Diagnosis of Amyloid Neuropathy

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Abstract
Systemic amyloidosis can be hereditary or acquired. The autosomal dominant, hereditary transthyretin amyloidosis and the acquired light-chain amyloidosis, the result of a plasma cell dyscrasia, are multi-system disorders with cardiovascular, autonomic and peripheral nerve involvement. There are numerous investigational modalities available to diagnose systemic amyloidosis and extent of organ involvement, but it is a frequently misdiagnosed condition due to heterogeneous clinical presentations, and misleading investigation findings. An accurate and timely diagnosis of amyloid neuropathy can greatly impact outcomes for patients, especially with the imminent availability of new, gene silencing treatments for hereditary transthyretin amyloidosis.

INTRODUCTION

The amyloidoses are a rare group of diseases that result from extracellular deposition of amyloidogenic proteins (Table 1).

Form of amyloidosis	Acquired or hereditary	Underlying diagnosis	Precursor protein	Organ Involvement								Treatment
				Peripheral Nervous System	Autonomic Nervous System	Heart	Kidney	Liver	GIT	Eyes	Tongue	
AL	Acquired	Plasma cell dyscrasia	Monoclonal immunoglobulin light chain	++	++	+++	+++	++	++	-	+++	Chemotherapy/ ASCT
hATTR	Hereditary	Mutations in TTR gene	Abnormal TTR	+++	+++	++	+/-	-	-	++	-	Liver transplant for younger patients with V30M-related ATTR, TTR stabilisers or genetic therapies
ATTRwt	Acquired		Wild-type TTR	+	-	+++	-	-	-	-	-	Supportive
AA	Acquired	Inflammatory disorders	SAA	-	++	+/- (late)	+++	+ (Late)	+	-	+/-	Suppression of inflammation
AFib	Hereditary	Mutations in fibrinogen α-chain gene	Abnormal fibrinogen	-	-	+/-	+++	+/-	-	-	-	Supportive, organ transplant
AAPoA1	Hereditary	Mutations in apolipoprotein A1 gene	Abnormal ApoA1	+	-	+	++	++	-	-	-	Supportive, organ transplant
ALys	Hereditary	Mutations in lysozyme gene	Abnormal lysozyme	-	-	+/-	+++	++	++	-	-	Supportive, organ transplant
AGel	Hereditary	Mutations in gelsolin gene	Abnormal gelsolin	++ (Cranial)	-	+	+	-	-	-	-	Supportive
Aβ2M	Acquired or hereditary	Long-term dialysis	β2M	- (CTS)	-	+/-	-	+/-	-	-	-	Supportive, renal transplant

Table 1: Summary of the common types of amyloid and most frequently affected organs[1,2,3,17]

Abbreviations: β2M=β2-microglobulin-related. AFib= fibrinogen A α-chain. AGel= gelsolin amyloid. AL-amyloid= amyloid light chain. ALys= lysozyme amyloid. ASCT= autologous stem cell transplant. ATTR= amyloid transthyretin CTS- Carpal tunnel syndrome GIT= Gastrointestinal SAA= serum amyloid. AA= amyloid A. AApoA1= apolipoprotein A1 amyloid. +++ very common; ++ common; + less common, +/- rare; - does not occur or not applicable

The hereditary amyloidoses, of which transthyretin (hATTR) is the most prevalent, are a rare group of autosomal dominant disorders characterised by varying severity of peripheral and/or autonomic neuropathy, and other systemic manifestations, particularly cardiomyopathy. Hereditary ATTR has been reported throughout the world, particularly in Europe, with marked phenotypic heterogeneity[3]. TTR is primarily synthesized in the liver and misfolding of the ATTR protein causes aggregation and formation of insoluble amyloid fibrils which deposit systemically[4]. Wild-type TTR is also a precursor of amyloid fibrils usually resulting in a late onset cardiomyopathy affecting approximately 25% of people over 80 years of age[5]. AL-amyloidosis is the result of a plasma cell dyscrasia in which monoclonal plasma cells produce immunoglobulin light chain fragments that abnormally fold and deposit[6]. AL-amyloidosis may be associated with myeloma or other B-cell malignancies, but most commonly the underlying haematological diagnosis is a benign monoclonal gammopathy of undetermined significance (MGUS). Lambda light chains are four times more commonly associated with AL-amyloidosis than kappa[7].

