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A treatable case of hereditary transthyretin amyloidosis with polyneuropathy masquerading as motor neuron disease

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Abstract

Hereditary transthyretin amyloidosis is a progressive, life-threatening disease that typically presents as length-dependent symmetric axonal sensorimotor polyneuropathy, restrictive cardiomyopathy, or a combination of both. In this case report, we describe a 50-year-old gentleman with a rare motor phenotypic variant of hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) masquerading as motor neuron disease. This case represents the first reported association between the motor phenotypic variants of hATTR-PN and mutations involving p.Ala117Ser, a mutation prevalent in the Chinese population.

Keywords: Hereditary transthyretin amyloidosis with polyneuropathy, familial amyloid polyneuropathy, p.Ala117Ser mutation, motor neuropathy, motor neuron disease

INTRODUCTION

Hereditary transthyretin amyloidosis is a progressive, life-threatening disease that typically manifests as length-dependent symmetric axonal sensorimotor polyneuropathy, restrictive cardiomyopathy, or a combination of both.[1] In the literature review conducted by Marcia *et al*., sensory deficit was documented in 87% of individuals diagnosed with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN). Moreover, all cases of hATTR-PN were explicitly characterized as having exhibited sensory neuropathy throughout the progression of the disease.[2] Motor neuropathy is a rare phenotypic variant of hATTR-PN. It is important for clinicians to recognise this rare clinical entity and use genetic testing as diagnostic tool. We report a rare case of a 50-year-old gentleman with motor phenotypic variant of hATTR-PN.

CASE REPORT

A 50-year-old man presented with proximal weakness in his limbs, exertional dyspnea, anorexia, and unintentional weight loss of 15 kg over the past year. He had a history of diabetes mellitus, hypertension, and dyslipidemia. Examination revealed symmetrical atrophy and weakness in the proximal muscles of all four limbs (Figure 1); their deep tendon reflexes were diminished, and weakness was observed in his neck extension. The extraocular, facial, bulbar, and pharyngeal muscles were functioning normally. There was neither fatigability nor accompanying sensory deficits. Nerve conduction studies and electromyography demonstrated features of bilateral carpal tunnel syndrome, as well as the presence of active denervation and chronic re-innervation in the cervical, thoracic, and lumbar innervated muscles (Table 1). He was subsequently suspected of having progressive muscular atrophy based on his clinical features and the results of the aforementioned ancillary tests.

The investigations, including serum creatine kinase, aldolase, antinuclear antibody, double-stranded DNA antibody, extractable nuclear antigens, retroviral antibody, hepatitis B surface antibody, hepatitis B core total antibody, hepatitis C enzyme immunoassays, venereal disease research laboratory antibody (VDRL), treponema pallidum particle agglutination (TPPA), myeloma panel, and antibodies such as myelin associated glycoprotein, GM1, GM2, GD1a, GD2B, GQ1b, paraneoplastic

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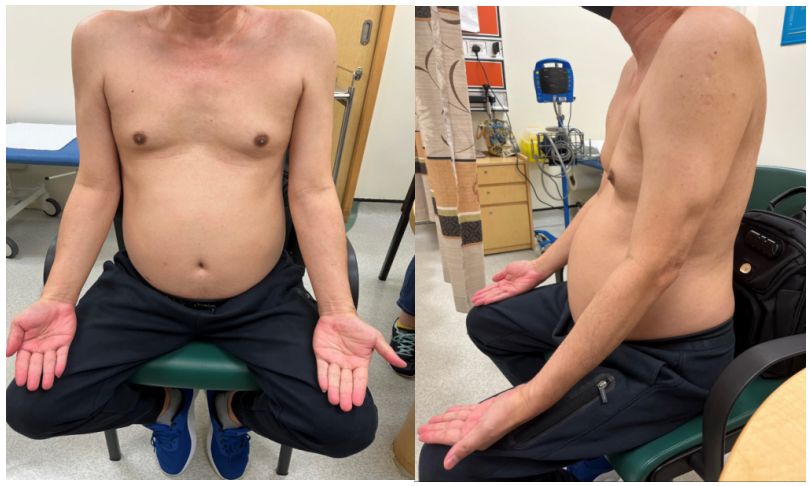


Figure 1. Symmetrical atrophy of bilateral deltoid and biceps brachii muscles.

panel (anti-neuronal antibodies such as anti-Hu antibody, anti-Yo antibody, anti-Ri antibody, anti-CV2 antibody, anti-Amphiphysin antibody, anti-PNMA2/Ta antibodies, anti-recoverin antibody, anti-SOX1 antibody, anti-titin antibody, anti-zic4 antibody, anti-GAD65 antibody, and anti-Tr antibody), all yielded unremarkable results. Magnetic resonance imaging (MRI) of the brain and whole spine revealed findings within normal limits. Computed Tomography (CT) of the thorax, abdomen, and gastroenteroscopy were conducted to explore the etiology of weight loss, yet yielded unremarkable results. Arterial blood gas analysis, echocardiogram, myocardial perfusion imaging, and cardiac MRI were employed to investigate breathlessness, all of which exhibited normal findings.

