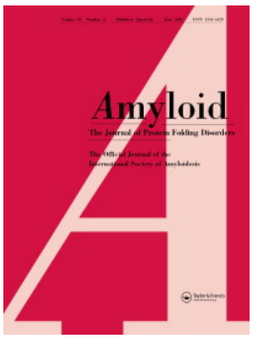

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RESEARCH ARTICLE

Early cardiovascular autonomic failure in ATTRv predicts poor prognosis and may respond to disease-modifying therapy

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ABSTRACT

Background: Hereditary transthyretin amyloidosis (ATTRv) is a life-threatening, but treatable disease presenting with autonomic dysfunction. This study investigates the progression of autonomic failure, response to treatment, and the impact of autonomic failure in ATTRv.

Methods: Clinical features and autonomic function test (AFT) results were evaluated in 126 patients (40 had treatment) and 12 asymptomatic TTR variant carriers. A subgroup had follow-up (FU) AFT. Kaplan-Meier estimates compared survival time between participants with and without neurogenic orthostatic hypotension (nOH), and logistic regression assessed its impact on mortality.

Results: Patients treated early with disease modifying therapies (DMT) had slower progression and did not develop nOH. In 59 individuals with repeat AFT, autonomic dysfunction worsened, with a decline in the Valsalva ratio ($p=0.002$), even in early-stage disease ($p=0.019$; median disease duration at FU 4 years). nOH at first assessment predicted worse outcome (mean survival time in individuals with nOH 7.0 vs. 14.9 years without nOH, $p<0.001$) and death (OR = 5.27; 95%CI: 1.94 – 14.31; $p=0.001$).

Conclusions: The early development of autonomic dysfunction and nOH is an independent predictive factor for shorter survival in ATTRv. Autonomic testing is a valuable biomarker to capture disease progression. Prospective studies need to confirm the benefit of DMT on autonomic dysfunction.

Abbreviations: AFT: autonomic function testing; ATTRv: hereditary/variant transthyretin amyloidosis; BP: blood pressure; DMT: disease modifying treatment; FU: follow-up; HR: heart rate; HUT: head-up tilt table test; nOH: neurogenic orthostatic hypotension; PND: polyneuropathy disability; SBP: systolic blood pressure; TTR: transthyretin

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Introduction

Hereditary or variant transthyretin amyloidosis (ATTRv) is an autosomal dominant, systemic, progressive, and life-threatening disease if untreated. It is caused by variants in the transthyretin (TTR) gene leading to the production of misfolded amyloidogenic precursor protein. The misfolded proteins form extracellular deposits in different organs, mainly the heart and peripheral nerves [1] causing a broad range of phenotypes, dominated by cardiomyopathy and/or sensorimotor and autonomic polyneuropathy. There has been an increasing recognition of sporadic cases, with an estimated prevalence of approximately 10'000 cases of ATTRv with polyneuropathy worldwide [2]. In the United Kingdom, most patients with a neuropathic or mixed phenotype carry the Thr60Ala (p.Thr80Ala) point mutation which can present with early autonomic involvement [3].

The ability to diagnose ATTRv has improved considerably. The combination of progressive axonal sensorimotor neuropathy and other features including autonomic dysfunction, gastrointestinal symptoms, positive family history, carpal tunnel syndrome, or cardiac hypertrophy is considered highly suggestive for ATTRv [4]. Nonetheless, diagnosis can remain challenging in patients with atypical phenotypes or in sporadic patients with no family history, often leading to initial misdiagnoses such as chronic inflammatory demyelinating polyneuropathy, thus delaying treatment [5].

Autonomic manifestations, predominantly disabling gastrointestinal dysfunction or neurogenic orthostatic hypotension (nOH) affect 78-94% of patients [6,7] and can represent

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the first symptom in 27-48% of patients with certain variants, possibly preceding and occurring independently of sensorimotor polyneuropathy and/or cardiomyopathy [6,8]. Cardiovascular sympathetic and parasympathetic autonomic failure can be quantitatively assessed at preclinical stages using autonomic function testing (AFT) [6,9]. As of today, the progression of autonomic failure throughout the course of the disease remains insufficiently described.

In addition to the TTR stabilisers tafamidis and diflunisal, disease modifying treatments (DMTs), namely the small interfering RNAs patisiran and vutrisiran [10,11] and antisense oligonucleotides such as inotersen [12], have become available, making early diagnostic accuracy quintessential to grant patients access in the initial, less symptomatic stages of the disease. However, no approved treatment is currently available for variant carriers at a pre-clinical stage, and the effects of DMTs on the progression of autonomic neuropathy have not been systematically evaluated yet. This gap highlights the need for further research in early intervention and the effects of treatment on autonomic dysfunction.

The aims of this longitudinal study were to: (1) evaluate the progression of autonomic failure in patients with ATTRv and asymptomatic carriers, (2) assess the response of autonomic failure to disease specific treatment (disease modifying or transthyretin stabilising drugs), and (3) investigate the impact of early autonomic failure on overall disease progression and survival.

Patients and methods

Participants

This single-centre, retrospective, longitudinal study was conducted at the Autonomic Centre, National Hospital for Neurology and Neurosurgery, London, UK. We included patients with a genetically confirmed diagnosis of ATTRv and asymptomatic TTR variant carriers who were referred to our centre from 1992 – 2023. As part of their clinical care and a natural history study of autonomic disorders, all individuals underwent baseline AFT at their initial evaluation (timepoint 1) and, where available, follow-up AFT (timepoint 2).

