphy allows non-invasive diagnosis. AM can precede other organ manifestations and allows early diagnosis and therapy initiation. Physicians should consider ATTR AM as an important red flag.

ABBREVIATIONS

99mTc-DPD: 99mTc-labelled-3,3-diphospono-1,2-propanodicarboxylic acid; 99mTc-PYP: 99mTc-labelled-pyro phosphate; AM: Amyloid Myopathy; ATTR: transthyretin; ATTRv: ATTR variant amyloidosis; ATTRwt: wild-type ATTR amyloidosis; EMG: electromyography; CK: creatine kinase

INTRODUCTION

Transthyretin (ATTR) amyloidosis is a fatal and progressive multisystemic disease, which may either be inherited (ATTR variant amyloidosis, ATTRv) or acquired (wild-type ATTR amyloidosis, ATTRwt) [1]. It is caused by the extracellular deposition of ATTR-derived amyloid fibrils in various organs, including the heart, nervous system, gastrointestinal tract, and musculoskeletal soft tissues [2]. Organ manifestation, onset of symptoms and disease severity can vary between ATTRwt and ATTRv. Cardiomyopathy and peripheral neuropathy are the cardinal manifestations of ATTRwt and ATTRv, and are frequently accompanied by musculoskeletal pathologies, such as carpal tunnel syndrome, spinal cord stenosis and myopathy [2]. In ATTRv, organ involvement differs depending on the underlying mutation, ranging from exclusive peripheral neuropathy to predominant cardiac involvement to mixed phenotypes [3]. ATTRwt mostly presents with cardiomyopathy in the elderly, although musculoskeletal manifestations are common and can precede the cardiomyopathy by several years [2,4]. ATTR amyloidosis is associated with poor prognosis and limited quality of life [5]. Novel pharmacologic developments have resulted in a decrease in morbidity and mortality [6-8]. As available disease-modifying therapies are most effective when employed early in the disease course, prompt and specific diagnosis is crucial [9-11].

ATTR amyloid myopathy (AM) refers to interstitial amyloid deposits in the skeletal musculature. Although the exact pathogenic mechanism is not yet known, causative ischemia, mechanical pressure, interference with electrical conduction of the muscle fibres, and toxicity to muscle fibres are assumed [12-15]. Previously considered a rare and insignificant clinical finding, Hutt et al. [16] reported on the presence of AM in more than 90 % of patients with ATTR cardiac amyloidosis. ATTR AM is still underrecognised in routine clinical practice. This is partly because symptoms are non-specific and may be attributed to peripheral neuropathy. As ATTR AM may precede the onset of cardiomyopathy or peripheral neuropathy by several years, increasing the awareness of its presence is crucial. This review will focus on clinical findings, diagnostic approaches and treatment strategies of ATTR AM. For this purpose, a literature search was conducted to identify studies on ATTR AM. Literature consisted of clinical case reports, case series and research articles.

When to Suspect Amyloid Myopathy?

Diagnosis of ATTR AM starts with the awareness of the disease entity. Myopathic symptoms are often difficult to distinguish from peripheral neuropathy [17]. Deceptively, coexistence of peripheral neuropathy is frequent and is found in nearly 90 % of patients [4].

AM can be the initial manifestation of ATTRwt, even before cardiac or neurological symptoms become apparent [4,17]. If AM is the initial symptom of ATTR amyloidosis, diagnosis might be delayed substantially. In contrast, peripheral neuropathy or cardiomyopathy usually precede the initial manifestation of AM in ATTRv [4,12,17-21]. Interestingly, AM may also occur after liver transplantation or heart transplantation in ATTRv, respectively [4,17].

AM is frequently associated with symmetric proximal weakness of the upper and lower extremities [2]. Besides, myalgia, amyotrophy, pseudo-muscular hypertrophy, muscle claudication, muscle contracture and fatigue can be present [22].

Laboratory and Neurophysiological Features

Myopathies in general are usually associated with elevated creatine kinase (CK) levels. In contrast, ATTR AM is characterised by normal or only slightly elevated CK levels [4,17]. Normal CK levels can be found in about two thirds of these patients [23]. However, CK levels may be elevated independently of the presence of AM, indicating cardiac involvement. In this context, a previous study [4] reported on five myopathy patients with elevated CK levels having coexisting cardiomyopathy.

