p.Val142Ile (p.Val122Ile) Transthyretin Mutation Presenting Exclusively As Small Fiber Neuropathy

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Introduction

Familial amyloid polyneuropathy is an autosomal dominant disorder caused by mutations in the transthyretin gene, TTR. More than 100 mutations in the *TTR* gene are known. P.Val30Met was identified first as a cause of FAP and is the most common mutation worldwide. This mutation has been described as associated with peripheral neuropathy while p.Val142Ile (C.424G>A) (also known as p.Val122Ile) is associated with cardiac amyloidosis [1, 2, 3] . In this context, we report a patient harboring p.Val142Ile mutation with exclusive small fiber neuropathy and absence of any cardiac involvement by cardiac MRI representing genotypic-phenotypic heterogenicity.

Case Presentation

A 58-year-old, African American woman presented with distal tingling and electric shock-like, piercing pain sensations for 10 years. She denied numbness and distal weakness. She had no history of diabetes mellitus, exposure to toxins or tick bite. She reported an impairment in detecting cold temperatures and dysesthesias. She denied autonomic symptoms of temperature dysregulation or intolerance and syncope, but did complain of gastrointestinal dysmotility and postural dizziness from sitting to standing position corroborated by reduced systolic blood pressures observed in the range of 90mmHg or lower in sitting position, albeit orthostatic drop in BP was not observed. The patient did not complain about visual disturbances. She was a daughter of nonconsanguineous parents with 7 siblings and has 2 children. Her family history was otherwise negative regarding any cardiac or neuromuscular disorders.

Pertinent findings on examination included normal cardiac, respiratory and gastrointestinal system exams but distal skin discoloration with loss of normal hair. No deformities involving feet were seen like hammer toes or high arch feet. On neurological examination, she demonstrated normal cranial nerves and normal muscle strength in both upper and lower extremities. Sensory testing demonstrated a symmetric, length- dependent loss to pinprick to 5 cm above ankle and up to distal IPJ in lower and upper extremity, respectively. Large fiber sensations showed normal proprioception and vibration sensations.

Extensive polyneuropathy and inflammatory etiology assessments were normal. Notably, there was no monoclonal gammopathy, diabetes mellitus (fasting and 2-hour GTT were normal), nutritional deficiencies of vitamin B12 or B6 nor hypervitaminosis of vitamin B6. Paraneoplastic antibodies were absent. ANA and RF were negative. Hepatitis and HIV testing and genetic testing of SCN9A mutation were normal. Because of significant pain symptoms, she was evaluated by a rheumatologist, and physical examination and thorough laboratory workup did not reveal any findings of autoimmunity or systemic inflammation.

Electrophysiological studies demonstrated that there was no electrodiagnostic evidence of a large fiber sensory or motor peripheral polyneuropathy but electrically mild, bilateral, compressive, median sensory mononeuropathies at or distal to the wrists affecting only sensory fibers.

Discussion

Corine Andrade [5] described 'A peculiar form of Peripheral Neuropathy: Familiar Atypical Generalized Amyloidosis with Special Involvement of The Peripheral Nerves' from Northern Portugal in 1952. This original description observed carpal tunnel syndrome as well as small fiber involvement with 'early impairment of thermal and painful sensibilities' as in our patient. The disease now has been identified worldwide due to the widespread availability of genetic testing [4]. To date, 123 amino acid substitutions, one deletion and one synonymous base substitution have been reported for the transthyretin protein and its encoding gene [6]. The ATTR-Val30Met mutation is the most common variant found in Europe and Latin America, whereas the ATTR-Val142Ile is most commonly found in the USA and West African populations [7]. It is observed that approximately 4% of black Americans carry the ATTR Val142Ile variant. This mutation is widely described in the literature as the leading cause of cardiac amyloidosis in patients with African ancestry [7] and is also seen in patients of European descent [4]. It is predominantly associated with cardiomyopathy and increased mortality from heart failure [8] with a primary expression as a hypertrophic restrictive cardiomyopathy. Delayed diagnosis and misdiagnosis are common because phenotypic heterogeneity can be compounded by a lack of family history in TTR-FAP [3]. In a study from Italy, the rate of misdiagnosis in this cohort of TTR-FAP was as high as 32% with CIDP as the most frequent diagnostic error in

about 20% of cases, followed by lumbosacral radiculopathy, lumbar central canal stenosis, paraproteinemic neuropathy, and AL amyloidosis. A study observed that such errors lead to not only an average delay in diagnosis of up to 46 months but inappropriate treatments such as immunomodulating therapy, chemotherapy, or spinal surgery in a number of cases [9].

