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Asymptomatic Carrier Neurologic Assessment: A Tool for Early Detection of Symptomatic Transition in Pathogenic *TTR* Gene Variant Carriers

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ABSTRACT

Background: Hereditary variant transthyretin amyloidosis (ATTRv) is caused by > 140 pathogenic *TTR* gene variants. The heterogeneous presentation of ATTRv clinical phenotypes complicates diagnosis and staging of patients. Tools that improve early detection of ATTRv symptoms and signs and identify risk of transition to clinically detectable disease are needed.

Methods: A retrospective, multicenter study at amyloid centers in France, Spain, Portugal, and the United Kingdom (December 2023–December 2024) assessed asymptomatic carriers (ACs) and ACs who transitioned to symptomatic disease within the previous 2 years (newly symptomatic carriers [NSCs]). A new 23-question asymptomatic carrier neurologic assessment (ACNA) was developed to screen for the potential transition to clinically detectable ATTRv-polyneuropathy (PN). Question topics spanned sensory, autonomic, and systemic signs and symptoms. Fisher's exact tests were conducted to evaluate the association between each individual question and disease status (i.e., NSC vs. AC). Logistic regression models with a Firth correction were used to estimate odds ratios and corresponding 95% confidence intervals.

Results: The study included 217 carriers (AC, $n = 128$; NSC, $n = 89$) with 18 unique transthyretin variants; 166 (76.5%) had p.Val50Met. Of 23 ACNA questions, 17 were significantly associated with transition to symptomatic disease for all patients. The pattern of neurologic signs and symptoms found to be associated with p.Val50Met and other common variants reflected what is known about variant-specific symptomatology. Confounding factors included age, medical center of treatment, and variant type.

Conclusion: The ACNA questionnaire may be a clinically valuable tool to screen ACs for risk of transition to symptomatic ATTRv-PN but requires validation.

1 | Introduction

Amyloidosis is a group of progressive multisystem diseases caused by misfolded proteins that build up and deposit in organ

systems and tissues [1]. Transthyretin (TTR) is one such protein that normally associates into stable tetramers [2, 3], but when dissociated into unstable monomers, it misfolds and aggregates into amyloid fibrils that deposit into tissues throughout the body

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[1]. Previous studies have demonstrated that amyloid deposition can occur in the absence of overt symptoms, both in skeletal muscle of patients with systemic amyloidosis and in cardiac tissue of older individuals [2, 3]. The burden of transthyretin amyloidosis (ATTR) may be underestimated due to underdiagnosis because of unrecognized signs and symptoms that overlap with those of several more common conditions [4].

ATTR occurs in the following two forms: the more common non-hereditary form, wild-type ATTR (ATTRwt), occurs due to age-related factors, whereas the hereditary form, variant ATTR (ATTRv), is caused by pathogenic *TTR* gene variants and may be present in younger adults [1]. In ATTRv, pathogenic variants destabilize the TTR tetramer, increasing its tendency to dissociate compared with ATTRwt. This results in reduced circulating serum TTR levels and is often associated with earlier disease onset, rapid disease progression, and an increased risk of mortality. More than 140 pathogenic variants have been identified, leading to a spectrum of predominant clinical phenotypes, including polyneuropathy (ATTRv-PN; an ascending axonal neuropathy affecting sensorimotor and autonomic systems), cardiomyopathy (an infiltrative, restrictive disease of the heart muscle leading to heart failure), and mixed presentations [1, 4–6].

Studies have demonstrated that early nerve dysfunction may become detectable before clinical recognition of amyloid deposits in some ATTRv carriers [7]. Several objective measures of early tissue or nerve involvement are available, including autonomic assessments, nerve conduction studies, skin biopsy for intraepidermal nerve fiber density, and measurements of circulating neurofilament light-chain levels [8–11]. These modalities may capture physiologic or structural signals of neuropathic involvement before symptoms become clinically evident, but they have not yet been integrated into a validated composite tool for early disease detection.

A considerable challenge arises from the fact that symptomatology during the period of transition from asymptomatic to symptomatic ATTRv-PN has not been fully described. Since the emergence of disease-modifying ATTR therapies, profound clinical benefits result from early diagnosis [12]. Given the evidence of widespread subclinical involvement, tools for early detection are critical. Hence, we sought to describe the signs and symptoms of ATTRv-PN that may have characterized the period of transition from asymptomatic to symptomatic disease in a retrospective analysis of a European cohort of patients with ATTRv-PN.