DMT was considered as small interfering RNA or antisense oligonucleotide drugs (patisiran, vutrisiran, inotersen). TTR stabilisers included diflunisal and tafamidis.

Ethics approval was obtained by national (London Harrow Research Ethics Committee) and institutional (University College London and Imperial College London) research authorities. The Research Ethics Committee reference number is 16/LO/1656. The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [13].

Cardiovascular autonomic assessments

Standardised AFT was performed to evaluate cardiovascular sympathetic and parasympathetic autonomic function as previously described [14] using digital photoplethysmography (Finapres® NOVA, TNO-TPD, Biomedical Instrumentation, Amsterdam, Netherlands). Briefly, sympathetic function was assessed by passive 60° head-up tilt table test (HUT) for up to 10 min, standing test for up to 5 min, and blood pressure (BP) response to pressor tests including sustained isometric exercise, mental arithmetic, and cold pressor stimuli, as well as to Valsalva manoeuvre. Parasympathetic cardiovagal function was evaluated by heart rate (HR) response to deep breathing (respiratory sinus arrhythmia), to Valsalva manoeuvre (Valsalva ratio), and to hyperventilation. Age-dependent normative values were defined as previously described [14]. Plasma noradrenaline levels were measured in blood samples collected in supine and tilted position [14].

Stages of autonomic failure

Degree of autonomic failure was defined according to AFT results as previously reported [6]: 0) normal AFT without meeting the criteria for stage I) or II); I) mild parasympathetic and/or sympathetic impairment (impaired cardiovascular function following deep breathing, Valsalva manoeuvre, or pressor tests), II) severe and widespread cardiovascular autonomic failure with nOH on tilt and/or standing test.

NOH was defined according to the consensus statement [15].

Polyneuropathy disability (PND) stage

PND scores were analysed in patients and carriers as previously described by Yamamoto et al. [16], ranging from stage 0 (no neurological/ambulatory impairment) to stage 4 (uses a wheelchair/bedridden).

Statistical analyses

Continuous variables were reported as mean ± standard deviation (normally distributed data) or median and interquartile range (non-normally distributed data). Nominal data were expressed as number or percentage. BP and HR responses were compared using t-test, Mann-Whitney-U test, Wilcoxon test, Chi Square test, or exact Fisher test, as appropriate.

The mean overall survival time of patients with ATTRv with and without presence of nOH at baseline AFT assessment was calculated using Kaplan-Meier curve estimates. Multivariable logistic regression analysis was used to investigate the association between presence of nOH at baseline and all-cause death. Accuracy of our predicted model was tested using receiver operator characteristics (ROC) curve analysis. Association between autonomic failure stage and age at death were assessed by multivariable linear regression analysis. Univariable logistic regression analysis was performed to assess the association between nOH at baseline assessment and worsening of PND stage at time of FU.

Statistical analyses were performed using SPSS 29 (Armonk, NY: IBM Corp).

Results

Demographic data

A total of 126 patients and 12 asymptomatic variant carriers were enrolled at baseline. The most common TTR variant

was Thr60Ala ($n=57$, thereof 5 carriers), followed by Val30Met (p.Val50Met; $n=33$ including 6 carriers), Ser77Tyr (p.Ser97Tyr; 6 patients), and others ($n=42$; Table 1). 42/138 individuals (30%) were female (8/12 carriers). The mean age at baseline assessment was 57.0 ± 12.9 years (58.1 years for patients and 43.9 years for carriers). Median disease duration at initial assessment was 4 (2–8) years.

Clinical phenotype and autonomic dysfunction in part of this cohort has been described in detail in our previous study [6]. This paper focuses on the progression of autonomic failure from baseline to FU assessment.

Of the 126 patients, 40 (eight females, mean age 58.2 ± 11.8 years) received disease specific treatment (Figure 1). Ten received DMT (nine on patisiran, one on vutrisiran), two had tafamidis, 22 had diflunisal, and six were treated with diflunisal and DMT (four had patisiran, two had inotersen). Treated patients presented a longer disease duration (median 5.5 (3.3 – 8.8) years) compared to patients without treatment (median 4.0 (2–6.5) years, $p=0.043$). Most untreated patients underwent AFT in the pre-treatment era (1992–2021) while treated patients were tested from 2005–2023. Patients not treated when therapies were available had non-neuropathic symptoms or intolerance/contraindications.

Of the 138 individuals, 53 patients and six asymptomatic carriers underwent autonomic assessments at a second timepoint. The mean age at baseline testing was 54.7 ± 5.5 years, with 19/59 being females (five carriers). The median disease duration at initial AFT was 4.0 (3–8) years (Figure 1). The median FU interval was 23 (15–36) months.

Cross-sectional autonomic responses to disease specific treatment

Detailed AFT results at baseline comparing patients with and without disease specific treatment are shown in Table 1. No significant differences were found when comparing

Table 1. Number of different TTR variants and results of autonomic function tests in individuals without and with treatment.

