Identifying Mixed Phenotype: Evaluating the Presence of Polyneuropathy in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Cardiomyopathy

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Introduction

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, progressively debilitating, fatal disease caused by a mutation in the transthyretin (*TTR*) gene that results in multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunction in multiple organs[1–5]
- Affects ~50,000 people worldwide[4]; median survival is 4.7 years following diagnosis, which is reduced to 3.4 years in patients presenting with cardiomyopathy[6–9]
- Non-specific heterogeneous clinical presentation with patients historically grouped by their predominant phenotype (cardiomyopathy or polyneuropathy[6,10]); however, recent evidence has shown that the majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[11–14]
- Overview of common pathogenic *TTR* mutations:
  - **Val122Ile:** Most common mutation in the US, with African Americans having ~4% prevalence for this mutation,[15] historically associated with predominant cardiomyopathy symptoms[15] although more recent research has led to increased recognition of polyneuropathy symptoms[16,17]
  - **Thr60Ala:** Common in the US,[16] UK, and endemic in certain parts of Ireland,[15] and typically associated with a mixed phenotype[8,15] although historically categorized as presenting with a predominant cardiac phenotype[15]
  - **Val30Met:** Most commonly reported mutation worldwide, historically associated with predominant polyneuropathy symptoms; recent growing evidence of cardiomyopathy has been described[18,19]

Objective

- Describe presence of polyneuropathy signs and symptoms in patients with hATTR amyloidosis and confirmed cardiomyopathy to evaluate prevalence of mixed phenotype presentation among these patients

Methods

- Baseline disease characteristics and medical history (MH) collected during screening period from a Phase 3 study of hATTR amyloidosis with cardiomyopathy (NCT02319005) were analyzed in the overall study population and in the 3 most commonly occurring mutations to evaluate for presence of polyneuropathy signs/symptoms
  - Patients enrolled in the Phase 3 ENDEAVOUR study had hATTR amyloidosis with cardiomyopathy (n=206) with a documented *TTR* mutation, amyloid deposition by biopsy or technetium scintigraphy, and echocardiographic evidence of cardiac amyloid involvement
  - Patients had a MH of heart failure (HF) with ≥1 prior hospitalization for HF or clinical evidence of HF that required or was requiring diuretic treatment or was associated with elevated cardiac biomarkers (brain natriuretic peptide >100 ng/L or N-terminal prohormone of brain-type natriuretic peptide >400 ng/L)
- Baseline disease characteristics collected during screening included New York Heart Association (NYHA) class, modified body mass index (mBMI), and polyneuropathy disability (PND) score
- MH was coded using Medical Dictionary for Regulatory Activities (MedDRA version 17.1); Standardized MedDRA Query (SMQ) for peripheral neuropathy was also used to capture peripheral neuropathy-related MH
  - Nervous system disorders within the SMQ combines the following high-level terms (HLTs): peripheral neuropathies, acute polyneuropathies, paresthesias and dysesthesias, sensory abnormalities, autonomic nervous system disorders, neuromuscular disorders, and mononeuropathies
- For the temporal analysis of MH, a clinical reviewer selected MedDRA-coded preferred terms and HLTs based on disease manifestations consistent with the natural history of hATTR amyloidosis

Results

Patient Baseline Demographics and Disease Characteristics

- Among the 206 patients enrolled in the study, the 3 most common genotypes in the Phase 3 study were Val122Ile (n=118), Thr60Ala (n=35), and Val30Met (n=9) (**Table 1**)
- Majority of patients had symptomatic HF at baseline (NYHA Class II/III, 92%)
- Based on baseline PND score, most patients had either sensory disturbances (PND I, 36%) or impaired ambulation (PND II, 17%) as a function of polyneuropathy

Results

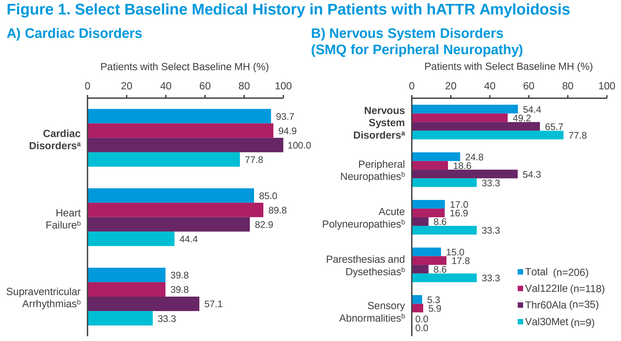
Table 1. Baseline Demographics and Disease Characteristics in Patients with hATTR Amyloidosis with Cardiomyopathy