Our objective was to identify potential signals of transition to clinically detectable ATTRv-PN in asymptomatic carriers (ACs) and retrospectively evaluate the performance of a new asymptomatic carrier neurologic assessment (ACNA). Each ACNA question was assessed for its strength of prediction from asymptomatic transition.

2 | Methods

2.1 | Patients and Study Design

A 23-question ACNA was developed to easily screen for the potential transition to clinically detectable ATTRv-PN in ACs

during normal clinical practice (Figure S1). In order to characterize the performance of each ACNA question as a predictor of transition to symptomatic disease, a retrospective, multicenter study was conducted at amyloid centers in France, Spain, Portugal, and the United Kingdom. Data were collected retrospectively from December 2023 to December 2024 on the following two groups: ACs and patients with ATTRv-PN (all variant carriers) who had transitioned to symptomatic disease within the 2 years (newly symptomatic carriers [NSCs]) before study entry. Transition from asymptomatic to symptomatic ATTRv-PN was determined retrospectively via chart review in patients or carriers without an ATTR-PN diagnosis based on the reporting of new signs/symptoms consistent with ATTR-PN [8] and confirmed by biopsy or a positive ^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid scan of grade 2 or higher.

Ancillary diagnostic investigations, including nerve conduction studies, autonomic function testing, skin punch biopsy, and imaging, were used at the discretion of the treating clinician. Although diagnostic criteria were not formally harmonized, all diagnoses were established by expert neurologists at specialized amyloid centers.

2.2 | Assessments and Outcomes

The ACNA tool (Figure S1) was developed using modified Delphi methodology, which comprised a structured process for achieving expert consensus facilitated through multiple rounds of expert opinion and revision. Question domains range across sensory, autonomic, and systemic signs and symptoms known to be associated with early ATTR-PN.

2.3 | Statistical Methods

Descriptive statistics were performed on baseline characteristics to assess heterogeneity. Fisher's exact tests were conducted to evaluate the association between each question and disease status (i.e., AC vs. NSC). Separate logistic regression models were fit with disease status (outcome) and each question response (yes vs. no) sequentially. Logistic regression models with a Firth correction were used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) based on the profile likelihood, with higher magnitudes of association indicating a higher probability of demonstrating early disease signs/symptoms, accounting for the small sample size. In addition, to account for multiple comparisons across the 23 questionnaire items in the overall population, *p*-values were further adjusted using the Benjamini–Hochberg procedure to control the false discovery rate at 0.05.

For each of the questions identified as statistically significantly related to disease status by univariate analysis, the following multivariate logistic regression model was estimated to evaluate the potential confounding and interactions by baseline characteristics (center, age, sex, and variant type):

$$\text{logit}(p) = \beta_0 + \beta_1 \text{Question} + \beta_2 \text{Covariate} + \beta_{12} (\text{Question} \times \text{Covariate}).$$

3 | Results

3.1 | Patients

Overall, 217 patients (asymptomatic AC, $n=128$; newly symptomatic NSC, $n=89$) were included in this analysis. The mean (SD) age of the analysis cohort was 48.7 (16.9) years, 130/217 (59.9%) were female, and patients were based in Portugal (94/217 [43.3%]), Spain (57/217 [26.3%]), the United Kingdom (50/217 [23.0%]), or France (16/217 [7.4%]) (Table 1). There were 18 unique *TTR* variants in the analysis population, but the vast majority (166/217 [76.5%]) were p.Val50Met (Table 1 and Table S1).

3.2 | Outcomes

Among the 23 questions in the ACNA tool, responses to 17 questions related to sensory, autonomic, and systemic signs or symptoms were associated with transition to clinically detectable ATTRv-PN ($p<0.05$) for all patients (Table 2), and these same 17 questions remained $p<0.05$ after Benjamini-Hochberg false discovery rate correction. In the overall population, ACNA Question 1, pertaining to neuropathic extremity pain, had the strongest association with transition to symptomatic ATTRv-PN disease (OR, 240.44 [95% CI, 33.13–30,602.73]; $p<0.0001$). Questions 4 and 12, pertaining to hot/cold sensory impairment and persistent unexplained weight loss ≥ 5 kg, had the next-strongest associations with transition to symptomatic ATTRv-PN disease (OR: 23.34 [95% CI: 2.78–3047.20]; $p=0.0017$; OR: 14.92 [95% CI: 4.59–75.86]; $p<0.0001$, respectively).