	Individuals without treatment	Individuals with treatment	p
TTR Variant (standard notation; number)	Thr60Ala (p.Thr80Ala; 38), Val30Met (p.Val50Met; 28), Ser77Tyr (p.Ser97Tyr; 4), Glu89Lys (p.Glu109Gln; 3), Ile107Phe (p.Ile127Phe; 3), Ser52Pro (p.Ser72Pro; 3), Glu89Gln (p.Glu109Gln; 2), Gly47Val (p.Gly67Val; 2), Ala97Ser (p.Ala117Ser; 2), Ala120Ser (p.Ala140Ser; 1), Arg34Gly (p.Arg54Gly; 1), Asp38Tyr (p.Asp58Tyr; 1), Gly47Ala (p.Gly67Ala; 1), Gly47Glu (p.Gly67Glu; 1), His90Asp (p.His110Asp; 1), Ile84Thr (p.Ile104Thr; 1), Ile107Val (p.Ile127Val; 1), Leu12Pro (p.Leu32Pro; 1), Ser23Asn (p.Ser43Asn; 1), Val122Ile (p.Val142Ile; 1), Val20Ile (p.Val40Ile; 1), Val94Ala (p.Val114Ala; 1)	Thr60Ala (19), Val30Met (5), Gly47Val (3), Glu54Gly (p.Glu74Gly; 2), Ser77Tyr (2), Gly53Ala (p.Gly73Ala; 1), Gly47Glu (1), Gly47Arg (p.Gly67Arg; 1), His90Asp (1), Ile84Ser (p.Ile104Ser; 1), Phe33Ile (p.Phe53Ile; 1), Phe33Val (p.Phe53Val; 1), Ser23Asn (1), Val120Ile (1)	
Cardiovascular autonomic function test			
Supine values	$n=98$	$n=40$	
Resting SBP [mmHg]	121.8 ± 19.6	120.3 ± 15.5	0.618
Resting DBP [mmHg]	73.0 ± 11.7	72.4 ± 10.3	0.778
Resting HR [bpm]	71.7 ± 12.8	69.8 ± 11.3	0.393
Head-up tilt test	$n=97$	$n=40$	
Δ SBP [mmHg]	11.5 (4.6 – 25.5)	14.0 (3.7 – 29.5)	0.812
Δ DBP [mmHg]	2.75 (−3.1 – 11.0)	5.3 (−1.38 – 12.9)	0.243
Standing test	$n=98$	$n=40$	
Δ SBP [mmHg]	10.0 (1.0 – 25.0)	13.8 (1.2 – 31.4)	0.736
Δ DBP [mmHg]	3.5 (−2.5 – 14.0)	6.2 (−2.4 – 14.4)	0.479
Prevalence of nOH on HUT and/or stand	43%	48%	0.618
Isometric exercise	$n=92$	$n=37$	
Δ SBP [mmHg]	11.0 (5.0 – 21.0)	9.0 (3.5 – 17.5)	0.253
Δ DBP [mmHg]	8.0 (1.25 – 14.0)	4.0 (−1.5 – 12.5)	0.099
Prevalence	51%	68%	0.088
Mental arithmetic	$n=89$	$n=40$	
Δ SBP [mmHg]	6.0 (0.0 – 13.0)	9.0 (1.0 – 16.8)	0.236
Δ DBP [mmHg]	4.0 (−2.0 – 9.0)	4.0 (0.0 – 8.8)	0.519
Prevalence	66%	55%	0.220
Cold pressure test	$n=95$	$n=40$	
Δ SBP [mmHg]	4.0 (0.0 – 12.0)	4.5 (0.0 – 12.8)	0.938
Δ DBP [mmHg]	2.0 (0.0 – 7.0)	4.0 (−1.8 – 8.5)	0.828
Prevalence	74%	72%	0.823
Hyperventilation	$n=85$	$n=30$	
Δ HR [bpm]	5.0 (2.0 – 11.5)	7.5 (2.8 – 13.5)	0.264
Prevalence	76%	60%	0.103
RSA	$n=76$	$n=33$	
Δ HR [bpm]	3.0 (0.0 – 11.0)	2.0 (0.0 – 12.0)	0.362
Prevalence	78%	76%	0.778
Valsalva Manoeuvre			
Valsalva Ratio	$n=61$	$n=26$	
	1.26 (1.05 – 1.63)	1.22 (1.05 – 1.82)	0.544
Prevalence	74%	62%	0.254
Abnormal BP profile	$n=64$	$n=27$	
Prevalence	56%	52%	0.700

Data are noted as the mean ± SD (normally distributed data) or median (IQR) for non-normally distributed data, and the prevalence of abnormal testing according to age. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. HR: Heart Rate. RSA: Respiratory Sinus Arrhythmia.

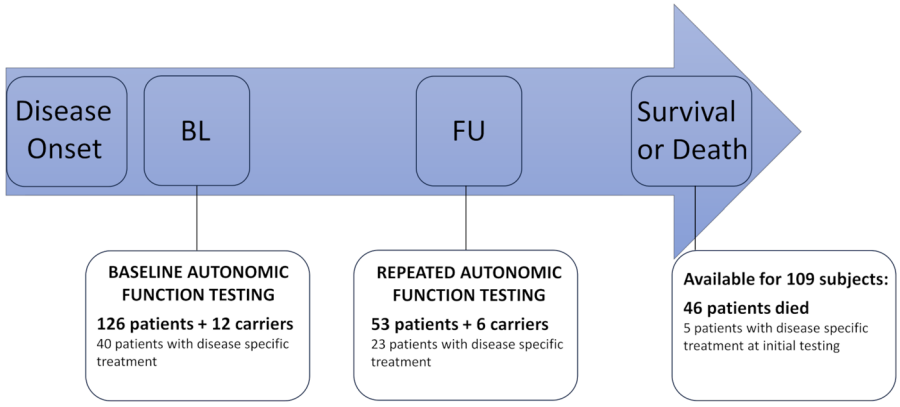

Figure 1. Overview of individuals including patients with disease specific treatment as well as variant carriers enrolled in the study at baseline, follow-up, and for whom survival data were available. BL: baseline; FU: follow-up.

autonomic parameters in patients receiving TTR stabilisers ($n=24$) versus patients receiving DMT ($n=10$). Despite having longer disease duration, treated patients tended to have a lower prevalence of parasympathetic abnormalities on AFT compared to untreated patients. No significant differences were found after matching for disease duration. Among treated patients, 5/39 (13%) had normal autonomic cardiovascular function (stage 0), 15/39 (38%) had stage I, and 19/39 (49%) stage II cardiovascular autonomic failure. In the treatment-naïve group, only 7/95 (7%) presented with autonomic failure stage 0, whereas 46/95 (49%) presented with stage I, and 42/95 (44%) with stage II.