This review will focus on hATTR and AL-amyloidosis as they are most commonly associated with a neuropathy. Recognising amyloid neuropathy is very important in this era of imminently available genetic therapies for hATTR, and improving therapies with better survival rates for patients with AL-amyloidosis[8].

MAJOR CLINICAL FEATURES

Hereditary ATTR and AL-amyloidosis have overlapping clinical manifestations and both may initially present with isolated carpal tunnel syndrome (CTS). Patients then generally develop a peripheral and autonomic neuropathy and frequently cardiac involvement. CTS can be the only symptom in hATTR in up to 33% of patients for a mean period of 4-6 years[9] before other organs are clinically involved, and in AL-amyloidosis, it can predate other symptoms by over a year[10]. The most common hATTR mutation worldwide is the V30M mutation that is endemic in Portugal, Japan and Sweden but there are now more than 100 known pathogenic ATTR mutations. In Portugal, V30M classically presents in the second or third decade with a painful or uncomfortable peripheral neuropathy

with most patients describing paraesthesia or neuropathic pain initially rather than numbness progressing in a length-dependent pattern. Autonomic involvement can also be an initial symptom. In the UK, the majority of patients have the T60A point mutation, which originally arose in north-west Ireland at least 200 years ago, and is widely prevalent in areas of high Irish immigration[11]. Classically, there is early cardiac involvement, which can be the presenting symptom usually around age 60. Symptoms and signs of peripheral neuropathy are the initial complaint in approximately 50% of patients, and are often characterised by numbness rather than a painful neuropathy[12].

As TTR is also produced within the choroid plexus and the epithelium of the retina, central nervous system (CNS) manifestations can also occasionally be seen in clinical practice, either from ongoing CNS deposition post liver transplant for V30M mutation or from hATTR mutations that have a predilection for the CNS. Oculoleptomeningeal amyloidosis, associated with the L12P mutation and other mutations can present with a variety of neurological problems including epilepsy, subarachnoid haemorrhage, hearing or visual loss and headaches[13]. hATTR-V30M patients have a 10-year survival rate from liver transplant of 75.4%, and focal neurological episodes are being reported a median of 11 years after transplant. These include ischaemic and haemorrhagic strokes, short-lived, stereotyped episodes suggestive of seizures, or cortical TIAs. They have been difficult to classify as most patients have normal EEGs and CT scans, and MRIs are often contraindicated due to a pacemaker or implantable cardioverter defibrillator. However, histopathological studies of post-transplant brains show extensive cerebral amyloid angiopathy, negative anti-Aβ immunostaining, thereby suggesting ATTR deposition[14].

Peripheral Neuropathy

Neuropathic symptoms can be the presenting feature in up to 15% of patients with AL-amyloidosis[10]. In both AL-amyloidosis and hATTR, patients typically describe a painful, length-dependent neuropathy starting in the feet, with numbness, burning, and allodynia, which can be particularly troublesome at night. However, this can vary in hATTR depending on the mutation such that patients with the V30M mutation from the endemic areas in Portugal present with this classic phenotype usually in the second or third decade whereas patients with the T60A Irish mutation present usually in the fifth or sixth decade and only 42% have a painful neuropathy. Presentation of hATTR in non endemic areas, including patients with late onset V30M, and many other mutations particularly if late onset, can be much more variable with a neuropathy characterised by the early involvement of all sensory fibers and in some cases more rapid progression[15]. In the classic presentation, examination at an early stage may show only features of small fibre involvement with abnormalities in pinprick sensation, and clinical features of median neuropathy at the wrists. Within months to years, large sensory fibres and motor nerve fibres become involved, resulting in impairment of vibration, proprioception and weakness starting distally but progressing proximally requiring walking aids and eventually wheelchair use, and impaired upper limb function[2]. Less commonly seen are focal cranial neuropathies, or plexopathies from focal deposition[2]. Isolated amyloid myopathy or myopathy associated with systemic amyloidosis, either genetic or acquired, is also recognised, and can occur with or without a neuropathy[16,17].