It was later discovered that his mother experienced progressive weakness in her 60s. Genetic analyses returned negative results for the survival motor neuron and androgen receptor genes, which were performed in consideration of spinal muscular atrophy and bulbospinal muscular atrophy, respectively. He then underwent genome sequence analysis, which detected a heterozygous missense mutation c.349G>T p.Ala117Ser, a pathogenic transthyretin variant. Although Congo Red staining of rectal and abdominal fat biopsy specimens was unremarkable, a 99m-Technetium-pyrophosphate (99mTc-PYP) scan displayed features consistent with cardiac transthyretin amyloidosis (Figure 2). He was thereafter diagnosed with hATTR-PN and cardiomyopathy. His condition improved after starting diflunisal and remained stable over the past three years.

DISCUSSION

Hereditary transthyretin amyloidosis is a rare autosomal dominant heritable disease associated with more than 130 transthyretin mutations. In this condition, the transthyretin protein misfolds to form amyloid, which is deposited in various organs, particularly in the heart and peripheral nerves.[3] Patients with hATTR-PN experience rapid deterioration in their functions, and their survival is limited to 7-10 years without treatment.[4]

Motor phenotypic variants of hATTR-PN are rare. In Italy, five patients, and one patient in Africa, presented with features resembling motor neuron disease. Mutations including p.Ile88Leu, p.Phe84Leu, p.Glu74Gln, and p.Val113Met were uncovered in these cases.[5,6] Uncommon neuropathy phenotypes, such as demyelinating polyneuropathy, mononeuropathy multiplex, polyradiculopathy, radiculoplexus neuropathy, and motor neuropathy, have previously been reported.[5-10] We postulate that the observed variety in phenotypes may be attributed to the heterogeneity of amyloid deposition in neurons.

The p.Ala117Ser mutation, while common among the Chinese in Asia, rarely causes motor neuropathy.[11-13] Therefore, our patient, described herein, represents the first reported case of the motor neuropathy variant of hATTR-PN associated with p.Ala117Ser mutations. This discovery substantiates the hypothesized notion that hATTR-PN is a disease characterized by greater phenotypic variability than conventionally acknowledged, even within specific genotypic mutations.

Notwithstanding the initial suspicion of motor neurone disease, the recognition of pivotal

Table 1: Nerve conduction study

Motor nerve conduction study	Onset latency (ms)	Amplitude (mV)	Conduction velocity (m/s)	F wave latency (ms)
		L median nerve		
Wrist – APB	**4.42**	13.2		29.7
Elbow – APB	9.50	12.0	53.1	
EP – APB	15.5	10.3	70.0	
		R median nerve		
Wrist – APB	**5.92**	10.3		31.2
Elbow – APB	10.6	9.6	54.5	
EP – APB	15.9	9.3	75.5	
		L ulnar nerve		
Wrist –ADM	2.63	9.8		29.4
Above elbow – ADM	8.38	9.2	52.2	
EP – ADM	13.6	7.4	72.8	
		R ulnar nerve		
Wrist –ADM	2.54	9.5		28.7
Above elbow – ADM	8.25	8.3	55.2	
EP – ADM	13.6	7.1	71.0	
		L tibial nerve		
Ankle – AH	3.13	15.0		50.4
Popliteal fossa – AH	12.3	11.2	45.8	
		R tibial nerve		
Ankle – AH	3.28	17.5		48.7
Popliteal fossa – AH	12.1	12.1	46.5	
		L peroneal nerve		
Ankle – EDB	3.85	8.5		49.3
Above fibular – EDB	13.4	8.4	44.5	
		R peroneal nerve		
Ankle – EDB	3.90	6.0		48.9
Above fibular – EDB	13.1	5.4	44.6	
		Lumbrical-interossei latency difference		
L ulnar – median			**-1.06**	
R ulnar – median			**-2.30**	