Progression of autonomic failure

FU autonomic testing was performed in a subset of individuals (53 patients and six carriers; 32% females).

In patients, the prevalence of autonomic symptoms increased from 77% at baseline to 89% at FU, with a higher need for anti-hypotensive treatment (17% vs 28%). Cardiac involvement also increased over time (79% vs 89%). Electrophysiologically assessed axonal polyneuropathy was confirmed in 22 patients at baseline, and additional four patients had developed neuropathy by FU. Carpal tunnel syndrome was present in 25 patients at baseline, with three more individuals diagnosed at FU.

Several indices of autonomic function worsened from baseline to FU including significantly decreased Valsalva ratio ($p=0.002$; exemplary Figure 2), mirrored by an increased prevalence of abnormal Valsalva ratio from 58% at baseline to 79% at FU ($p=0.016$), decreased HR response to deep breathing ($p=0.027$; exemplary Figure 2 and 3), and reduced change in systolic BP (SBP) during mental arithmetic ($p=0.044$). Detailed results are shown in Table 2, and progression of autonomic failure is described in two representative cases below.

This effect was particularly evident in patients with the shortest disease duration ≤ 4 years at baseline and carriers ($n=20$), for whom Valsalva ratio worsened over time ($p=0.019$), with notable increase in the prevalence of abnormal Valsalva ratio ($p=0.031$) by FU. Carriers also showed distinct worsening of Valsalva ratio ($p=0.028$).

In the subset of individuals with FU, 23/59 (39%) were receiving disease specific treatment at baseline and/or FU (Figure 1) and autonomic cardiovascular staging was available for 58/59 individuals. 40/58 individuals initially presented with mild autonomic cardiovascular dysfunction (stage 0/I) and the majority (35/40, 88%) remained stable without progression to widespread autonomic failure (stage II) over a FU period of up to 11.1 years, independent of treatment status. However, five patients progressed to stage II (within a maximum FU of 4.8 years), none of whom were on DMT.

Ten individuals (10/58, 17%) initially presented with normal autonomic function at baseline (stage 0), and only two patients remained stable (stage 0) for up to 18 months of FU, both of whom were on DMT (one switched from patisiran to inotersen, one was started on inotersen). Eighteen patients presented with severe autonomic failure (stage II) at baseline (median disease duration of 3 years). At repeat assessment, 12/18 (67%) remained untreated, while only 6 (33%) received treatment. In patients with widespread autonomic failure with nOH at baseline, there was no improvement in the severity of nOH over time (mean ΔSBP on tilt 36.3 mmHg at baseline versus 36.5 mmHg at FU), regardless of treatment status.

Among those with mild and stable autonomic dysfunction at FU (stage 0/I, $n=35$), 46% were female, whereas only 13% of patients with severe or worsening autonomic impairment were women ($\chi^2=6.73$; $p=0.01$).

Baseline noradrenaline values were available for 28/59 individuals (including three carriers). Of the 28 individuals who had plasma noradrenaline assessments, all had normal supine noradrenaline levels (mean supine noradrenaline 272.4 pg/ml) and 10/28 (36%) participants (including one carrier) showed a pathologic response (less than a 33% rise) to tilt. This was mostly consistent with abnormal adrenergic function documented on AFT including presence of nOH and impaired BP responses to pressor stimuli. Of the remaining18 individuals (two carriers) with normal supine and tilted baseline noradrenaline, 11/17 (65%) had abnormal AFT (data was insufficient for one patient).

Repeat noradrenaline levels were available for 18 individuals (two carriers). In a sub-analysis considering these 18 participants, there was no significant difference between