In univariate logistic modeling, ACNA questions showed strong associations with disease transition, with the strength of association differing by p.Val50Met carrier status (Table 2). Among

p.Val50Met carriers ($n=166$), Question 1, pertaining to neuropathic extremity pain, had the greatest association with transition to symptomatic ATTRv-PN disease (OR: 327.89 [95% CI: 43.61–42,015.48]; $p<0.0001$). Question 4, pertaining to hot/cold sensory impairment, also had meaningful association with transition (OR: 31.64 [95% CI: 3.73–4130.65]; $p=0.0005$), followed by Question 8, pertaining to autonomic early satiety or nausea/vomiting (OR: 19.26 [95% CI: 4.45–180.50]; $p<0.0001$). A total of 16 ACNA questions showed significant associations in this group.

Neuropathic extremity pain (Question 1) had the strongest association with transition to symptomatic ATTRv-PN disease among p.Val50Met carriers regardless of age of symptom onset, categorized as early (<50 years; $n=108$) or late (≥ 50 years of age; $n=58$) (early-onset OR: 330.27 [95% CI, 41.56–42,816.14]; $p<0.0001$; late-onset OR: 34.02 [95% CI, 3.27–4637.22]; $p=0.0032$) (Table S2). Questions 4 (reduced ability to feel hot or cold temperatures normally in lower and/or upper limbs) and 7 (impaired sexual functions not explained by other causes) were strongly associated with transition to symptomatic ATTRv-PN among p.Val50Met carriers regardless of onset age. For Question 4, the OR was 14.92 (95% CI, 1.53–1997.66; $p=0.0230$) for early onset and 24.35 (95% CI, 2.16–3360.78; $p=0.0147$) for late onset; for Question 7, the OR was 26.90 (95% CI, 3.13–3530.68; $p=0.0012$) for early onset and 6.49 (95% CI, 1.27–41.46; $p=0.0338$) for late onset. For autonomic and systemic symptoms, associations were consistently stronger in the early-onset group, most notably for unexplained weight loss ≥ 5 kg (Question 12 early-onset OR: 21.13 [95% CI, 4.85–199.13]; $p<0.0001$; late-onset OR: 5.25 [95% CI, 0.64–61.14]; $p=0.1611$).

Findings in the “Other” and “Signs” categories were more strongly associated with transition to symptomatic disease in the late-onset group, particularly “new difficulties in walking or running accompanied by signs of neuropathy on physical examination”

TABLE 1 | Baseline characteristics of patients included in this analysis.

Characteristic	All ($N=217$)	AC (asymptomatic) ($n=128$)	NSC (newly symptomatic) ($n=89$)
Center, n (%)			
Portugal	94 (43.3)	54 (42.2)	40 (44.9)
Spain	57 (26.3)	49 (38.3)	8 (9.0)
UK	50 (23.0)	22 (17.2)	28 (31.5)
France	16 (7.4)	3 (2.3)	13 (14.6)
Age, mean (SD), years	48.7 (16.9)	46.4 (15.5)	52.0 (18.4)
Sex, n (%)			
Female	130 (59.9)	86 (67.2)	44 (49.4)
Male	87 (40.1)	42 (32.8)	45 (50.6)
Variant type, n (%)			
p.Val50Met	166 (76.5)	108 (84.4)	58 (65.2)
p.Val142Ile	14 (6.5)	5 (3.9)	9 (10.1)
p.Thr80Ala	14 (6.5)	5 (3.9)	9 (10.1)
Other	23 (10.6)	10 (7.8)	13 (14.6)

Abbreviations: AC, asymptomatic carrier; NSC, newly symptomatic carrier (asymptomatic carrier who transitioned to symptomatic disease within the previous 2 years); UK, United Kingdom.

TABLE 2 | Strength of association between individual questions from the asymptomatic carrier neurologic assessment questionnaire and transition to symptomatic disease in the overall population.