Autonomic Neuropathy

Up to 75% of patients with hATTR, and 65% of patients with AL-amyloidosis develop symptoms of an autonomic neuropathy, affecting the cardiac, gastrointestinal, and genitourinary systems[18,19]. In our experience, diarrhoea and postural hypotension are among the most disabling symptoms of systemic amyloidosis. Orthostatic hypotension can be asymptomatic, or can cause persistent fatigue, light-headedness upon standing or syncope. Gastrointestinal manifestations include gastroparesis, weight loss from early satiety, and socially prohibitive, unexpected diarrhoea, which can be nocturnal, especially initially, and cause incontinence. Erectile dysfunction may be an early feature in men, and urinary frequency and retention can also occur. Pupillary and sweating abnormalities have been reported[2].

Extra-neurologic manifestations

Amyloidosis can affect any organ or space, causing either dysfunction or organomegaly, for example hepatomegaly from AL-amyloid. Certain patterns of involvement are very suggestive of amyloidosis, such as macroglossia and bilateral periorbital bruising, (‘racoon eyes’) for AL-amyloidosis. Nephritic or nephrotic syndrome can occur with both genetic and acquired forms[9]. In addition, vitreous deposits occur in about 10% of patients with hATTR (never described with the Irish T60A mutation) and can sometimes be seen by direct ophthalmoscopy. Significant cachexia in both hATTR and AL-amyloid is frequently seen, with patients easily losing more than 10% of bodyweight.

Symptoms of cardiac amyloidosis can present from either restrictive cardiomyopathy or arrhythmias. The

cardiomyopathy causes symptoms of heart failure, which can be difficult to manage, requiring careful consideration of the patient's fluid status and hypotension from autonomic neuropathy. Symptoms of arrhythmias such as syncope, reduced exercise tolerance and fatigue can also be difficult to distinguish from symptoms of orthostatic hypotension. Typical findings on echocardiography include thickening of ventricular walls, however, cardiac magnetic resonance imaging (MRI) is more sensitive[20].

The diagnosis of amyloid is easier to recognise when patients present with a classic phenotype of symptomatic cardiomyopathy, previous bilateral CTS release and a progressive, length dependent, painful sensorimotor neuropathy (Figure 1). However, the neuropathy may be the only presenting feature and not be painful, and actively searching for other organ involvement can help strengthen the case for investigating for amyloidosis.

APPROACH TO DIAGNOSIS

Confirm neuropathy

Patients are likely to present to a neurologist with symptoms suggestive of a peripheral neuropathy or be referred with a known diagnosis of amyloidosis to be investigated for a clinical or subclinical neuropathy. Standard nerve conduction studies (NCS) can be normal in early small fibre neuropathy (SFN). Testing for small fibre dysfunction is dependent on resources available locally. Quantitative sensory testing (QST) is often used in assessment for SFN and includes thermal detection and pain thresholds. The most validated technique to diagnose SFN is quantification of intra-epidermal nerve fibre density on a skin punch biopsy. In studies where SFN was clinically suspected, this assessment had a sensitivity of 90% and specificity of 95%[21]. With time the large fibres are involved and classically, NCS show a sensory more than motor, lower limb predominant axonal neuropathy with median nerve entrapment at the wrists[22]. However, in both hATTR and AL amyloidosis, slow conduction with prolonged distal motor latencies can be seen which may lead to a neurophysiological diagnosis of a demyelinating neuropathy and subsequently a clinical diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Asymmetry can be seen in up to 50% of patients.

Investigate cause of neuropathy

Once a neuropathy is confirmed, the extent of investigations for the cause could be very minimal if there is a strong family history. Given the recent development of effective treatments for hATTR, we have a low threshold for requesting TTR gene sequencing in idiopathic axonal neuropathy or treatment resistant/atypical CIDP especially if accompanied by CTS, autonomic or cardiac involvement or the patient is of Irish ancestry. Testing is available on the NHS with results available within 4-6 weeks or sooner in an urgent situation. ATTR amyloidosis can be excluded if genetic testing for TTR is negative (no mutation), as sequence analysis of the gene detects more than 99% of pathogenic variants[23]. An online database (http://www.amyloidosismutations.com/main_menu.html) provides an updated list of amyloidogenic mutations and their phenotypes[7]. Wild-type ATTR remains a possibility as it cannot be excluded on genetic testing.