Sensory nerve conduction study	Onset latency (ms)	Amplitude (μV)	Conduction velocity (m/s)
		L median nerve	
Digit II – Wrist	**3.58**	**20.2**	**36.3**
		R median nerve	
Digit II – Wrist	**4.55**	**13.3**	**28.6**
		L ulnar nerve	
Digit V – Wrist	2.06	39.3	53.4
		R ulnar nerve	
Digit V – Wrist	2.01	35.0	54.7
		L superficial peroneal nerve	
Calf – Ankle	2.71	15.3	44.3
		R superficial peroneal nerve	
Calf – Ankle	2.50	16.4	48.0
		L sural nerve	
Mid lower leg – Lateral malleolus	2.52	20.7	47.6
		R sural nerve	
Mid lower leg – Lateral malleolus	2.48	20.1	48.4

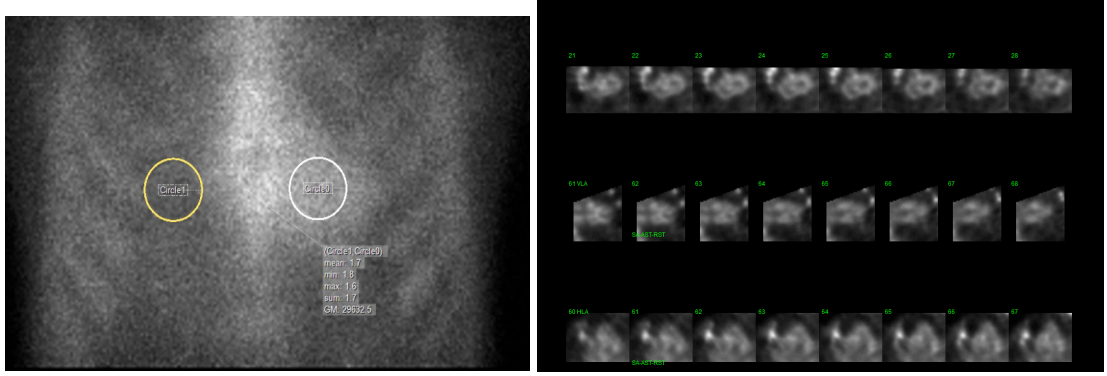
L, left; R, right; APB, abductor pollicis brevis; EP, Erb's point; ADM, abductor digiti minimi; AH, abductor hallucis.

Table 2: Needle electromyography

Muscle	Spontaneous Activity		Motor unit potential		
	Fibrillation	**PSW**	**Amplitude**	**Duration**	**Recruitment**
L glossus	0	0	Normal	Normal	Normal
R glossus	0	0	Normal	Normal	Normal
L paravertebral C6	0	0	Normal	Normal	Normal
L paravertebral C7	+	+	Normal	Normal	Normal
L paravertebral L4	+	+	Normal	Normal	Normal
L biceps	0	+	**Increase**	**Increase**	**Reduced**
L deltoid	0	0	Normal	Normal	**Reduced**
L FDI	0	0	Normal	Normal	**Reduced**
L vastus lateralis	0	0	Normal	Normal	Normal
L tibialis anterior	+	0	Normal	Normal	**Reduced**
R paravertebral C6	0	0	Normal	Normal	Normal
R paravertebral T10	+	++	Normal	Normal	Normal
R deltoid	0	0	Normal	**Increase**	**Reduced**
R FDI	0	0	**Increase**	Normal	**Reduced**
R vastus lateralis	0	0	Normal	Normal	**Reduced**
R tibialis anterior	0	+	Normal	Normal	**Reduced**

L, left; R, right; FDI, first dorsal interosseous; PSW, positive sharp wave.

features including a probable family history, concurrent bilateral carpal tunnel syndrome, breathlessness, and unintentional weight loss subsequently directed our attention towards systemic amyloidosis as the more plausible diagnosis.[14] The diagnostic specificity of amyloid deposition demonstrated in tissue biopsies is notably high. However, its sensitivity is markedly influenced by factors such as the quantity of tissue sampled and the site of biopsy. The sensitivities of biopsies at specific sites, such as the sural nerve (79-80%) and abdominal fat pad (14-83%), vary. Consequently, negative biopsy results do not conclusively rule out amyloidosis, a scenario similarly observed in our patient. In comparison, 99mTc-PYP scans exhibit a high level of accuracy in depicting the characteristics of cardiac amyloidosis, boasting both elevated



(A) Planar (B) SPECT

Figure 2. 99m-Technetium-pyrophosphate scan. The heart to contra-lateral lung ratio was 1.7 at 1 hour. Semi-quantitative visual grading of cardiac myocardial uptake was grade 3, uptake greater than ribs. (A) Single-photon emission computed tomography (SPECT) imaging revealed significant myocardial uptake of tracer. (B)

sensitivity (99%) and specificity (86%) as documented in previous studies.[15] The myocardial radiotracer uptake observed in bone scintigraphy utilizing 99mTc-PYP holds potential value in cases presenting with peripheral neuropathy, the presence of an amyloidogenic transthyretin (TTR) mutation, and suspected cardiac involvement, particularly when confronted with negative biopsy results. This diagnostic approach has the potential to obviate the necessity for an endomyocardial biopsy.[16]

In conclusion, the timely identification and management of the motor phenotypic variant in hATTR-PN is imperative, given its profound and frequently incapacitating manifestations. Additionally, the case of our patient represents the initial documented correlation between motor phenotypic variants of hATTR-PN and mutations involving p.Ala117Ser, a mutation prevalent in the Chinese population. This demonstrates that phenotypic diversity can exist despite a shared genetic mutation.