Symptoms: New development occurring regularly for a duration of ≥ 3 months ^{a,b,c}	Overall odds ratio (95% CI) <i>p</i> value (N = 217)	p.Val50Met odds ratio (95% CI) <i>p</i> value (n = 166)	Non-p.Val50Met ^d odds ratio (95% CI) <i>p</i> value (n = 51)
Sensory			
1. Neuropathic pain to include burning, electric shock like, knife like, stabbing in lower, and/or upper limbs	240.44 (33.13–30,602.73) < 0.0001	327.89 (43.61–42,015.48) < 0.0001	14.83 (1.67–1961.34) 0.0164
2. Tingling, pins and needles in lower, and/or upper limbs	4.12 (2.31–7.49) < 0.0001	6.60 (3.30–13.62) < 0.0001	1.15 (0.37–3.71) 1
3. Hypersensitivity or increased sensitivity to touch in the lower and/or upper limbs (e.g., unpleasant sensation to clothing or bed sheets)	13.53 (1.42–1801.10) 0.0272	17.94 (1.86–2390.60) 0.0139	N/A
4. Reduced ability to feel hot or cold temperatures normally in lower and/or upper limbs	23.34 (2.78–3047.20) 0.0017	31.64 (3.73–4130.65) 0.0005	N/A
5. Partial or complete numbness in lower and/or upper limbs	4.67 (1.78–14.10) 0.0016	8.17 (2.21–43.97) 0.0014	1.27 (0.31–5.97) 0.7294
6. Altered sensation not described above (e.g., lower and/or upper limbs feel different than normal)	2.33 (0.61–10.30) 0.2744	1.87 (0.15–23.41) 1	1.21 (0.24–7.55) 1
Autonomic			
7. Impaired sexual functions (e.g., inability to initiate and maintain erections) not explained by other causes	9.28 (3.18–36.09) < 0.0001	10.32 (2.90–54.66) 0.0002	3.98 (0.77–40.06) 0.1273
8. Early satiety and/or recurrent nausea, vomiting	11.36 (3.42–58.31) < 0.0001	19.26 (4.45–180.50) < 0.0001	2.13 (0.36–22.45) 0.6364
9. Dizziness, lightheadedness, and/or blackouts precipitated by postural change (e.g., standing or sitting from lying) or after a meal or micturition	5.21 (2.14–14.32) 0.0002	8.28 (2.93–28.21) < 0.0001	1.21 (0.24–7.55) 1
10. New diarrhea and/or constipation, both, or alternating	6.91 (3.16–16.66) < 0.0001	6.18 (2.54–16.47) < 0.0001	7.29 (1.51–71.79) 0.0169
11. Urgency, urge incontinence, incontinence, incomplete emptying, and/or recurrent UTIs (in absence of stress incontinence in females)	4.23 (1.30–17.35) 0.0172	3.10 (0.79–13.81) 0.1291	6.71 (0.66–907.97) 0.1453
Systemic			
12. Persistent unexplained weight loss ≥ 5 kg	14.92 (4.59–75.86) < 0.0001	16.54 (4.88–85.86) < 0.0001	6.71 (0.66–907.97) 0.1453
Other			
13. Difficulty using hands (e.g., clumsiness, dropping objects, writing) consistent with objective signs of neuropathy on physical examination	13.53 (1.42–1801.10) 0.0272	N/A	6.71 (0.66–907.97) 0.1453
14. Weakness in lower and/or upper limbs consistent with objective lower motor neuron weakness on physical examination	7.34 (0.59–1017.58) 0.1671	5.65 (0.30–831.51) 0.3494	2.01 (0.10–300.22) 1
15. Unsteadiness (including unsteadiness in the dark or with eyes closed)	2.43 (0.32–26.87) 0.5693	9.59 (0.76–1333.18) 0.1207	0.21 (0.00–4.07) 0.3922

(Continues)

TABLE 2 | (Continued)