If there is no family history, usually a broad, routine neuropathy screen will be conducted for acquired causes. When considering AL-amyloidosis, it is important to identify the monoclonal plasma cells through searching for a paraprotein as well as the culpable light chain causing the amyloidosis. In patients with AL-amyloidosis, the sensitivity of serum protein electrophoresis for detecting a monoclonal protein is 66% but increases to greater than 90% if one combines serum electrophoresis with immunofixation and Bence Jones protein testing on urine. Serum free light chain assay has a sensitivity of 88%[24]. Lambda is the causative amyloid light chain four times more often than kappa light chains[7]. The absolute values and the ratio need to be interpreted with caution in patients with renal impairment. Referral to a haematologist is necessary upon the identification of an abnormal light chain or paraprotein.

Amyloidosis is a histologic diagnosis. Given its multi-system involvement, in cases of an appropriate neurologic phenotype, with no other obvious cause, and identification of a TTR mutation on genetic testing, or haematological findings suspicious for AL-amyloidosis, we do not necessarily pursue a nerve biopsy and sometimes use less invasive tissues to biopsy to achieve a diagnosis, such as an abdominal fat biopsy. However, in the absence of strongly supportive clinical findings, we do a nerve biopsy to search for amyloid and exclude other treatable causes. Identifying amyloid on sural nerve biopsies has a sensitivity cited as high as 86%, however, in real life, it can be challenging in an individual patient, given the patchy and sometimes proximal nature of amyloid deposition. It is not uncommon to only identify axonal degeneration in a nerve biopsy without identifying amyloid deposits, despite meticulous examination by the pathologist[25].

In the UK, once a diagnosis of amyloidosis is confirmed or strongly suspected, these patients are usually referred

to the National Amyloidosis Centre (NAC) for assessment of the extent of systemic involvement. Patients will usually undergo an abdominal fat aspiration, which is a simple and safe, bedside procedure if histological confirmation of amyloidosis has not been achieved previously. The specificity of this test in identifying systemic amyloidosis approaches 100% with sensitivity varying between 52% to 88%[22]. Congo red-positive areas of the formalin-fixed paraffin-embedded biopsy undergo immunohistochemistry for typing of the amyloid protein (TTR vs. AL vs. other), and if this is equivocal, the biopsy undergoes laser microdissection followed by mass spectrometry[26]. These tests to identify protein type can be performed on any affected tissue including salivary gland, nerve, rectal mucosa, endomyocardial biopsy specimens and tenosynovial tissues obtained at carpal tunnel release surgery.

The NAC and other specialist centres also have specialised imaging modalities to identify the degree of systemic amyloidosis and the pattern of uptake can provide clues to type of amyloid. Serum amyloid P (SAP) is a glycoprotein found in all types of amyloid deposits. SAP scintigraphy uses radiolabelled SAP as a tracer to quantify and identify amyloid deposition, however, heart, peripheral nerve and the CNS are poorly visualised. SAP scintigraphy has high sensitivity, 90%, in AA and AL amyloidosis[27], but only 48% in ATTR amyloidosis[28] (Figure 2). Another radionuclide tracer used is 99m-technetium-3,3,-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD). It is particularly sensitive and specific in identifying cardiac ATTR amyloid deposits, and ATTR deposits have different uptake and much higher sensitivity than AL-amyloid deposits[27] (Figure 3).

The coexistence of MGUS with wild-type or hATTR is recognised, especially in older people, but not widely appreciated. In a study of 57 patients with V122I mutation related hATTR, aged between 50-90, median age 71 years, 49% had abnormal serum free light chain ratios and/or paraprotein on immunofixation[29], suggesting neurologists may see abnormal haematological investigations commonly in these patients. Therefore, even in the presence of TTR-FAP mutations, AL-amyloidosis is possible and vice versa. Hence, biopsies from different sites and organs may be necessary and typing the amyloid fibrils is essential when there is concurrent ATTR mutation and a paraprotein.