	Total n=206	Val122Ile n=118	Thr60Ala n=35	Val30Met n=9
Mean (SD) age, years	67.8 (9.4)	71.4 (7.7)	66.9 (5.2)	69.3 (7.2)
Male, %	76.7	83.1	65.7	77.8
Race, %				
Black or African-American	50.5	85.6	0.0	11.1
White	46.1	10.2	97.1	88.9
NYHA class, %				
I	8.3	7.6	5.7	0.0
II	60.7	59.3	71.4	88.9
III	31.1	33.1	22.9	11.1
Mean (SD) mBMI, kg/m^2×g/L	1104.6 (236.6)	1121.7 (246.1)	1046.5 (217.5)	983.8 (144.9)
PND score, %				
0: no symptoms	47.1	53.4	37.1	33.3
I: sensory disturbances but preserved walking capability	36.4	36.4	37.1	33.3
II: impaired walking capacity but ability to walk without a stick or crutches	16.5	10.2	25.7	33.3

Evidence of Neuropathy in Patients with hATTR Amyloidosis with Cardiomyopathy Using Medical History

- In MH, 93.7% of all patients reported terms that coded to cardiac disorders, including 85% with a history of HF (**Figure 1A**)
- 54.4% of all patients and 49.2% of those with the Val122Ile mutation reported terms that coded to nervous system disorders within the peripheral neuropathy SMQ (**Figure 1B**)
- MH of diabetes mellitus was reported in 14.6% of all patients and in 18.6% of patients with the Val122Ile mutation, 8.6% with the Thr60Ala mutation, and 11.1% with the Val30Met mutation
  - 59.7% of all patients reported terms that coded to metabolism and nutrition disorders based on MedDRA SOC (72.9% Val122Ile, 48.6% Thr60Ala, and 33.3% Val30Met)

Figure 1. Select Baseline Medical History in Patients with hATTR Amyloidosis



For nervous system disorders (SMQ for peripheral neuropathy), HLTs are shown that were >5% in the total population
[a]MedDRA SOC; [b]MedDRA HLT

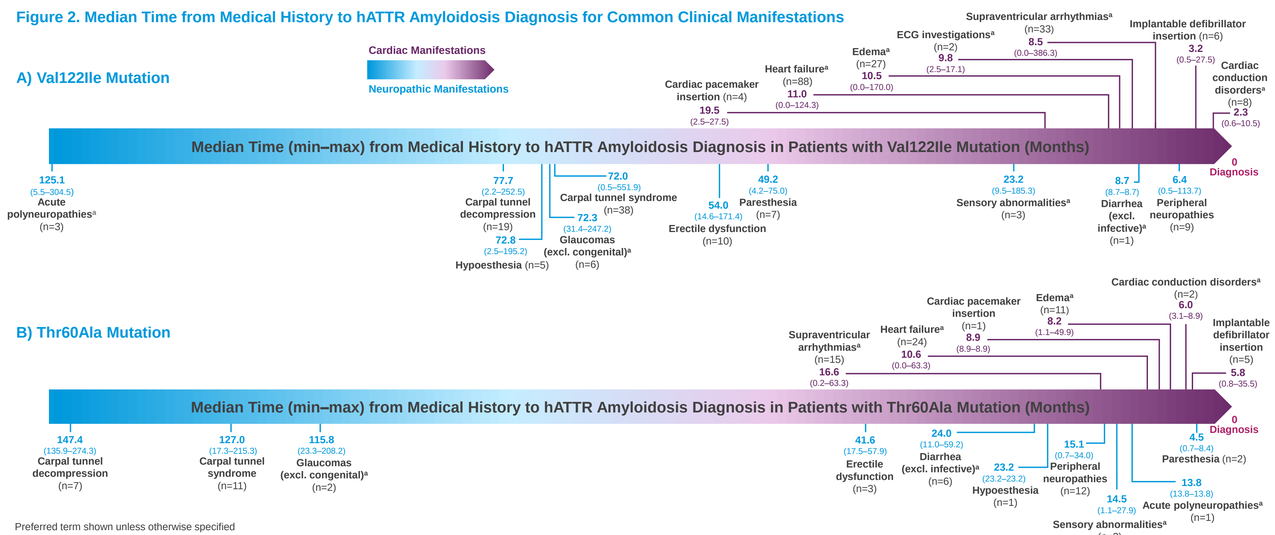
Symptom Timeline from Medical History to hATTR Amyloidosis Diagnosis