Symptoms: New development occurring regularly for a duration of ≥ 3 months ^{a,b,c}	Overall odds ratio (95% CI) <i>p</i> value (N = 217)	p.Val50Met odds ratio (95% CI) <i>p</i> value (n = 166)	Non-p.Val50Met ^d odds ratio (95% CI) <i>p</i> value (n = 51)
16. New difficulties in walking or running accompanied by signs of neuropathy on physical examination	10.02 (2.25–94.77) 0.0017	7.37 (1.42–73.16) 0.0202	6.71 (0.66–907.97) 0.1453
Signs^{a,c}			
17. 20-mmHg drop in systolic BP and/or 10-mmHg drop in diastolic BP with fixed heart rate after 3 min of standing	2.89 (0.92–10.30) 0.0753	3.52 (0.75–20.71) 0.1848	1.21 (0.24–7.55) 1
18. Signs suggestive of cardiac autonomic dysfunction defined as persistent tachycardia > 100 bpm for more than 5 min at rest	2.34 (0.79–7.56) 0.1496	3.91 (1.23–14.13) 0.0256	0.21 (0.00–4.07) 0.3922
19. Absent reflexes in association with other motor or sensory symptoms or signs (allow for age with absent ankle jerks)	5.92 (2.46–16.14) < 0.0001	4.56 (1.62–14.39) 0.0048	6.35 (1.30–62.72) 0.0341
20. Loss of vibration (Rydell fork) for age distally in lower and/or upper limbs	7.45 (3.16–20.12) < 0.0001	9.22 (2.55–49.21) 0.0005	3.44 (1.04–13.24) 0.0737
21. Reduced or absent pin prick in feet and/or hands	6.13 (2.87–14.23) < 0.0001	5.62 (1.90–19.64) 0.0018	3.86 (1.21–13.74) 0.0249
22. Absent proprioception in feet and/or hands	10.39 (0.99–1404.88) 0.0676	9.59 (0.76–1333.18) 0.1207	2.01 (0.10–300.22) 1
23. Lower motor neuron weakness in lower and/or upper limbs	10.02 (2.25–94.77) 0.0017	13.70 (1.29–1852.43) 0.0412	3.31 (0.62–33.72) 0.2232

Note: Data cutoff: December 2024. Bold text signifies that question reached nominal statistical significance (*p* < 0.05 from Fisher's exact test).
Abbreviations: BP, blood pressure; bpm, beats per minute; UTI, urinary tract infection.
^aAll new signs and symptoms must occur without attribution to another etiology.
^bA symptom is considered significant if it falls into one of the above sensory, autonomic, systemic, or other symptom categories, and occurs regularly for a duration ≥ 3 months.
^cA sign is considered significant if it occurs at least once.
^dNon-p.Val50Met variants included p.Thr80Ala, p.Val142Ile, p.Ile127Val, p.Val48Met, p.Ile88Leu, p.Val107Ala, p.Ala59Asp, p.Ala74Gly, p.Ala117Ser, p.Lys55Asn, p.Glu62Asp, p.Glu109Lys, p.Gly67Glu, p.His110Asp, p.Glu81Lys, p.Val40Ile, and p.Tyr134Cys (Table S1).

(Question 16 OR: 45.56 [95% CI, 4.60–6162.49]; *p* = 0.0007), “loss of vibration (Rydell fork) for age distally in lower and/or upper limbs” (Question 20 OR: 25.00 [95% CI, 4.61–260.92]; *p* = 0.0001), “lower motor neuron weakness in lower and/or upper limbs” (Question 23 OR: 24.35 [95% CI, 2.16–3360.78]; *p* = 0.0147) and consistent with the known cardiomyopathic phenotype of late-onset p.Val50Met disease, “signs suggestive of cardiac autonomic dysfunction defined as persistent tachycardia > 100 bpm for more than 5 min at rest” (Question 18 OR: 24.35 [95% CI, 2.16–3360.78]; *p* = 0.0147).

Among non-p.Val50Met carriers (*n* = 51), four questions showed significant associations with transition, with Question 1 similarly being the best predictor (OR: 14.83 [95% CI: 1.67–1961.34]; *p* = 0.0164); additional predictors were Questions 10, 19, and 21, pertaining to autonomic symptoms of new diarrhea or constipation, absent reflexes in association with other motor or sensory symptoms or signs, and reduced or absent pin prick in the feet and/or hands, respectively.