MISDIAGNOSES/ DIFFERENTIALS

The most common misdiagnosis of amyloidosis is CIDP. This is plausible given patients with hATTR or AL-amyloidosis can have significant motor conduction velocity slowing. In one study, seven misdiagnosed patients fulfilled EFNS/PNS criteria for definite demyelinating polyneuropathy (See clinical case 1). Reduced conduction velocities as low as 33 m/s in the upper limbs and 30 m/s in the lower limbs were observed[30]. In a study of 150 patients with hATTR, 32% had been misdiagnosed, 61% of these were initially diagnosed as CIDP, and 2% as vasculitic neuropathy, which can also present as a painful, axonal neuropathy[30]. Contributing to the risk of misdiagnosis is raised CSF protein in patients with systemic amyloidosis and the clues of autonomic and systemic involvement being absent at initial presentation. Given the frequent misdiagnosis, there should be high suspicion for hATTR in patients diagnosed with CIDP that do not respond to immunomodulatory treatment[31] (Other pitfalls are listed in Table 2).

Table 2: Pitfalls in diagnosing amyloid neuropathy

PITFALLS IN DIAGNOSING AMYLOID NEUROPATHY
History
No family history Minimal pain at onset Paraesthesia rather than pain Asymmetric No cardiac or autonomic symptoms
Examination
Cranial nerve involvement Proximal weakness early
Investigations
Concurrent paraprotein with hATTR

Raised CSF protein Slow conduction velocities on NCS Myopathic units on EMG Failure to identify amyloid on first tissue biopsy- may need repeat and varied tissues biopsied to confirm diagnosis

TREATMENT

For AL-amyloidosis, high dose melphalan and autologous stem cell transplantation (HDM-ASCT) is the preferred first-line treatment for patients up to 65–70 years of age and eligibility depends on the extent of renal, cardiac, autonomic and bone marrow involvement. HDM-ASCT, in a carefully selected patient population, is associated with the best progression free survival and overall survival, with treatment related mortality of 4-13%[32]. Patients not eligible for HDM-ASCT generally receive systemic chemotherapy with melphalan and dexamethasone or cyclophosphamide-bortezomib-dexamethasone (VCD)[33]. Prognosis depends on the extent of cardiac involvement (monitored through serum biomarkers) and the difference in quantities (rather than ratio) between involved (amyloidogenic light chain) and uninvolved serum free light chain levels.

It is an exciting time for patients and clinicians in the field of hATTR. Historically, liver transplant was the first treatment option for hATTR, first performed in 1990 and while it increases survival in early onset ATTR-V30M (patients less than 50 years old), outcomes in non-V30M and older V30M patients are not as good. In recent times, TTR stabilisers, Tafamidis and diflunisal have been used to treat patients with hATTR. These drugs bind to thyroxine-binding sites of TTR and inhibit TTR tetramer dissociation (an essential step for amyloid formation) and there is some evidence that they may slow disease progression, especially in the V30M patient population[34]. This year, there has been significant progress made in treatment for hATTR with two types of gene silencing therapies, inotersen, an antisense oligonucleotides (ASOs) and patisiran, a small interfering RNAs (siRNAs), achieving their primary outcome measures in two separate randomised placebo-controlled, phase 3 trials [35,36]. Inotersen is a subcutaneous preparation and is administered weekly, while patisiran is administered intravenously, three-weekly. They both reduce the production of mutant and wild-type TTR through different mechanisms (for further information on mechanisms, please read [8]). These therapies are a welcome addition to the treatment options for patients with V30M and non-V30M mutations.

Conclusion

In this era of rapidly evolving gene therapies for hATTR and improving therapies for AL-amyloidosis, an accurate and timely diagnosis of amyloid neuropathy can greatly impact outcomes for patients. There is considerable heterogeneity in the clinical presentation of amyloid neuropathy but having a high clinical suspicion together with knowledge of the advantages and limitations of the various diagnostic techniques used is key to making a diagnosis.