It is observed that heterogeneity in the clinical course with similar mutations also complicates the scenario. French patients with the TTR-FAP genotypes Ile107Val, Ser77Tyr, and late-onset Val30Met show a more rapid and severe disease progression compared to Portuguese Val30Met patients, with onset of gait disorders three times faster [10]. A study has demonstrated that non-coding variants contribute to the clinical heterogeneity and thus provided novel insights into the molecular mechanisms as the basis of the genotype–phenotype correlation of TTR amyloidosis. However , the study also observed strong genotype–phenotype correlations with p.Val422Ile mutations with the cardiac phenotype as supported by previous studies [11]. Because Val142Ille has been viewed as a traditionally cardiac phenotype, minimal data exist on the breadth and presentations of patients with coexistent PN and there is no data on patients presenting with PN prior to cardiomyopathy development. Other variants typically show development of PN prior to cardiomyopathy such as in the original Portuguese cohort. However, as described our patient represents a significant variation in presentation with sole neurological and not cardiological manifestations in the form of a small fiber neuropathy.

Conclusion

Diagnostic work-up of our patient with biopsy proven small fiber neuropathy demonstrated a heterozygous pathogenic transthyretin mutation p.Val142Ile (p.Val122Ile) (C.424G>A). In patients with SFN, TTR should be considered in the differential diagnosis, despite lack of family history and absence of other organs system involvement. As the precise etiology of small fiber neuropathy (SFN) often remains elusive, TTR testing should be integrated in the SFN diagnostic algorithm to prevent delay in diagnosis and potential therapeutic options. This is important considering that our ability to recognize these disorders have improved with more recent availability of genetic testing and treatment options, other than liver and/or heart transplantation for FAP. These newer treatment modalities include TTR stabilizer drugs which appear safe and could delay the disease progression, TTR gene modifiers, e.g. silencing RNA and antisense oligonucleotide therapies as well as immunotherapies targeting the amyloid deposits [4]. One of such therapy is Patisiran, approved in the USA for the treatment of the polyneuropathy of hereditary TTR-mediated amyloidosis (hATTR). It is a double-stranded, small, interfering RNA encapsulated in a lipid nanoparticle which is delivered to hepatocytes where it binds to a genetically conserved sequence in the 3' untranslated region of mutant and wild-type transthyretin (TTR) messenger RNA, causing a reduction in serum TTR protein levels and tissue TTR protein deposits [12]. Another therapy approved in the USA for the treatment of the polyneuropathy of hereditary TTR-mediated amyloidosis (hATTR) is Inotersen, a 2'- O-methoxyethyl-modified antisense oligonucleotide, which inhibits hepatic production of transthyretin [13]. Our patient noticed improved sensory symptoms following initiation of a gene silencer therapy. As these currently available gene silencer treatments significantly decrease TTR protein levels and improve patient outcomes, it is highly important to consider TTR as an etiology even if no family history in selected cases or coexistence of cardiomyopathy are present in addition to the awareness of such genotype-phenotype variability.

Abbreviations

TTR: Transthyretin

TTR-FAP: Transthyretin-associated familial amyloidotic polyneuropathy

SFN: Small Fiber Neuropathy

CIDP: Chronic Inflammatory Demyelinating Peripheral Neuropathy

hATTR: hereditary TTR-mediated amyloidosis

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Appendix 1: ELECTRODIAGNSOTIC FINDINGS

A punch skin biopsy showed severely reduced intradermal nerve fiber density consistent with a severe, length-dependent, small fiber neuropathy. Paraffin-embedded nerve tissue processed for Congo red staining did not demonstrate endoneural deposits of amyloid.

Motor NCS

Nerve / Sites	Rec. Site	Lat	Amp	Rel Amp	SPAR	Segments	Dist.	Vel	Dur.	Area
		ms	mV	%	%		cm	m/s	ms	mVms
L MEDIAN - APB										
Wrist	APB	4.05	10.9	100		Wrist - APB	8		5.50	28.6
Ref.		4.20	4.2		50	Ref.				
Elbow	APB	8.10	9.9	91.1		Elbow - Wrist	21.5	53.1	5.55	26.8
Ref.			4.2			Ref.		49.0		
L ULNAR - ADM										
Wrist	ADM	2.75	8.8	100		Wrist - ADM	8		4.85	24.9
Ref.		4.20	5.6		50	Ref.				
B.Elbow	ADM	5.60	8.1	91.8		B.Elbow - Wrist	18.5	64.9	5.10	25.0
Ref.			5.6			Ref.		49.0		
A.Elbow	ADM	7.25	8.0	91.7		A.Elbow - B.Elbow	10.5	63.6	5.35	24.2
Ref.			5.6			Ref.		49.0		
L COMM PERONEAL - EDB										
Ankle	EDB	3.70	4.6	100		Ankle - EDB	8		5.20	13.8
Ref.		5.70	2.2		50	Ref.				
Fib Head	EDB	9.15	4.0	86.8		Fib Head - Ankle	27	49.5	5.90	12.8
Ref.			2.2			Ref.		39.0		
Knee	EDB	11.25	3.8	82.6		Knee - Fib Head	10.5	50.0	5.70	13.1
Ref.			2.2			Ref.		39.0		
L TIBIAL (KNEE) - AH										
Ankle	AH	3.95	9.0	100		Ankle - AH	8		5.10	21.8
Ref.		5.70	2.8		50	Ref.				
Knee	AH	11.35	7.1	79.2		Knee - Ankle	35	47.3	5.85	20.0
Ref.			2.8			Ref.		39.0		