Although in smaller numbers, potential signals associated with the period of transition from asymptomatic to symptomatic disease were found for ACNA questions in carriers of specific non-p.Val50Met variant types (e.g., p.Thr80Ala and

p.Val142Ile) in this European patient cohort. In those with variant p.Thr80Ala, Question 10, pertaining to new diarrhea and/or constipation, showed a meaningful trend for association with transition (*n* = 14; OR: 5.92 [95% CI: 0.42–865.28]) (Table S3). In carriers of variant p.Val142Ile, Question 20, pertaining to loss of vibration sensation for age distally in the lower and/or upper limbs, showed the strongest association with transition (*n* = 14; OR: 20.43 [95% CI: 1.55–2998.37]).

Analysis of potential confounding variables showed that ACNA Question 2 (paresthesia), a demonstrable neurosensory symptom, had significant interactions with age, region of treatment center, and *TTR* variant type (*p* < 0.05), which are also known to be associated with the predominantly neurologic p.Val50Met variant [13].

4 | Discussion

Responses to 17 ACNA items representing sensory, autonomic, and systemic manifestations of ATTRv-PN were significantly associated with subsequent transition to symptomatic disease in European carriers of pathogenic *TTR* variants. In the

overall population, neuropathic extremity pain (Question 1), impaired hot/cold sensation (Question 4), and persistent unexplained weight loss ≥ 5 kg (Question 12) showed the strongest associations with transition to ATTRv-PN. Variant-specific patterns emerged, with p.Val50Met carriers showing particularly strong associations with extremity pain (Question 1), impaired hot/cold sensation (Question 4), and autonomic early satiety and/or recurrent nausea/vomiting (Question 8), consistent with the known sensory and autonomic polyneuropathy manifestations associated with this variant. The confounding factors identified—age, medical center, and variant type—are consistent with the known early onset, geographic localization to Portugal, and sensory neuropathic predominance of the p.Val50Met variant, respectively [13], and suggest that interpretation may need to account for patient and variant-specific factors.

With respect to p.Val50Met carriers assessed by age of onset of autonomic and systemic symptoms, associations with transition were consistently stronger in the early-onset group, most notably for unexplained weight loss ≥ 5 kg. Consistent with the known cardiomyopathic phenotype of late-onset disease, signs suggestive of cardiac autonomic dysfunction, defined as persistent tachycardia > 100 bpm for more than 5 min at rest, were stronger in the late-onset p.Val50Met group.

In ATTRv neuropathy, peripheral nerve damage results from amyloid deposition within the endoneurium and endoneurial blood vessels, with disruption of the blood–nerve barrier [14, 15]. In early-onset ATTRv in p.Val50Met carriers, pathology begins in the dorsal root and autonomic ganglia, where amyloid exerts direct toxicity on Schwann cells, leading to early small-fiber involvement and the characteristic dying-back pattern with distal sensory and autonomic dysfunction [14, 15]. In contrast, late-onset ATTRv is thought to involve predominant vascular injury, with mutant TTR inducing endothelial dysfunction and barrier disruption [16]. This mechanism preferentially affects large sensory and motor fibers, explaining the frequent presentation with mixed sensorimotor neuropathy [16]. Importantly, nerve damage may precede electrodiagnostic abnormalities, underscoring the need for sensitive screening tools for early disease detection.

In patients with established ATTRv, multiple assessment tools and markers (e.g., Rasch-built Overall Disability Scale [17], polyneuropathy disability score [18], Small-Fiber Neuropathy and Symptom Inventory Questionnaire [19], Neuropathy Impairment Score [20], Sudoscan [21], Composite Autonomic Symptom Score-31 [22], 10-min walk test and 6-min walk test [23, 24], 12-lead electrocardiogram [25], cardiac magnetic resonance imaging [26], Kansas City Cardiomyopathy Questionnaire [27], estimated glomerular filtration rate [28], modified body mass index [29], Norfolk Quality of Life-Diabetic Neuropathy [30], and 36-item Short-Form Healthy Survey [31]) have been leveraged to monitor disease progression and quality of life. The modified Neuropathy Impairment Score + 7 has been used as a registrable endpoint to assess polyneuropathy impairment and measure the rate of disease progression in ATTR-PN clinical trials for patients with ATTRv and established polyneuropathy [32]. However, not a lot is known about the period of transition from asymptomatic to symptomatic ATTRv-PN disease [33].

