Rapid progression of familial amyloidotic polyneuropathy

A multinational natural history study

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ABSTRACT

Objectives: To assess the association between severity of neuropathy and disease stage, and estimate the rate of neuropathy progression in a retrospective cross-sectional analysis of a multinational population of patients with familial amyloidotic polyneuropathy (FAP).

Methods: We characterize neuropathy severity and rate of progression in available patients with FAP in France, the United States, Portugal, and Italy. Neuropathy Impairment Scores (NIS), time from symptom onset to NIS measurement, polyneuropathy disability (PND) scores, FAP disease stage, and manual grip strength data were collected. We estimated neuropathy progression using Loess Fit and Gompertz Fit models.

Results: For the 283 patients studied (mean age, 56.4 years), intercountry genotypic variation in the transthyretin (*TTR*) mutation was observed, with the majority of patients in Portugal (92%) having early-onset Val30Met-FAP. There was also marked intercountry variation in PND score, FAP stage, and *TTR* stabilizer use. NIS was associated with PND score (NIS 10 and 99 for scores I and IV, respectively; $p < 0.0001$) and FAP stage (NIS 14 and 99 for stages 1 and 3, respectively; $p < 0.0001$). In addition, there was an association between NIS and *TTR* genotype. The estimated rate of NIS progression for a population with a median NIS of 32 was 14.3 points/year; the corresponding estimated rate for the modified NIS+7 is 17.8 points/year.

Conclusions: In a multinational population of patients with FAP, rapid neuropathic progression is observed and the severity of neuropathy is associated with functional scales of locomotion.

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GLOSSARY

ANOVA = analysis of variance; **FAP** = familial amyloidotic polyneuropathy; **IQR** = interquartile range; **mNIS+7** = modified Neuropathy Impairment Score plus 7; **NIS** = Neuropathy Impairment Score; **PND** = polyneuropathy disability; **THAOS** = Transthyretin Amyloidosis Outcomes Survey; **TTR** = transthyretin; **V30M** = Val30Met.

Familial amyloidotic polyneuropathy (FAP) is a progressive, fatal condition, with survival after diagnosis of 5 to 15 years.¹ This rare, hereditary, autosomal dominant form of amyloidosis is caused by transthyretin (*TTR*) gene mutations,^{2–4} which can result in misfolding and aggregation of the *TTR* protein and formation of insoluble amyloid fibrils.⁵ Tissue deposition of mutant and wild-type *TTR* fibrils results in intractable peripheral sensorimotor neuropathy, autonomic neuropathy, and/or cardiomyopathy.^{6–9}

Clinical manifestations of FAP are influenced by a patient's *TTR* genotype and geographic location.¹⁰ Val30Met (V30M) is the most common gene mutation in FAP, with the largest patient cluster reported in Portugal.^{10,11} Symptoms at presentation and clinical progression in patients with V30M-FAP differ among countries. Early-onset FAP is common in Portugal,¹² while late-onset cases of FAP are predominant in the United States and in France, with variation reported in the clinical presentation of neurologic phenotypes.¹³

In FAP clinical trials, change in neurologic function over time has been assessed using the Neuropathy Impairment Score (NIS), the NIS–lower limb, and the NIS plus 7 (NIS+7)^{14–17}

Supplemental data
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From the National Reference Center for FAP (NNERF) (D.A., Z.M.), APHP, Univ Paris Sud, INSERM Unité 1195, Le Kremlin-Bicêtre, France; Hospital de Santo António (T.C.), Centro Hospitalar do Porto, Portugal; Amyloidosis Research and Treatment Center (L.O., G.M.), Foundation IRCCS Policlinico San Matteo and University of Pavia, Italy; Mayo Clinic (N.S., W.J.L., P.J.D.), Rochester, MN; and Alnylam Pharmaceuticals (B.R.B., J.A.G., P.J.G.), Cambridge, MA.

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(figure e-1 on the *Neurology*[®] Web site at Neurology.org). Recently, the modified NIS+7 (mNIS+7) was developed specifically to improve quantification and monitoring of neuropathy in patients with FAP.¹⁸

The objective of the present study was to use NIS to determine the association between the severity of neuropathy and disease stage as well as estimate the rate of neuropathy progression from cross-sectional analysis of a large multinational population of patients with FAP.

METHODS Study design and patients. This was a retrospective, multicenter, cross-sectional, chart review study to characterize neuropathy severity and rate of progression in patients with FAP from national reference centers for FAP across 4 countries: France, United States, Portugal, and Italy. Patients with a confirmed tissue biopsy diagnosis of FAP and without a liver transplant were eligible for inclusion in this study. The US and Portuguese centers included untreated patients only; at the other centers, treatment with TTR stabilizers was permitted.

Clinical and neuropathic assessments. Single NIS measurements, and the time from symptom onset to NIS measurement, were available for patients with FAP.

Demographic data available included age, sex, height, weight, genotype, and use of tetramer stabilizers. Where possible, polyneuropathy disability (PND) scores,¹⁵ the FAP disease stage,² and manual grip strength (kPa) measures with the Jamar Hydraulic Hand Dynamometer were also included for evaluation in this study.