Myopathic changes in electromyography (EMG) comprise short-duration, low-amplitude motor unit potentials without fibrillation potentials or myotonic discharges [2,4]. In general, changes in EMG are often not very pronounced.

The absence of CK elevation and significant EMG abnormalities is due to primarily interstitial amyloid localisation. In contrast, muscle fibre necrosis and/or muscle fibre alterations, causing changes in CK levels and EMG, are rarely present [17].

Confirming the Presence of Amyloid Myopathy

In general, the definite diagnosis of AM is based on histological confirmation by muscular biopsy [2,4]. Amyloid deposition may be seen in the perivascular region and further in the perimysium and endomysium on Congo red-stained sections [2,4,17,19]. Subsequent amyloid subtyping is obligatory and is either performed by immunohistochemistry or by mass spectrometry [3].

It should be noted that amyloid deposits may be easily overlooked in hematoxylin and eosin-staining, highlighting the need for additional Congo red-staining. In a previous study [24], it was shown that routine Congo red-staining of muscular biopsies, obtained from patients with non-specific myopathies, showed ten times higher detection of AM compared to when this was only done in suspected cases.

Hutt et al. [16] clearly demonstrated extensive uptake of 99mTc-labelled-3,3-diphospono-1,2-propanodicarboxylic acid (99mTc-DPD) in the skeletal musculature, indicating AM. This was most pronounced in ATTRwt and ATTR-Val122Ile. Similarly, in individual cases of ATTR amyloidosis (ATTRwt, ATTR-Val40Ile, ATTR-Val122Ile) 99mTc-DPD uptake in the skeletal musculature was confirmed histologically as ATTR AM [17,19].

In a retrospective analysis including 57 patients with ATTR cardiac amyloidosis, Sperry et al. [25] investigated the skeletal muscle uptake of 99mTc-labelled-pyrophosphate (99mTc-PYP). It was noted that skeletal muscle uptake of 99mTc-PYP was minimal when assessed by qualitative and quantitative metrics. The study group concluded that the properties of 99mTc-PYP may be different from 99mTc-DPD in terms of non-cardiac uptake and that 99mTc-PYP cannot be used to image extracardiac ATTR deposition.

On the contrary, a recent study [26] outlined increased 99mTc-PYP uptake in deltoid muscles of ATTR patients (n=11) when compared to non-ATTR patients (n=14), indicative of an underlying ATTR AM. Nevertheless, the authors advise caution in drawing premature conclusions due to several limitations, including the small sample size, the lack of data on 99mTc-PYP uptake in the lower extremities and the absence of a systematic histological confirmation.

Based on the encouraging results published by Hutt et al. [16], we propose to first consider a non-invasive diagnosis of AM using 99mTc-DPD scintigraphy. However, in the case of compelling tissue-derived diagnosis – i.e. evidence of monoclonal protein and/or grade < 2 cardiac uptake on planar scintigraphy – muscular biopsy can be considered as an alternative compared to the gold standard method, endomyocardial biopsy [27].

TREATMENT

To date, no specific therapies are available for the treatment of AM. Yet, the general principles of treatment are independent of the particular organ manifestation: 1) reduce the amount of the amyloid precursor protein, 2) increase the amyloid clearance, 3) supportive therapy.

Approved medication for ATTR neuropathy and/or cardiomyopathy comprises two ATTR gene silencers and one ATTR tetramer stabiliser [6-8]. In a previous case report [17] we reported on the efficacy of the antisense oligonucleotide inotersen in an ATTRv patient developing AM after heart transplantation. The patient showed thereafter clinical relieve of muscular complaints. Whether this pharmacologic success also applies to other patients with symptomatic ATTR AM remains to be seen.

DISCUSSION

ATTR AM is still underrecognised. This is mainly due to non-specific symptoms, which often resemble symptoms of peripheral neuropathy, inconclusive laboratory and neurophysiological features, and a general lack of awareness for this organ manifestation. There is no consensus on treatment strategies, and whether AM impacts on prognosis.

However, AM can precede other organ manifestations and thus allows early diagnosis and therapy initiation, which has a favourable effect on the course of the disease [4,17]. 99mTc-DPD scintigraphy appears to allow non-invasive diagnosis of ATTR

AM and is widely available, low-risk, cost-effective and highly amyloid-specific [16].

CONCLUSION

ATTR AM is an important red flag of which physicians need to be keenly aware in order to catch patients at an early stage of the disease.

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