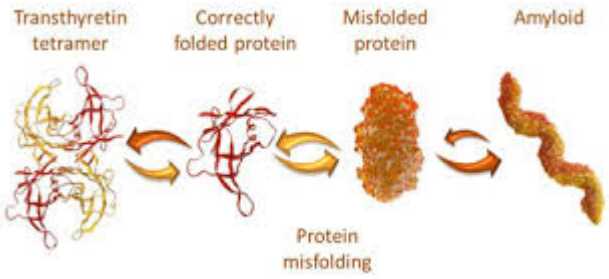
Transthyretin amyloidosis



Systemic amyloidosis is a diseased condition where misfolded proteins deposit in various organs in the form of amyloids, and transthyretin deposition, termed ATTR amyloidosis, can be either an age-related amyloid formation from misfolded wild-type TTR (ATTRwt) or by hereditary TTR malfunction due to mutation in the TTR gene (ATTRv). Although ATTRwt amyloidosis can cause various diseases, such as cardiac failure, conduction disturbances, arrhythmias and carpal tunnel syndrome, it is still under-recognised considering its clinical significance.

Hereditary transthyretin amyloidosis (ATTR) is usually characterised by a progressive peripheral and autonomic neuropathy often with associated cardiac failure and is due to dominantly inherited transthyretin mutations causing accelerated amyloid deposition. The UK population is unique in that the majority of patients have the T60A missense mutation in ATTR where tyrosine is replaced by adenine at position 60. This has been traced to a single founder mutation from north-west Ireland [1)].

An accurate and timely diagnosis of amyloid neuropathy can greatly impact on the outcomes for patients, especially as there will soon be new gene-silencing treatments for hereditary transthyretin amyloidosis [2)].

Results raise the possibility of a diagnostic role for MIBG scintigraphy at an early stage of cardiac involvement in TTR-mutated carriers, in addition to its well-established prognostic value [3)].

Case series

Godara et al. investigated consecutive patients undergoing surgery for spinal stenosis (SS) for ATTR deposition in the resected ligamentum flavum (LF) and concomitant risk of cardiac amyloidosis. Each surgical specimen (LF) was stained with Congo red, and if positive, the amyloid deposits were typed by mass spectrometry. Patients with positive specimens underwent standard of care evaluation with fat pad aspirates, serum and urine protein electrophoresis with immunofixation, free light-chain assay, TTR gene sequencing and technetium 99 m-pyrophosphate-scintigraphy. In 2018-2019, 324 patients underwent surgery for SS and 43 patients (13%) had ATTR in the LF with wild-type TTR gene sequences. Two cases of ATTRwt cardiac amyloidosis were diagnosed and received treatment. In this large series, ATTRwt was identified in 13% of the patients undergoing laminectomy for SS. Patients with amyloid in the ligamentum flavum were older and had a higher prevalence of CTS, suggesting a systemic form of ATTR amyloidosis involving connective tissue. Further prospective study of patients with SS at risk for systemic amyloidosis is warranted [4)].

Carr et al. presented the findings from an observational cohort study of patients with ATTR attending the National Hospital Inherited Neuropathy Clinic between 2009 and 2013. Detailed clinical neurological and electrophysiological data were collected on all patients alongside correlating autonomic and cardiac assessments. Follow-up data were available on a subset.

Forty-four patients with genetically confirmed ATTR were assessed; 37 were symptomatic; mean age at onset=62 years, range=38-75 years; 75.7% male. T60A was the most common mutation (17/37), followed by V30M (5/37). A severe, rapidly progressive, predominantly length dependent axonal sensorimotor neuropathy was the predominant phenotype. T60A patients were distinguished by earlier and more frequent association with carpal tunnel syndrome; a predominance of negative sensory symptoms at onset; significant vibration deficits; and a non-length dependent progression of motor deficit. Progression of the neuropathy was observed over a relatively short follow-up period (2 years) in 20 patients with evidence of clinically measurable annual change in Medical Research Council (MRC) sum score (-1.5 points per year) and Charcot Marie Tooth Neuropathy Score (CMTNS:2.7 points per year), and a congruent trend in the electrophysiological measures used.

The description of the ATTR neuropathy phenotype, especially in the T60A patients, should aid early diagnosis as well as contribute to the understanding of its natural history [5)].

Case reports

Ozaki et al. reported a case of Transthyretin amyloidosis leading to carotid artery stenosis requiring surgical intervention. The current report is the first that described histopathological evidence of amyloid deposition in the carotid artery due to ATTRwt amyloidosis [6)].

Carret al., described a patient with genetically confirmed Transthyretin amyloidosis (ATTR), a family history of the disease and histological confirmation following carpal tunnel release surgery but no other manifestations. The first major neurological or systemic manifestation was cauda equina syndrome with ATTR deposits contributing to lumbar spinal stenosis. Recent gene therapy trials showed improvement in the neuropathy in TTR amyloidosis. This case highlights the need for awareness of the heterogeneous neurological phenotype seen in ATTR to aid earlier diagnosis especially now that disease modifying therapies are available [7)].

Patel et al., reported a case of transthyretin amyloidosis with myopathy, neuropathy, and cardiomyopathy resulting from an exceedingly rare mutation transthyretin Ala120Ser (c.418G > T, p.Ala140Ser) [8)].

Oculoleptomeningeal amyloidosis (OLMA) represents a rare subtype of familial transthyretin (TTR) amyloidosis, characterized by deposition of amyloid in cranial and spinal leptomeninges along with ocular involvement. Of >100 TTR mutations identified, few have been associated with OLMA. Herein we describe the first report of leptomeningeal amyloidosis associated with the c.381T>G

(p.Ile127Met) TTR mutation, linking this variant to the OLMA phenotype. CASE DESCRIPTION:

A 53 year-old man presented with a 2-year history of progressive symptoms including upper and lower limb weakness, ataxia, and peripheral and autonomic neuropathy. Neuroimaging, including gadolinium-enhanced magnetic resonance imaging of the brain and spinal axis, identified diffuse leptomeningeal enhancement along the brainstem and spinal cord plus evidence of hemosiderosis. Pathologic and genetic analyses of biopsy material from enhancing intradural extramedullary tissue at the thoracolumbar junction was diagnostic of amyloidosis of a transthyretin type secondary to a TTR c.381T>G (p.Ile127Met) mutation.

OLMA represents a rare subtype of heritable transthyretin amyloidosis that may present with progressive neurological decline secondary to central nervous system leptomeningeal amyloid deposition. This case identifies the c.381T>G (p.Ile127Met) TTR mutation variant as being implicated in the OLMA phenotype [9].

Cervicomedullary compression as the main manifestation of wild-type transthyretin amyloidosis [10].

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present an unusual case of V122I amyloidosis with features of amyloid neuropathy and myopathy, supported by histological confirmation in both sites and diffuse tracer uptake on (99m)Tc-3,3-Diphosphono-1,2-Propanodicarboxylic acid (DPD) scintigraphy throughout skeletal and cardiac muscle. A 64 year old Jamaican man presented with cardiac failure. Cardiac MR revealed infiltrative cardiomyopathy; abdominal fat aspirate confirmed the presence of amyloid, and he was homozygous for the V122I variant of transthyretin. He also described general weakness and EMG demonstrated myopathic features. Sural nerve and vastus lateralis biopsy showed TTR amyloid. The patient is being treated with diflunisal, an oral TTR stabilising agent. Symptomatic myopathy and neuropathy with confirmation of tissue amyloid deposition has not previously been described. Extracardiac amyloidosis has implications for diagnosis and treatment [11]

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