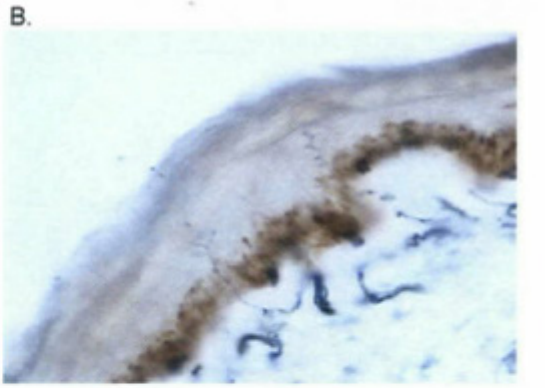
F Wave

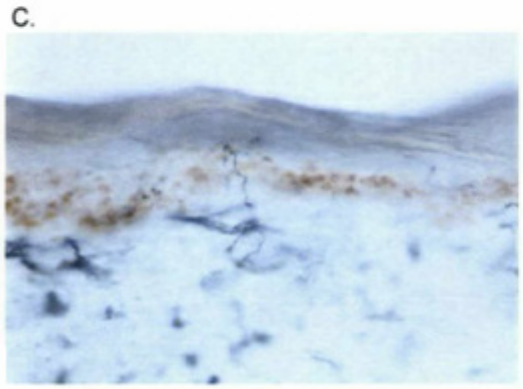
Nerve	Fmin
	ms
L COMM PERONEAL	46.70
REF	56.00
L TIBIAL (KNEE)	48.75
REF	56.00
L MEDIAN	25.30
REF	31.00
L ULNAR	25.05
REF	31.00

Sensory NCS

Nerve / Sites	Rec. Site	Onset Lat	Peak Lat	NP Amp	PP Amp	SPAR	Segments	Distance	Velocity
		ms	ms	µV	µV	%		cm	m/s
L MEDIAN - Dig II Antidr									
Wrist	Dig II	3.20	***4.10***	19.6	26.7		Wrist - Dig II	14	43.8
Ref.			3.80	10.0		50	Ref.		
L MEDIAN - Palmar Ortho									
Palm	Wrist	2.30	***3.05***	***20.2***	27.9	***35.6***	Palm - Wrist	8	34.8
Ref.			2.20	40.0		50	Ref.		
R MEDIAN - Palmar Ortho									
Palm	Wrist	1.60	***2.40***	56.7	58.4	100	Palm - Wrist	8	50.0
Ref.			2.20	40.0		50	Ref.		
L ULNAR - Dig V Antidr									
Wrist	Dig V	2.40	3.05	18.8	24.7		Wrist - Dig V	14	58.3
Ref.			3.80	10.0		50	Ref.		
L ULNAR - Palmar Ortho									
Palm	B Elbow	1.35	1.70	23.0	27.6	100	Palm - B Elbow		
Ref.			2.20	20.0			Ref.		49.0
R ULNAR - Palmar Ortho									
Palm	Wrist	1.30	1.80	21.4	24.4	93.1	Palm - Wrist	8	61.5
Ref.			2.20	20.0		50	Ref.		
L SURAL - Lat Mall Antidr									
Calf	Lat Mall	3.10	3.65	7.8	0.79		Calf - Lat Mall	14	45.2
Ref.			4.20	5.0		50	Ref.		
L SUP PERONEAL - Ankle Antidr									
Lat Leg	Ankle	1.95	2.50	7.1	11.1		Lat Leg - Ankle	10	51.3
Ref.			3.20	5.0		50	Ref.		

Appendix 2. In absence of etiology of her small fiber neuropathy, she underwent genetic testing for TTR (transthyretin) which demonstrated a p.Val142lle (C.424G>A) (also known as p.Val122lle) transthyretin mutation consistent with hereditary amyloidosis. As this mutation is predominantly associated with cardiac involvement, she underwent a cardiac evaluation with echocardiography which was normal and showed normal ejection fraction as well as cardiac MRI which did not show any amyloid infiltration. With the negative cardiac MRI, PYP scan was not performed .





Microscopic Findings

Location	Nerve Fiber Density	Normal Value
A. Right Foot	0.0/mm	>3.0/mm
B. Right Calf	2.4/mm	>4.3/mm
C. Right Lower Thigh	4.2/mm	>6.0/mm