DISCLOSURE

Ethics: Informed written consent was obtained and documented.

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Conflict of interest: None

REFERENCES

1. Ando Y, Coelho T, Berk JL, *et al*. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis* 2013; 8: 31. doi: 10.1186/1750-1172-8-31.
2. Waddington-Cruz M, Schmidt H, Botterman MF, *et al*. Epidemiological and clinical characteristics of symptomatic hereditary transthyretin amyloid polyneuropathy: a global case series. *Orphanet J Rare Dis* 2019; 14: 34. doi: 10.1186/s13023-019-1000-1.
3. Rowczenio DM, Noor I, Gillmore JD, *et al*. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. *Hum Mutat* 2014;35 9:E2403-12. doi: 10.1002/humu.22619.
4. Adam D, Coelho T, Obici L, *et al*. Rapid porgression of familial amyloidotic polyneuropathy: a multinational natural history study. *Neurology* 2015;85:675-82. doi: 10.1212/WNL.0000000000001870.
5. Salvi F, Pastorelli F, Plasmati R, *et al*, Genotypic and phenotypic correlation in an Italian population of hereditary amyloidosis TTR-related (HA-TTR): clinical and neurophysiological aids to diagnosis and some reflections on misdiagnosis. *Amyloid* 2012; 19-58-60. doi: 10.3109/13506129.2012.682187.
6. Lozeron P, Lacroix C, Theaudin M, *et al*. An amyotrophic lateral sclerosis-like syndrome revealing an amyloid polyneuropathy associated with a novel transthyretin mutation. *Amyloid* 2013;20:188-92. doi: 10.3109/13506129.2013.818535.
7. Brett M, Persey MR, Reilly MM, *et al*. Transthyretin Leu12Pro is associated with systemic, neuropathic and leptomeningeal amyloidosis. *Brain* 1999; 122: 183-90. doi: 10.1093/brain/122.2.183.
8. Mathis S, Magy L, Diallo L, *et al*. Amyloid neuropathy mimicking chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2012;45:26-31. doi: 10.1002/mus.22229.
9. Sole G, Casenave P, Vital C, *et al*. Familial amyloid polyneuropathy associated with nodular lumbosacral radiculoplexopathy. *J Peripher Ner Syst* 2012;17:138-9. doi: 10.1111/j.1529-8027.2012.00385.x.
10. Zivkovic SA, Mnatsakanova D, Lacomis D. Phenotypes of late-onset transthyretin amyloid neuropathy: a diagnostic challenge. *J Clin Neuromuscul Dis* 2019; 21:1-6. doi: 10.1097/CND.0000000000000252.
11. Chao HC, Liao YC, Liu YT, *et al*. Clinical and genetic profiles of hereditary transthyretin amyloidosis in Taiwan. *Ann Clin Transl Neurol* 2019; 6(5): 913-22. doi: 10.1002/acn3.778.
12. Chen ZY, Koh JS, Saini M, *et al*. Hereditary transthyretin amyloidosis- Clinical and genetic characteristics of a multiracial South-East Asian Cohort in Singapore. *J Neuromuscul Dis* 2021;8(4): 723-33. doi: 10.3233/JND-210656.
13. Low SC, Md Sari NA, Tan CY, *et al*. Hereditary transthyretin amyloidosis in multi-ethnic Malaysians. *Neuromuscul Disord* 2021; 31(7): 642-50. doi: 10.1016/j.nmd.2021.03.008.
14. Conceicao I, Gonzalez-Duarte A, Obici L, *et al*, 'Red -flag' symptom clusters in transthyretin familial amyloid polyneuropathy. *J peripher Nerv Syst* 2016;21:5-9. doi: 10.1111/jns.12153.
15. Adam D, Ando Y, Beirao JM, *et al*. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol* 2021; 268(6): 2109-22. doi: 10.1007/s00415-019-09688-0.
16. Rapezzi C, Quarta CC, Guidalotti PL, *et al*. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. *JACC Cardiovasc Imag* 2011;4:659-70. doi: 10.1016/j.jcmg.2011.03.016.