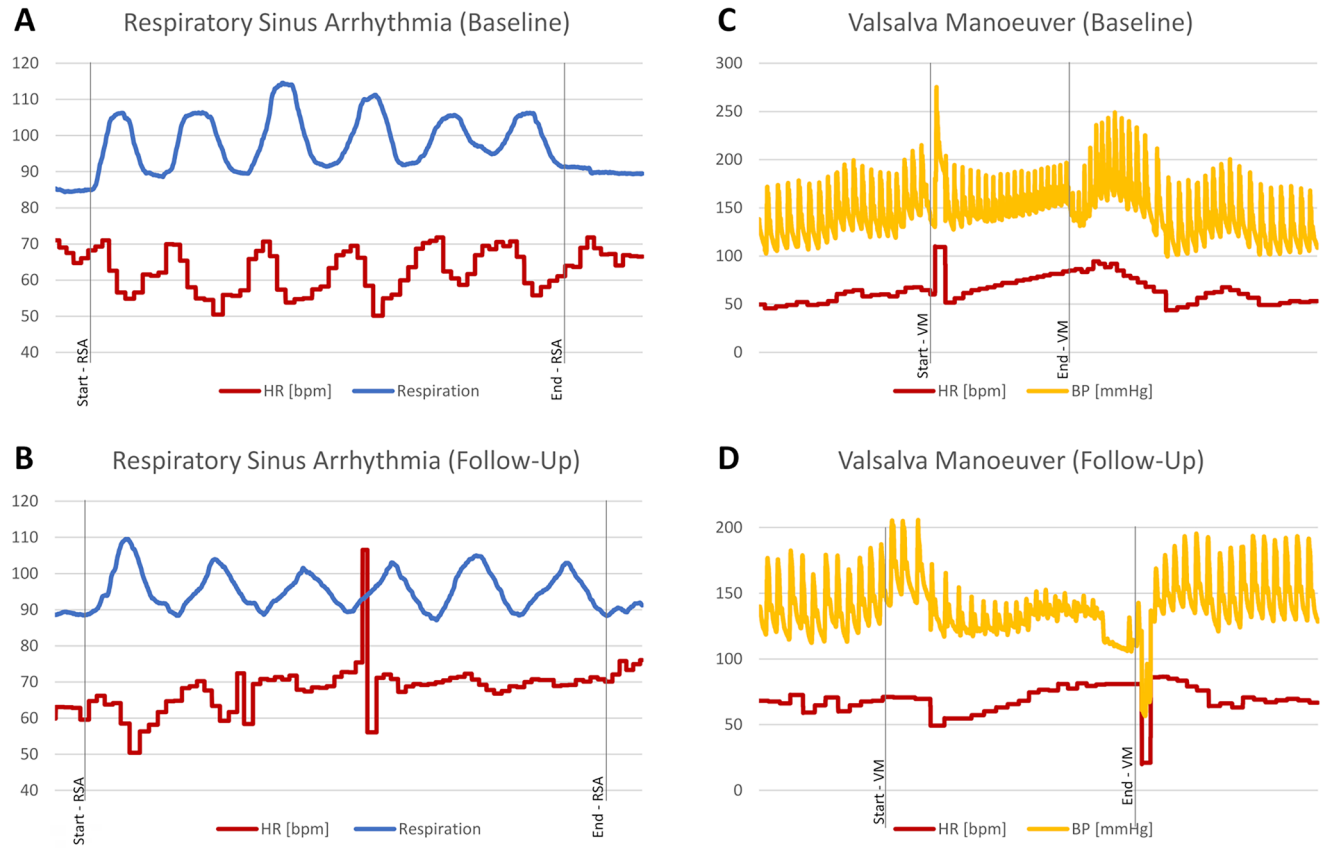

Figure 2. Respiratory sinus arrhythmia and Valsalva manoeuvre in a patient with transthyretin amyloidosis: normal HR variability to deep breathing (A) and normal HR and BP responses to Valsalva manoeuvre (C) at baseline, with loss of HR variability to deep breathing (B) as well as reduced Valsalva ratio and loss of late phase II BP recovery and phase IV BP overshoot to Valsalva manoeuvre (D) at follow-up. bpm: beats per minute; BP: blood pressure; HR: heart rate; RSA: respiratory sinus arrhythmia; VM: Valsalva manoeuvre.

noradrenaline levels (both supine and tilted) at baseline and FU. Two patients with initially normal noradrenaline showed a reduced noradrenaline rise on tilt at FU. No improvement of noradrenaline rise on tilt was noted over time.

Early autonomic failure with nOH is a predictor for poor outcome

In this cohort, survival status was known for 109/138 individuals: 46 patients and no carrier died during the FU period (Figure 1). Patients presenting with nOH at baseline AFT assessment had considerably shorter survival time from baseline assessment compared to individuals without nOH (mean survival time from baseline assessment 7.0 (95% CI: 4.8 - 9.1) years versus 14.9 (95% CI: 13.0 - 16.9) years, $p < 0.001$; Figure 4A). No participant with autonomic failure stage 0 at initial assessment died during the observation period spanning up to 20 years.

Of the 46 deceased patients, 25 (54%) had nOH at baseline assessment, but only five of these (20%) were on disease specific treatment at time of AFT: four had diflunisal and only one was on patisiran. In surviving individuals, only 15/63 (24%) had nOH at initial AFT, but 10/15 (67%) received disease specific treatment.

In a multivariable logistic regression analysis, presence of nOH at initial AFT predicted all-cause death (OR = 5.27; 95% CI: 1.94 – 14.31; $p = 0.001$), after adjustment for age (OR = 1.09, 95% CI: 1.05-1.15, $p < 0.001$), sex, and disease specific treatment (yes/no). Although not statistically significant treatment appeared to have a protective effect (65%), (OR = 0.35; 95% CI: 0.12 – 1.01, $p = 0.052$). The model demonstrated high accuracy, with an area under the curve (AUC) of 0.81 (95% CI: 0.73 – 0.89, $p < 0.001$; Figure 4B).

In a multivariable linear regression analysis, autonomic failure stage was found to be negatively correlated with age at death ($p = 0.029$, standardised regression coefficient $\beta = -0.428$), after adjusting for sex and disease specific treatment status.

When considering other disease manifestations, presence of nOH at initial AFT assessment was associated with worse PND stage at time of FU ($p = 0.034$; not statistically significant after adjustment for age and sex, likely due to small sample size).