- Among the Val122Ile mutation, many neuropathic diagnoses presented in advance of cardiac manifestations; earliest manifestations seen were acute polyneuropathies, hypoesthesia, and erectile dysfunction (**Figure 2A**)
- Similarly, among the Thr60Ala mutation (**Figure 2B**), as well as in the overall cohort, neuropathic manifestations (both peripheral and autonomic neuropathy) tended to precede or coincide with cardiac manifestations
  - Carpal tunnel decompression and syndrome were among the earliest symptoms in the overall cohort as well as in the patients with Val122Ile and Thr60Ala mutations

Limitations

- MH was limited to medical records/patient reports and not based on a targeted questionnaire or comprehensive clinical evaluation; distinguishing whether MH terms are truly related to hATTR amyloidosis or from other comorbidities is often difficult
- Conditions captured in this analysis may not be inclusive of all manifestations related to hATTR amyloidosis
- Further research to replicate these findings in larger cohorts and other genotypes can help confirm the findings

Figure 2. Median Time from Medical History to hATTR Amyloidosis Diagnosis for Common Clinical Manifestations



Preferred term shown unless otherwise specified
[a]MedDRA HLT

Conclusions

- hATTR amyloidosis is a rapidly progressive, multisystem disease with a variable genotype–phenotype relationship
  - Recently, there has been increased evidence of a mixed phenotype with both cardiac and neuropathic features in patients across the range of known pathogenic *TTR* mutations
- In patients with hATTR amyloidosis with confirmed cardiomyopathy, signs and symptoms of polyneuropathy were found in more than half of the patients based on clinical evaluation (PND scores) and analysis of MH
- MH of polyneuropathy tended to precede or coincide with signs and symptoms of cardiomyopathy, even in Val122Ile patients traditionally thought of as presenting with predominant cardiac symptoms
- Owing to the debilitating and fatal nature of this disease, identification of early signs and symptoms is crucial for prompt diagnosis of hATTR amyloidosis
  - The evidence presented here demonstrates that polyneuropathy may be an early sign that is potentially overlooked in patients with hATTR amyloidosis with cardiomyopathy
  - The finding that polyneuropathy precedes or coincides with cardiomyopathy is generally consistent with results from a previous publication in patients with ATTR amyloidosis with cardiomyopathy[20]
  - Multisystem disease assessment and earlier clinical suspicion may help in identifying patients prior to greater disease burden

Abbreviations: ECG, electrocardiogram; hATTR, hereditary transthyretin-mediated; HF, heart failure; HLT, high-level term; mBMI, modified body mass index; MedDRA, Medical Dictionary for Regulatory Activities; MH, medical history; NYHA, New York Heart Association; PND, polyneuropathy disability; SD, standard deviation; SMQ, Standardized MedDRA Query; SOC, system organ class; TTR, transthyretin.

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References: 1. Adams et al. *Neurology* 2015;85:675–82; 2. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 3. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 4. Hawkins et al. *Ann Med* 2015;47:625–38; 5. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 6. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 7. Swiecicki et al. *Amyloid* 2015;22:123–31; 8. Castaño et al. *Heart Fail Rev* 2015;20:163–78; 9. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 10. Conceição et al. *J Peripher Nerv Syst* 2016;21:5–9; 11. Adams et al. *N Engl J Med* 2018;379:11–21; 12. Benson et al. *N Engl J Med* 2018;379:22–31; 13. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 14. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 15. Ruberg et al. *Circulation* 2012;126:1286–300; 16. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 17. Khella et al. *Peripheral Nerve Society (PNS)* 2018. Poster P26; 18. Parman et al. *Curr Opin Neurol* 2016;29(Suppl. 1):S3–S13; 19. Suhr et al. *Amyloid* 2006;13:154–9; 20. Papoutsidakis et al. *J Card Fail* 2018;24:131–3.