Case 1 (TTR misdiagnosed as CIDP):
A 70-year-old lady, of Northern Irish background, was initially diagnosed as having CIDP based on asymmetrical, distal, sensory-onset neuropathy, raised CSF protein of 0.69 g/L and prolonged distal motor latencies and slowed conduction velocities on neurophysiology. She was referred to our centre after failing to respond to prednisolone, intravenous immunoglobulin and plasma exchange. At age 66, she developed unilateral, uncomfortable paraesthesia in her left foot, which over a year spread to both knees. Following this she developed proximal weakness with trouble standing up from sitting which progressed such that she required a wheelchair 3 years after disease onset. There was no weight loss, early satiety, bowel or bladder symptoms but she did have postural dizziness, which developed two years in to her illness. Her other history included atrial fibrillation (AF), diagnosed at age of 68. There was no family history of neurological disease.
On examination, four years after the onset of her illness, she had upper limb weakness of MRC 4 proximally and 0-1 distally. Lower limb examination revealed pitting oedema to her ankles, global weakness with proximal power of MRC 2-3, and distal power of 0-2. She was areflexic and had downgoing plantars. Sensory examination revealed reduced pinprick to her knees and elbows, normal joint position sense, and reduced vibration to ankles. Neurophysiology showed a mixed, demyelinating and axonal neuropathy (Table 3).

Table 3: Case 1 Neurophysiology

Sensory Nerve Conduction Studies		
	Right	**Left**
Median (D3- wrist)	Absent	Absent
Ulnar (D5- wrist)	Absent	Absent
Sural (calf- ankle)	Absent	Absent
Sup. peroneal (calf- ankle)	Absent	Absent
Motor Nerve Conduction Studies		
Median (SE on APB)		
DML (wrist)	13 ms	7.0 ms
CV(wrist-elbow)	47 m/s	35 m/s
CMAP(wrist)	2.5 mV	1.2 mV
CMAP(elbow)	1.7 mV	0.9 mV
Ulnar (SE on ADM)		
DML	4.6 ms	3.6 ms
CV(wrist-below elbow)	47 m/s	44 m/s
CV(around elbow)	42 m/s	45 m/s
CV(above elbow-axilla)	43 m/s	45 m/s
CMAP(wrist)	2.5 mV	4.0 mV
CMAP(below elbow)	1.7 mV	3.5 mV
CMAP(above elbow)	1.7 mV	2.9 mV
CMAP(axilla)	1.5 mV	-
Minimal F-wave latency (wrist)	absent	-
Common Peroneal (SE on EDB)		
CMAP(ankle)	absent	-
Tibial (SE on AH)		
CMAP(ankle)	absent	-

Cerebrospinal fluid analysis showed a raised protein of 0.69 g/L. Sural nerve biopsy identified endoneurial deposits that stained strongly with Congo Red and displayed apple-green birefringence when viewed under polarized light (Figure 4). Immunotyping was suggestive of transthyretin type of amyloid. Sequencing of the TTR gene revealed the T60A pathogenic mutation. DPD scan at the NAC showed moderate amount of cardiac amyloid. She was treated with diflusinal, a TTR stabiliser.

Case 2 (AL difficult to diagnose on tissue):
A 70-year-old lady with a six-year history of Waldenstrom's macroglobulinemia, previously treated with fludarabine and cyclophosphamide, with partial haematological response secondary to early cessation of treatment due to side effects, presented with a year history of shooting pains in the calves and burning in the soles of the feet. Three months prior to referral to our centre, she developed weakness in her feet and difficulty climbing stairs progressing to using a wheelchair after a further three months.

On initial examination, there was no postural hypotension. Cranial nerve examination was normal except for a left tonic pupil. In her upper limbs, there was bilateral wasting of the intrinsic hand muscles. Power was normal proximally and MRC 4 to 5 in the intrinsic hand muscles. Reflexes were present. In the lower limbs, she could not stand from a chair without using her hands and had bilateral wasting of EDB. Tone was normal and there was proximal and distal weakness, with hip flexors weak at MRC 4, and ankle dorsiflexion was 4 on the right and 2 on the left. Knee reflexes were present, ankle jerks were absent, and plantars were unresponsive. Sensory examination showed pinprick abnormal to mid-thighs with no abnormality in the upper limbs, vibration was reduced to the costal margins and proprioception was normal.
Initial investigations showed an IgM lambda paraprotein of 5.1g/L, normal serum free light chains with a normal ratio and no urine Bence Jones protein. Neurophysiology revealed abnormal thermal thresholds in the lower limbs suggesting a small fibre neuropathy with no large fibre involvement. Repeat neurophysiology six months later showed an axonal, asymmetric neuropathy (Table 4).