Case report of a TTR variant carrier

A 43-year-old woman with *TTR* Val30Met variant did not present any symptoms of autonomic dysfunction, polyneuropathy, or cardiac disease. Initial AFT resulted normal. At repeat assessments four, six, and thirteen years later, she presented mild parasympathetic impairment with abnormal HR response to deep breathing (Figure 3), without clinical symptoms of autonomic dysfunction. Cardiac and neurologic assessments including large and small fibre studies

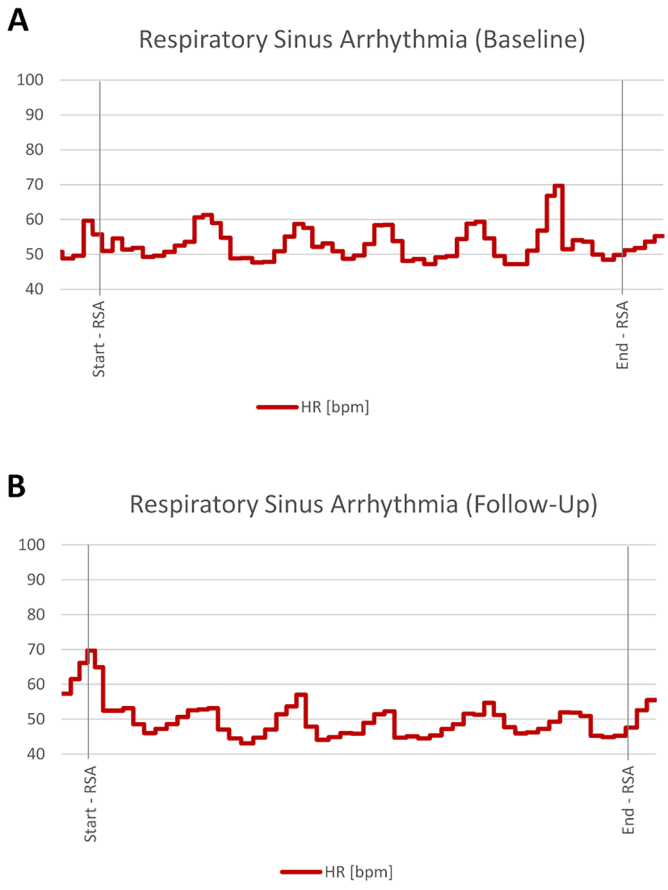

Figure 3. Respiratory sinus arrhythmia in a variant carrier: normal HR variability to deep breathing at baseline (A) and reduced HR variability to deep breathing at follow-up (B). bpm: beats per minute; HR: heart rate; RSA: respiratory sinus arrhythmia.

were normal at repeat testing during the FU period. A similar trajectory with progressive autonomic dysfunction on AFT, but normal cardiac and neurologic examination was observed in four other carriers.

Case report of a patient with ATTRv

A 59-year-old gentleman with cardiac symptoms, bilateral carpal tunnel syndrome and diagnosis of ATTRv with Thr60Ala variant has been treated with diflunisal since 2015 and inotersen since 2019. When he was referred to our unit in 2019, he reported sweating over the face and chest, but not on other areas of his body. He did not present other autonomic symptoms. His initial AFT in 2020 yielded normal results.

During the following months, he reported dizziness upon standing up from kneeling. He also noticed opening his bowels more frequently, as well as urinary urgency with nocturia, and a dry mouth. His repeat autonomic testing after 16 months revealed impaired BP response to Valsalva manoeuvre and reduced HR variability to deep breathing (Figure 2).

By end of 2021, he reported onset of erectile dysfunction, and he developed symptoms of mild polyneuropathy. Under treatment with inotersen, he had about 75% TTR knockdown and therefore was switched to patisiran. Repeat AFT showed a worsening of sympathetic function with mild nOH. His treatment was changed to vutrisiran in 2023. He did not report any progression of his autonomic symptoms and AFT performed 9 months later showed some improvement with initial orthostatic hypotension only. A similar progression of autonomic failure was observed in ten more patients in our cohort (five presented with progression of autonomic failure stage 0 to stage I, and five with progression of stage I to stage II).

Table 2. Comparison of subtest results at baseline and follow-up.

Cardiovascular autonomic function test	Baseline	Follow-Up	*p*
Supine values	*n* = 59		
Resting SBP [mmHg]	126.2 ± 17.9	121.6 ± 19.3	0.072
Resting DBP [mmHg]	75.5 ± 11.6	73.1 ± 10.7	0.122
Resting HR [bpm]	71.3 ± 10.7	71.5 ± 12.9	0.881
Head-up tilt test	*n* = 58		
Δ SBP [mmHg]	7.8 (3.25 – 18.88)	9.4 (1.0 – 21.88)	0.868
Δ DBP [mmHg]	1.2 (−6.08 – 7.75)	1.2 (−4.0 – 9.71)	0.508
Standing test	*n* = 58		
Δ SBP [mmHg]	7.0 (0.75 – 19.75)	6.5 (−0.25 – 21.5)	0.403
Δ DBP [mmHg]	3.0 (−2.54 – 12.25)	3.8 (−3.75 – 9.5)	0.509
Prevalence nOH on HUT and/or stand	31%	41%	0.063
Isometric exercise	*n* = 47		
Δ SBP [mmHg]	12.0 (3.5 – 18.5)	10.0 (4.0 – 18.0)	0.147
Δ DBP [mmHg]	6.0 (−0.5 – 14.0)	6.0 (0.5 – 12.0)	0.808
Prevalence	51%	58%	0.629
Mental arithmetic	*n* = 53		
Δ SBP [mmHg]	8.0 (2.75 – 18.5)	4.0 (0.0 – 12.0)	**0.044**
Δ DBP [mmHg]	4.5 (0.0 – 9.25)	2.0 (0.0 – 5.0)	0.107
Prevalence	57%	70%	0.189
Cold pressure test	*n* = 54		
Δ SBP [mmHg]	7.0 (0.5 – 16.0)	6.1 (1.0 – 13.75)	0.801
Δ DBP [mmHg]	4.0 (−2.0 – 10.0)	5.0 (−1.0 – 9.75)	0.497
Prevalence	57%	69%	0.263
Hyperventilation	*n* = 38		
Δ HR [bpm]	7.0 (3.0 – 15.75)	6.0 (2.0 – 14.0)	0.110
Prevalence	63%	68%	0.754
RSA	*n* = 41		
Δ HR [bpm]	5 (1.0 – 14.5)	3 (0.0 – 12.0)	**0.027**
Prevalence	66%	81%	0.070
Valsalva Manoeuvre			
Valsalva Ratio	*n* = 33		
	1.40 (1.11 – 1.82)	1.27 (1.07 – 1.57)	0.002
Prevalence	58%	79%	0.016
Abnormal BP profile	*n* = 25		
Prevalence	48%	52%	1.0