Despite the availability of these tools and their established utility for evaluating disease progression in ATTRv, the heterogeneity of ATTRv disease manifestations and the subtlety of their associated changes during the earliest stages of transition require a more tailored and fit-for-purpose approach to better characterize the period of transition from asymptomatic to symptomatic ATTRv-PN.

The ACNA tool offers the potential to recognize patterns in seemingly disparate symptoms as potentially indicative of transition from AC to clinically detectable ATTRv-PN. It is important to note that, unlike the assessments listed above, the ACNA tool does not currently provide a composite score or diagnostic threshold; instead, it identifies and describes individual symptoms or sign signals or patterns of signals that may be associated with transition from asymptomatic to symptomatic ATTRv-PN disease. If such signals suggest possible clinical conversion, further evaluation with established diagnostic methods—including neurological examination, nerve conduction studies, tissue biopsy (e.g., skin biopsy for small-fiber neuropathy), or cardiac imaging such as bone scintigraphy when clinically indicated—would be required to confirm disease manifestation. With further prospective validation in larger cohorts, a composite signal specific to age, geography, and variants may emerge from a constellation of statistically significant associations across individual questions. Further, the ACNA tool can be easily administered in routine clinical practice, typically taking about 20–30 min to complete at the bedside. Early detection of potential transition to diagnosable ATTRv-PN disease among ACs of a pathogenic variant could help reduce the time to diagnosis, thereby limiting the duration and cumulative effects of untreated disease progression [5]. Research is currently underway to further assess the ACNA associations prospectively in the randomized, phase 3 AG10-501 ACT-EARLY clinical trial (NCT06563895; EudraCT 2024-513547-82-00). Future studies should also evaluate the correlation between ACNA-identified signals of transition to symptomatic ATTRv-PN and diagnostic markers such as intraepidermal nerve fiber density and serum neurofilament light-chain levels.

Limitations to this analysis include the retrospective study design, which may have introduced a recall bias in subjective symptom reporting for the ACNA questionnaire, potentially causing an overestimation of associations. In addition, the transition window of 2 years defining NSC classification, while seemingly narrow, may have captured patients at different stages of early disease, particularly variants associated with early-onset ATTR-PN (e.g., p.Val50Met) [34], potentially affecting the specificity of identified predictors. Therefore, the predictors identified should not be viewed as the first or most important indicators of transition to symptomatic ATTRv-PN, but rather as predictors generally associated with the period of transition to symptomatic ATTRv-PN disease within this European population. The variability in diagnostic workup across the specialized amyloid centers is also a limitation of this retrospective multicenter study. Additionally, as this analysis was limited to European countries, results may not be generalizable to other geographic regions, particularly for variants endemic to other populations. Although early-onset p.Val50Met was well represented, the limited sample sizes for

other variants (e.g., p.Thr80Ala, p.Val142Ile) in this preliminary analysis are hypothesis generating and preclude conclusive data interpretation in these groups. Prospective validation of the ACNA is required both to confirm the utility of this tool for identifying early signs and symptoms of ATTRv in clinical practice and to prioritize symptoms versus signs. In its current form, the ACNA does not incorporate a composite score, item weighting, diagnostic threshold, or formal measures of sensitivity and specificity and should not be used as a standalone diagnostic instrument until such validation is completed. The administration time of 20–30 min may limit the real-world implementation of this tool. However, the ACNA may be useful as a screening tool in future clinical trials in asymptomatic populations. Following prospective validation, the questionnaire could be reduced to the most informative items, shortening administration time and facilitating real-world implementation. Finally, several estimated ORs were large with wide CIs, reflecting sparse data and potential instability of the estimates despite the use of Firth correction; accordingly, these results should be interpreted with caution, with emphasis on the direction rather than the magnitude of associations.