Table 4: Case 2 Neurophysiology

Sensory Nerve Conduction Studies				
	Right		**Left**	
Radial (forearm-snuffbox)	37µV	69m/s	-	-
Median (D3- wrist)	12µV	60m/s	-	-
Ulnar (D5- wrist)	9µV	57m/s	-	-
Sural (calf- ankle)	5µV	60m/s	4µV	55m/s
Sup. peroneal (calf- ankle)	absent	-	absent	-
Motor Nerve Conduction Studies				
	Right		**Left**	
Median (SE on APB)				
DML (wrist)	3.2 ms		-	
CV (wrist-elbow)	50 m/s		-	
CMAP (wrist)	5.5		-	
CMAP (elbow)	4.7		-	
Minimal F-wave latency	28.2 ms		-	
Ulnar (SE on ADM)				
DML	2.6 ms		-	
CV (wrist-below elbow)	58 m/s		-	
CMAP (wrist)	8.0 mV		-	
CMAP (below elbow)	6.1 mV		-	
CMAP (above elbow)	7.4 mV		-	
Minimal F-wave latency	27.3 ms		-	
Common Peroneal (SE on EDB)				
DML	4.7 ms		4.9 ms	
CMAP (ankle)	1.2 mV		0.2 mV	
CMAP (fib neck)	1.0 mV		0.2 mV	
F latency	56.1 ms			
Tibial (SE on AH)				
DML	5.5 ms		5.9 ms	
CMAP (ankle)	1.4 mV		2.1 mV	
Minimal F-wave latency	65.0 ms		51.8 ms	

She underwent a superficial peroneal and peroneus brevis biopsy which showed a moderate loss of large myelinated fibres and moderate loss of all axons. Immunohistochemical studies showed endoneurial labelling for lambda light chains, however, Congo red staining at our institution was negative. The biopsy was sent to NAC for further studies, and using antibodies against SAP, they were able to show amyloid deposits present in the nerve bundles. Antibodies against SAP, which co-deposits with amyloid, can be used to distinguish light chain deposits of AL amyloidosis from monoclonal immunoglobulin deposition disease (19). Assessment at the NAC revealed nephritic range proteinuria and SAP scintigraphy showed moderate splenic amyloid load as well as equivocal liver involvement, with no evidence of cardiac amyloidosis.

Her mobility continued to deteriorate and she developed features of autonomic neuropathy with urinary retention, diarrhoea and orthostatic hypotension. She was treated with cyclophosphamide, dexamethasone and rituximab and achieved sustained partial remission.

Box 2: Key Messages

- Systemic amyloidosis can be hereditary or acquired with hereditary transthyretin (TTR) amyloidosis being the most common inherited form.
- Systemic amyloidosis is a multi-system disorder with varying involvement of the peripheral and autonomic nerves, and particularly, cardiac involvement.
- The classic neuropathic presentation is of a painful, length dependent neuropathy but atypical presentations without pain or presentations of focal neuropathies, plexopathies or myopathy, are not uncommon.
- Classically, neurophysiology suggests an axonal neuropathy, but standard nerve conduction studies can be normal in early small-fibre neuropathy, and slow conduction velocities or prolonged distal motor latencies can also be seen leading to a clinical misdiagnosis of CIDP.
- Older patient may have concurrent hereditary TTR amyloidosis and a paraprotein which can complicate identifying AL vs. TTR amyloidosis.
- Consider requesting TTR gene sequencing in patients diagnosed with CIDP who do not respond to immunomodulatory treatment.
- There is exciting progress being made in treating hereditary TTR amyloidosis with 2 gene-silencing therapies showing promising results in separate randomised, placebo-controlled, phase 3 trials.

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