Data are noted as the mean ± SD (normally distributed data) or median (IQR) for non-normally distributed data, and percentage of abnormal testing according to age (prevalence). Significance was set at $p<0.05$.
SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. HR: Heart Rate. RSA: Respiratory Sinus Arrhythmia.

Discussion

This study provides valuable longitudinal data on autonomic dysfunction in a large cohort of asymptomatic variant carriers and patients with ATTRv. Using standardised and quantitative non-invasive AFT, we identify key autonomic biomarkers that can effectively track disease progression and demonstrate the significant impact of autonomic failure on overall outcomes and survival. Furthermore, our findings indicate that early initiation of DMTs may help stabilise

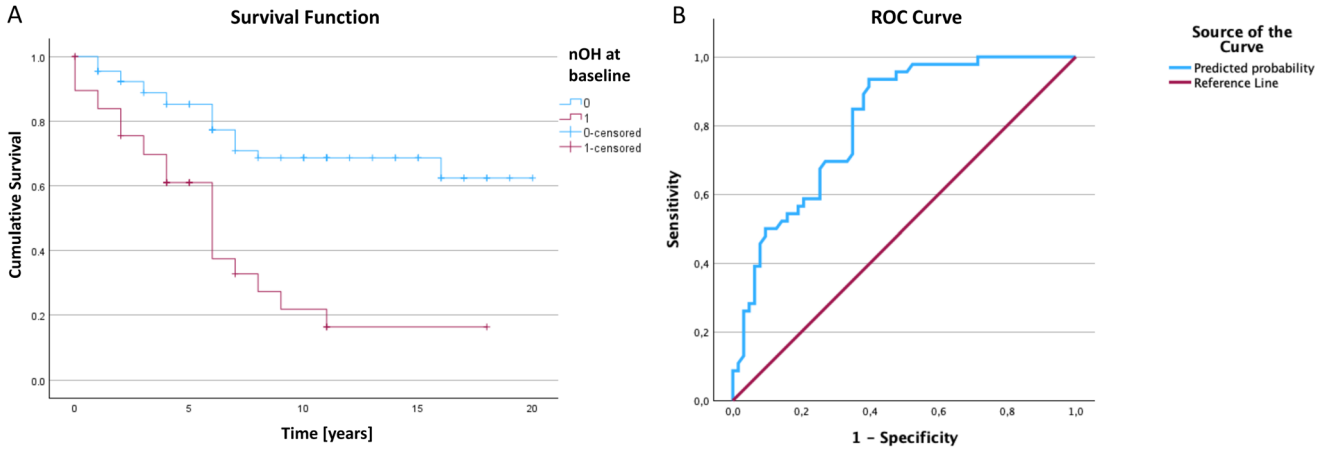

Figure 4. Survival in ATTRv. A) Kaplan-meier curves for overall survival from first autonomic assessment. Patients with nOH at baseline (red) had a mean survival time of 7.0 (95% CI: 4.8 - 9.1) years, while patients without nOH at baseline (blue) presented a mean survival of 14.9 (95% CI: 13.0 - 16.9) years. B) ROC curve for prediction of all-cause death based on presence of nOH at initial autonomic assessment, age, sex, and existence of disease specific treatment. The AUC was 0.81. AUC: area under the curve; nOH: neurogenic orthostatic hypotension; ROC: receiver operating characteristic.

autonomic dysfunction and potentially slow disease progression at early stage of disease.

Most patients showed abnormal test results at baseline assessment during first evaluation at our centre, within a median disease duration of 4 years. In line with previous studies [6,9] and as illustrated by the first clinical case, variant carriers presented with abnormal autonomic function at a pre-symptomatic stage. Differences of autonomic parameters in patients receiving TTR stabilisers versus DMT were not significant, but the group receiving DMT was small ($n = 10$). Due to small sample sizes, no comparison of autonomic parameters between patients receiving different DMTs could be performed. Despite a longer disease duration, patients on any disease specific treatment were more likely to initially present with autonomic failure stage 0 compared to untreated individuals. Treated patients demonstrated a lower prevalence of abnormal parasympathetic function results, indicating that treatment was started at an early stage of autonomic impairment. Statistical significance was likely not met due to small sample sizes and heterogeneity of treatment duration and type of medication (TTR stabilisers as well as DMT). These findings suggest a potential therapeutic effect primarily on parasympathetic dysfunction, especially when treatment begins before severe sympathetic denervation and development of nOH, but results will need to be confirmed prospectively in a larger group of patients. Similar findings with improvement of parasympathetic cardiovascular dysfunction by exercise training were found in diabetic neuropathy [17].

With recently available DMTs, there is an unmet need to detect autonomic dysfunction, potentially in the absence of somatic neuropathy. Quantitative autonomic testing could play a critical role in therapeutic decision making, shifting care towards preventive treatment.

