CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Peripheral Neuropathy in p.Val142Ile (Val122Ile) Variant Hereditary Transthyretin-Mediated Amyloidosis

United Kingdom Experience

Victor Jia Wei Zhang,[1] Luke F. O'Donnell,[1] Mariola Skorupinska,[1] Roy Carganillo,[1] Alexander M. Rossor,[1] Marianna Fontana,[2] Dorota Rowczenio,[2] Janet Gilbertson,[2] Julian D. Gillmore,[2] and Mary M. Reilly[1]

Correspondence
Prof. Reilly
m.reilly@ucl.ac.uk

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Abstract

Background and Objectives

p.Val142Ile (p.V142I) is one of the most common pathogenic transthyretin (TTR) variants typically presents as transthyretin amyloid cardiomyopathy (ATTRv-CM), although frequent concurrent peripheral nerve involvement has been reported (94%). We aimed to characterize the polyneuropathy in p.V142I ATTR amyloidosis (ATTRv-PN) from the UK amyloidosis cohort.

Methods

We performed a retrospective cohort study of all confirmed p.V142I Variant Transthyretin Amyloidosis (ATTRv) individuals in the National Hospital for Neurology and Neurosurgery Inherited Neuropathy Clinic between January 2019 and October 2024. Because presence of ATTRv-PN was required to access disease-modifying therapy for amyloidosis during this time, all individuals with p.V142I ATTRv were evaluated for neuropathy, providing an unselected cohort.

Results

We identified 52 individuals with p.V142I ATTRv among whom the clinical presentation was cardiac in 47 (90%) and neuropathic in 5 (10%). Age at diagnosis was 71.3 ± 12.2 years. Twenty of the 52 individuals (38%) had symptoms suggestive of neuropathy with an average duration of symptoms of 4.9 ± 3.5 years 20/52 (38%) had signs suggestive of neuropathy with average Neuropathy Impairment Score being 9.0 ± 10.5. After investigations, 21/52 (40%) individuals had clinical features, neurophysiology, and/or skin biopsies consistent with ATTRv-PN (8 large-fiber/13 small-fiber). Six of the 52 individuals (12%) had neuropathies because of alternative etiologies (e.g., diabetes).

Discussion

Real-world experience from the UK national cohort of p.V142I ATTRv indicates that peripheral neuropathy is of a mild severity and less frequent than previously reported.

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Supplementary Material

Introduction

Variant Transthyretin Amyloidosis (ATTRv) is an inherited condition in which variants in the transthyretin gene resulting in transthyretin (TTR) protein misfolding and deposition. ATTR amyloid particularly affects the heart and nerves, causing cardiomyopathy and peripheral neuropathy (ATTRv-PN). In addition, amyloid deposition in ligaments commonly causes carpal tunnel syndrome (CTS) and lumbar canal stenosis.

[1]Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, National Hospital for Neurology and Neurosurgery (NHNN), London, United Kingdom; [2]National Amyloidosis Centre, UCL Division of Medicine, Royal Free Hospital, London, United Kingdom.

There are over 100 variants in the transthyretin gene associated with ATTRv.[1] p.Val142Ile/p.V142I (NM_000371.4 (TTR): c.424G > A) previously known as Val122Ile, is one of the most common, found predominantly in those with West-African heritage. Its typical presentation is cardiomyopathy, although concurrent peripheral nerve involvement has been reported to be frequent (94%).[2] We aimed to characterize the frequency, severity, and clinical features of polyneuropathy in p.V142I ATTRv from the UK National Amyloidosis Centre cohort.

Methods

We performed a retrospective review of all individuals referred from the National Amyloidosis Centre to the National Hospital for Neurology and Neurosurgery (NHNN) Inherited Neuropathy Clinic with confirmed symptomatic p.V142I ATTRv between January 2019 and October 2024. Gene silencers were the only available disease-modifying therapy for ATTR amyloidosis before August 2024 when tafamidis, a transthyretin stabiliser, was funded. Because presence of ATTRv-PN is required for eligibility for gene silencers, all symptomatic p.V142I ATTRv individuals, whether symptomatic for neuropathy or not, were referred during this period. This cohort is therefore an unselected cohort.

We reviewed individuals' records for their clinical assessments, including Neuropathy Impairment Scores (NIS) and Charcot-Marie-Tooth Symptom, Examination and Neuropathy Scores (CMTSSv2, CMTESv2, and CMTNSv2, respectively) as well as functional assessments captured by their Familial Amyloid Polyneuropathy (FAP) Stage and Polyneuropathy Disability (PND) Scores.

We reviewed investigations results including, 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scans, neurophysiology (large and small-fiber, eTable 1), and skin biopsies.