Current clinical practice lacks established guidelines for clinical surveillance of ATTRv in at-risk asymptomatic individuals [32], and none of the approved disease-modifying therapies have been evaluated or approved for prevention in ACs. However, accumulating evidence that early intervention in the natural history of ATTRv yields greater clinical benefit suggests the importance of identifying ATTRv disease in appropriately selected at-risk individuals who may benefit from initiation of disease-modifying therapy as early as possible [12, 35–38]. Whether there is a role for prophylactic disease-modifying therapy even earlier in the disease spectrum among ACs of a pathogenic *TTR* variant is a scientific question worthy of investigation. The ACT-EARLY trial (NCT06563895; EudraCT 2024-513547-82-00) is evaluating precisely this, whether prophylactic treatment with acoramidis can delay, or prevent entirely, the development of ATTRv-PN disease among ACs of a pathogenic *TTR* variant who are at risk for developing disease [39].

5 | Conclusion

The easy-to-use ACNA can potentially be a clinically useful tool to characterize the period of transition in carriers of a pathogenic *TTR* variant from asymptomatic to symptomatic ATTRv-PN disease. Signs and symptoms, or patterns thereof, identified by the ACNA tool in patients harboring a pathogenic *TTR* variant may help highlight potential disease transition and prompt further investigation to establish a definitive diagnosis of ATTRv-PN. Prospective analysis of this new ACNA tool is currently underway in larger cohorts, with a diverse array of *TTR* variants pooled from broader geographies to further delineate its performance for early detection of ATTRv-PN.

Author Contributions

Andoni Echaniz-Laguna: writing – original draft, writing – review and editing, validation, formal analysis, data curation, resources. **Jonathan**

C. Fox: conceptualization, writing – original draft, writing – review and editing, validation, methodology. **Julian D. Gillmore:** conceptualization, writing – original draft, writing – review and editing, validation, formal analysis, data curation, resources, methodology. **Mary M. Reilly:** conceptualization, writing – original draft, validation, writing – review and editing, formal analysis, resources, data curation, methodology. **Pablo Garcia-Pavia:** conceptualization, writing – original draft, validation, writing – review and editing, formal analysis, data curation, resources, methodology. **Juan González-Moreno:** writing – original draft, writing – review and editing, validation, formal analysis, data curation, resources. **Adam Castaño:** conceptualization, writing – original draft, writing – review and editing, validation, methodology. **Isabel Conceição:** conceptualization, data curation, resources, writing – original draft, validation, writing – review and editing, formal analysis, methodology. **Kuangnan Xiong:** writing – original draft, writing – review and editing, validation.

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Ethics Statement

This study has been performed in accordance with the ethical standards defined in the 1964 Declaration of Helsinki and its later amendments. Ethical approval from an institutional review board was not required, as the data used in this study were collected from institutional databases that were de-identified, researchers could not readily reidentify patients, and the data were not collected specifically for the current study through interaction with patients.

Conflicts of Interest

I.C.: research support from Alnylam Pharmaceuticals, Ionis Pharmaceuticals, and Pfizer; consultancy for THAOS; J.G.-M.: nothing to disclose. A.E.-L.: consultancy for BridgeBio Pharma, Inc.; K.X., A.C., and J.C.F.: employees and stockholders of BridgeBio Pharma, Inc.; J.D.G.: consultancy for Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio Pharma, Inc., Intellia Therapeutics, Ionis Pharmaceuticals, and Pfizer; P.G.-P.: research support from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Inc., Intellia Therapeutics, Novo Nordisk, and Pfizer; consultancy for Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio Pharma, Inc., Intellia Therapeutics, Ionis Pharmaceuticals, Pfizer, Neuroimmune, Novo Nordisk; M.M.R.: consultancy for Alnylam and BridgeBio Pharma, Inc.

Data Availability Statement

Qualified academic investigators may submit requests for access to data presented in this manuscript at medinfo@bridgebio.com. Requests for access to data presented here will be evaluated by BridgeBio Pharma, Inc., and access will be provided contingent on the approval of a research/study proposal and the execution of a data sharing agreement.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Asymptomatic carrier neurologic assessment questionnaire. BP = blood pressure, bpm = beats per minute, UTI = urinary tract infection. **Table S1:** Distribution of variants among study population. **Table S2:** Baseline characteristics and strength of association between individual questions from the asymptomatic carrier neurologic assessment questionnaire and transition to symptomatic disease stratified by age group in p.Val50Met carriers. **Table S3:** Strength of association between individual questions from the asymptomatic carrier neurologic assessment questionnaire and transition to symptomatic disease in p.Thr80Ala and p.Val142Ile carriers.