Our longitudinal data show progression of autonomic failure in individuals with ATTRv, including in patients with a very short disease duration (baseline assessment within the first 4 years of disease onset), and even in carriers at a pre-clinical stage, as presented in the first case report. AFT, particularly the subtests assessing Valsalva ratio and respiratory sinus arrhythmia, effectively captured early progression of parasympathetic dysfunction over a median FU period of 23 months, as highlighted by our illustrative cases. Early cardiovagal impairment was reported in previous studies, but its progression in carriers has not been described yet. In this cohort, significant progression of adrenergic failure measured as severity of nOH was not observed. However, orthostatic tolerance time, which might be a better marker to capture progression of nOH [18], was not systematically assessed. Additionally, sympathetic impairment seems to occur later during the disease course, and monitoring of potential disease progression appeared to be more reliable if performed during earlier, milder stages of the disease.

Catecholamines are a useful additional marker for assessing autonomic adrenergic denervation. Already asymptomatic carriers showed impaired catecholamine levels, and there was progressive sympathetic denervation over time. However, as expected, catecholamine levels alone are insufficient to fully capture disease progression emphasising the need for comprehensive quantitative AFT.

Patients receiving DMT showed stable disease at the earliest stage of autonomic involvement (stage 0) and did not present progression to widespread autonomic failure including nOH over a FU period of up to 11.1 years. In contrast, the majority (66%) of patients who experienced severe autonomic failure during their disease course (stage II at baseline and FU) had not received any disease specific treatment. Our data including the presented case reports highlight the need of considering the presence of early autonomic dysfunction and progressive autonomic impairment in future treatment decisions. No improvement of widespread autonomic failure was seen, independent of treatment status. This is likely due to irreversible denervation, indicating that the presence of autonomic failure may be resistant to treatment. The heterogeneity in treatment duration and type (TTR stabiliser versus DMT) further complicates the interpretation of outcomes.

These findings are in line with previous reports: a recent study showed that reduced intraepidermal nerve fibre density and amyloid deposition can serve as early markers for diagnosing and tracking disease progression in ATTRv, and can be slowed by early treatment with tafamidis [19]. This further highlights the importance of early intervention and preventing the advancement of autonomic and peripheral neuropathy. Prospective studies will need to systematically investigate the response of autonomic impairment to different therapeutic approaches allowing to potentially broaden the approval of DMT even in the absence of sensorimotor polyneuropathy.

Our data indicate that women present with a milder course of autonomic involvement compared to men, highlighting potential sex differences in disease progression. Although cardiac involvement was found to be more frequent and pronounced in males [20], a more recent study did not demonstrate overall differences between sexes in TTR cardiomyopathy due to the Thr60Ala and Val122Ile (p.Val142Ile) variant [21].

Although cardiomyopathy may develop only in the later stages of the disease in certain variants [22], comprehensive cardiac screening is essential in all individuals with ATTRv to ensure accurate interpretation of AFT results. Cardiac involvement, including the use of beta-blockers or the presence of pacemakers, can alter heart rate responses and potentially confound the interpretation of tests such as deep breathing or the Valsalva manoeuvre. In this study, relevant autonomic subtests were either not interpreted in affected patients or, when possible, medications were withheld prior to testing to minimise interference. Moreover, cardiac amyloidosis can impair diastolic function [23], which is why a significant fall in systolic blood pressure and an abnormal blood pressure response during the Valsalva manoeuvre were required to confirm a diagnosis of nOH in patients with cardiomyopathy.

This study was able to demonstrate early presence of nOH as an independent predictor of overall survival in ATTRv, with a mean survival time from baseline assessment of 7.0 years for patients with nOH versus 14.9 years without nOH. This finding aligns with a previous study identifying OH, diagnosed using active standing test, as a prevalent feature and potential marker for monitoring disease progression [24]. In other neuropathies presenting with autonomic impairment such as diabetic polyneuropathy or Guillain-Barré Syndrome, autonomic failure is a known cause of increased morbidity and mortality [25,26].

Moreover, the presence of nOH at initial assessment is associated with worsening of PND stage from baseline to FU, indicating poorer mobility outcome. Similarly, a higher prevalence of autonomic symptoms was previously found in patients with more severe PND stages [27].

Limitations of this study include the genetic diversity of the cohort and the retrospective design with varying disease durations at timepoint of baseline autonomic assessment and only a subgroup of patients having had repeat autonomic testing which could potentially cause biases. However, autonomic FU data in 59 individuals is substantial given the rare nature of the disorder, and the ratio of variant carriers was similar at baseline (12/138; 9%) and FU (6/59; 10%) assessments. Due to small sample size, patients were considered to have disease specific treatment with DMT and/or TTR stabilising drugs. Besides, autonomic function was exclusively evaluated by cardiovascular autonomic testing, and assessment of other autonomic systems such as sudomotor function is lacking.

In summary, quantitative cardiovascular autonomic tests assessing parasympathetic function are valuable biomarkers to detect early-stage and pre-clinical autonomic impairment, disease progression, and possibly response to treatment in individuals with ATTRv. Although the number of patients receiving DMT was small, DMT might slow the progression of autonomic dysfunction when initiated in early stages, with no progression to nOH observed in patients receiving DMT. The early presence of autonomic failure with nOH predict poor prognosis with shorter survival and may be a useful factor for stratifying patients in future clinical trials. Standardised, quantitative testing of both sympathetic and parasympathetic function should be included in the initial clinical work-up. Further prospective studies are urgently needed to evaluate the response of autonomic impairment to DMT, potentially guiding more effective treatment strategies for disease management.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, VI, upon reasonable request.

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