Where applicable, we reviewed the results of distal leg skin biopsies which were stained with Congo red and evaluated for presence of amyloid and intraepithelial nerve fiber layer density (IENFD) as per published criteria.[3] Skin biopsies were performed in individuals who had clinical, examination, and/or neurophysiologic features suggestive, but not diagnostic, of a small-fiber neuropathy (SFN). When TTR amyloid was identified on skin biopsy and/or there was a reduced IENFD compared with age/sex-matched controls, this was considered representative, in the appropriate clinical context, of SFN because of amyloidosis.

When neuropathy was present and an alternative aetiology was present, careful consideration was given to most likely aetiology causing the neuropathy and the final decision was made by the treating neurologist (M.M.R/A.R.).

To determine potential associations between baseline characteristics and ATTRv-PN, Welch 2-sample t test was performed for continuous variables (age at diagnosis of amyloidosis, cardiac symptom duration) and Pearson χ^2 test with Yates continuity correction for discrete variables (p.V142I homozygosity, sex), using R-studio v4.2.0 and a 2-sided p value significance level of 0.05.

Data Availability

The study was approved by the NHNN Research Ethics Committee (REC:09/H0716/61). Anonymized data not published within this article will be made available by request from a qualified investigator.

Results

Baseline Characteristics

We identified 52 individuals with p.V142I ATTRv. Forty-seven individuals were heterozygote while 5 were homozygous.

Of the individuals with p.V142I ATTRv, 24/52 (46%) had Afro-Caribbean heritage, 19/52 (37%) had West African heritage, 1/52 (2%) Caucasian, and 8/52 (15%) unclassified.

The presenting symptom was cardiac in 47/52 (90%) with predominantly symptomatic cardiac failure. Neuropathic symptoms were the presenting symptom in 5/52 (10%). 25/52 (44%) were female. Average age at diagnosis was 71.3 ± 12.2 (male 69.4 ± 12.1, female 72.7 ± 12.2). Average age at neurologic assessment was 72.2 ± 12.1.

Average duration of cardiac symptoms was 2.6 ± 1.1 years. Regarding DPD scans, 13/52 had Perugini Grade 3 cardiac uptake, 31/52 Grade 2, 3/52 Grade 1, and 5/52 Grade 0.

Ninety percent (47/52) of the individuals had symptoms of CTS. Ninety-six percent (47/49) of the individuals had neurophysiologic CTS. Three were not tested for median nerve entrapment (2 had previous surgery).

Twenty-seven percent (14/52) of the individuals had a history of lumbar canal stenosis.

Polyneuropathy

Thirty-eight percent (20/52) of the individuals had symptoms suggestive of neuropathy, including pins-and-needles, hyperaesthesia, aesthesia, distal limb pain, and weakness. Average duration of neuropathic symptoms was 4.9 ± 3.5 years. Examination showed 20/52 (38%) with signs suggestive of neuropathy and 9/52 (17%) with equivocal signs. Average NIS was 9.0 ± 10.5. Average total CMTNS2 score was 4.8 ± 4.8 with subscores 1.9 ± 2.5 CMTSS2 and 4.4 ± 4.3 CMTES2, indicative of neuropathy of mild severity. Considering only individuals with neuropathy, average NIS was 11.5 ± 11.9 and CMTNS 5.5 ± 4.1.

Table 1 Summary of Individuals With Symptomatic p.V142I ATTRv Neuropathy Assessments

Categories	Number (percentage %)	Subcategories where applicable Number (percentage %)
Neuropathy because of amyloidosis	21 (40)	
Large-fiber axonal neuropathies (diagnosed on large-fiber neurophysiology with symptoms and/or signs of neuropathy)		8 (15)
Small-fiber neuropathies		
Diagnosed on small-fiber neurophysiology with symptoms and/or signs of neuropathy		5 (10)
Diagnosed on skin biopsy which demonstrates amyloid deposits with symptoms and/or signs of neuropathy		2 (4)
Both amyloid and IENFD with symptoms and/or signs of neuropathy		2 (4)
Diagnosed on skin biopsy with decreased IENFD with symptoms and/or signs of neuropathy and a DPD scan Perugini Grade 2 or 3		4 (8)
Neuropathy because of alternative diagnosis	6 (12)[a]	
No neuropathy	25 (48)	
Excluded based on history, examination, and normal neurophysiology		12 (23)
Excluded based on equivocal history, examination, and/or neurophysiology with normal skin biopsy		13 (25)
Total	52	

Abbreviation: IENFD = intraepithelial nerve fiber layer density.
[a] Breakdown of alternative diagnosis = 2 diabetic neuropathies, 2 chemotherapy induced neuropathy, 1 renal failure-associated neuropathy, and 1 concurrent nonamyloidosis hereditary sensory neuropathy.

FAP Stage was 0 in 7 (13%) individuals, 1 in 33 (63%), and 2 in 12 (23%). PND Score was Not Applicable in 10 (19%) individuals, I in 28 (54%), II in 2 (4%), IIIa in 7 (13%), and IIIb in 5 (10%).

After assessment and investigations, 21/52 (40%) individuals had clinical features, neurophysiology, and/or skin biopsies consistent with an ATTRv-PN. 8/21 individuals had large-fiber axonal neuropathies (6 sensorimotor and 2 sensory). 13/21 individuals had SFN, of which 5 were based on clinical assessment and abnormal small-fiber neurophysiology testing while 8 based on clinical assessment and abnormal skin biopsy results (4 had reduced IENFD, 2 had presence of amyloid, and 2 had both reduced IENFD and presence of amyloid). These findings are summarized in Table 1.

Twelve percent (6/52) had neuropathies because of alternate etiologies—2 diabetic neuropathies, 2 chemotherapy induced neuropathy, 1 renal failure-associated neuropathy, and 1 concurrent nonamyloidosis hereditary sensory neuropathy.

Seven of 52 individuals were on medication for neuropathic symptoms secondary to neuropathy, CTS, or lumbar canal stenosis.

There was no statistically significant association between ATTRv-PN and age ($p = 0.83$), sex ($p = 0.17$), homozygosity of p.V142I variant ($p = 0.87$), or duration of cardiac symptoms ($p = 0.48$).

Seventeen of 21 individuals with ATTRv-PN were commenced on patisiran/vutrisiran and 4/21 on tafamidis.

Skin Biopsies

Forty-four percent (23/52) of the individuals underwent distal leg skin biopsies. Thirteen of 23 biopsies demonstrated normal IENFD and no evidence of amyloid. Eight of 23 biopsies were abnormal and consistent with a SFN ATTRv-PN while 2/23 biopsies were abnormal and consistent with a nSFN because of an alternative etiology—Table 1 for more detail.

Discussion

We characterize the frequency, features, and severity of neuropathy in the p.V142I ATTRv cohort from the UK national referral centre.

In our cohort, the frequency of ATTRv-PN was 40%. Contrastingly, Zampino et al. 2023 identified 94% of their p.V142I ATTRv cohort had peripheral nerve involvement which was defined as, regardless of aetiology, abnormal neurophysiology, abnormal skin biopsy, or prescription of medications for

neuropathic pain. Applying the same criteria in our cohort, only 60% had peripheral nerve involvement.

Indeed, the identification of the etiology of neuropathy is important to ensure an individual's suitability for gene silencing therapy or other treatment implications if the neuropathy is due to an alternative aetiology.

Our cohort underwent UK best practice for assessment of neuropathy in amyloidosis which is similar to that in Zampino et al. 2023. However, there are some differences. For instance, in our cohort, skin biopsies were only performed if there was clinical equipoise based on clinical assessment and neurophysiology. Thus, skin biopsy would aid in the diagnosis of SFN. Contrastingly, all individuals in Zampino et al. 2023 underwent skin biopsy.

Moreover, our skin biopsy protocol, as aforementioned, is a distal leg skin biopsy for IENFD and amyloid staining. The location is chosen given that ATTRv-PN is predominantly length-dependent.[4] Zampino et al. 2023 also performed distal and proximal thigh skin biopsies and sweat gland nerve fiber density analysis.

Regarding neuropathy severity and functional disability, average CMTNS2 scores in our cohort was 4.8 ± 4.8, falling in the mild neuropathy range.[5] Similarly, average NIS score was 9.0 ± 10.5—lower than 22 ± 16 in Zampino et al. 2023. Correspondingly, there was also a lower degree of functional impairment and disability in our cohort, with earlier FAP and PND Stages. In addition, the FAP and PND stages can be influenced by the presence of lumbar canal stenosis and cardiomyopathy. Hence, these scores may overestimate the impairment and disability individuals experience from neuropathy.

In summary, in our p.V142I ATTRv cohort referred from the UK National Amyloidosis Centre, ATTRv-PN was present in 40% and of a mild severity and functional impairment.

Author Contributions

V.J.W. Zhang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. L.F. O'Donnell: drafting/revision of the manuscript for content, including medical writing for content. M. Skorupinska: major role in the acquisition of data. R. Carganillo: major role in the acquisition of data. A.M. Rossor: drafting/revision of the manuscript for content, including medical writing for content m fontana: major role in the acquisition of data. D. Rowczenio: major role in the acquisition of data. J. Gilbertson: major role in the acquisition of data. J.D. Gillmore: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M.M. Reilly: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

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