The NIS was originally developed for broad neuropathic scaling of weakness, muscle stretch reflex decrease, and sensation loss of hands and feet for therapeutic trials in chronic inflammatory demyelinating polyneuropathy.¹⁹ For study of diabetic sensorimotor polyneuropathy, composite scoring of signs and neurophysiologic tests were used.¹⁶ The lower limb NIS+7, or NIS+7, was modified for use in generalized length-dependent sensorimotor polyneuropathy (e.g., TTR FAP) to more comprehensively assess sensation topographically.²⁰ The scores include different attributes of nerve conduction from those used in earlier studies,¹⁸ in addition to more and different autonomic endpoints. The mNIS+7 score for evaluation of patients with FAP used in the present study is shown in figure e-1.

Only highly standardized test items are examined in NIS, and test results are compared with a healthy subject cohort and expressed as percentage abnormality.^{21–23} The CI vs NPhys study series of clinical vs neurophysiology tests has previously demonstrated the proficiency (accuracy and intra- and intertest reproducibility) of the clinical assessment of polyneuropathy signs performed specifically, i.e., only unequivocal abnormalities graded (trials 1 and 2),^{21,24} attributes of nerve conduction (trials 3 and 4),^{23,25} and the value of smart quantitative sensation tests (including vibratory detection threshold assessments with CASE IVc) (trial 5), for monitoring patients with sensorimotor polyneuropathy.²² The rational and specific algorithm of Smart Somatotopic Quantitative Sensation Testing utilized in the FAP-specific mNIS+7 was developed by one of us (P.J.D.)^{20,22} and programmed for personal computer use by WR Medical Electronics, Maplewood, MN.

Statistical analyses. Statistical analyses were conducted using R version 3.0.1 software, including descriptive, parametric, and

linear- and nonlinear regression analyses. Where appropriate, continuous variables were log-transformed and analyzed via analysis of variance (ANOVA). Tukey post hoc tests (given particular ANOVA models) were conducted using the Tukey HSD (honest significant difference) function. Time from symptom onset vs NIS data were initially fit via the locally weighted scatterplot smoothing (loess) method, using the default parameters found in the `geom_smooth` function of the R `ggplot2` package. The approximately sigmoidal shape of the loess fit was confirmed via formal fit to the Gompertz equation $NIS(t) = ae^{-(be^{-ct})}$, where t = time since symptom onset; parameters were estimated using the `nls2` package.²⁶ Prediction of future NIS scores for particular starting point/time combinations (e.g., NIS progression in 12 months for a hypothetical subject starting with NIS of 30) was conducted by solving the inverse Gompertz equation.

RESULTS Patient baseline demographics and disease characteristics. Data from a total of 283 patients in France, Italy, Portugal, and the United States between 1997 and 2013 (table) were retrospectively analyzed. The mean (interquartile range [IQR]) time from FAP symptom onset to the NIS measurement for the total patient population was 3.95 (1.17–5.0) years, with country-specific durations ranging from 1.19 (0.5–1.46) years for the Portuguese cohort to 7.03 (2.0–10.0) years for the US cohort (median 33 months, range 0–31 years) (table). For the 46 Portuguese patients with early-onset V30M (defined as <50 years of age at symptom onset), the mean time from FAP symptom onset to NIS measurement was 12.3 (IQR 6–12.75) months.

The majority of patients (70.3%) were male; this male predominance was more apparent in patients from Italy (80.6%) than in Portuguese patients (58%). The overall mean age was 56.4 (IQR 41.0–69.6) years, with a lower mean age of 38.5 (IQR 33.3–41.0) years for the Portuguese cohort and a higher mean of 65.4 (IQR 58.9–73.1) years for patients in Italy (table). Intercountry genotypic variation was observed, with the majority of patients in Italy (19/31; 61.3%) and the United States (38/67; 56.7%) with non-V30M compared with 42.2% of patients (57/135) in France. Most of the patients in Portugal had early-onset V30M (92%).

The majority of the French and Italian cohorts complained of walking difficulties (PND > I; 69.7%–80.6%): one-third of the French patients used a walking aid (FAP stage 2, PND stage IIIa or IIIb) compared with half of the Italian cohort (table). Between 3.8% and 9.7% in these cohorts were wheelchair-bound (FAP stage 3, PND stage IV). Baseline PND scores were unavailable for the Portuguese and US cohorts. The entire Portuguese cohort and the majority of the French cohort (61.4%) had FAP stage 1, while more than half (51.6%) of the Italian cohort had stage 2 (table).

TTR stabilizers were used at the time of examination by 38.7% and 3% of the Italian and French cohorts, respectively.

NIS distribution by country. Overall, the median NIS was 32.0. Marked differences were seen between the countries in the distribution of NIS: the lowest country-specific median was 9.0 (Portugal) and the highest was 87.5 (Italy) (figure 1). There was a difference in distribution between Portugal and the other countries: a large majority of Portuguese patients had an NIS <20 compared with a broader distribution in the other countries. The low NIS for patients from Portugal may be associated with the shorter mean time from symptom onset for this patient cohort compared with the total population (1.19 vs 3.95 years, respectively).

Effect of disease characteristics on NIS. The median NIS scores of 59.6 and 38.4 for patients with late-onset V30M and non-V30M *TTR* genotypes, respectively,

were statistically significantly higher than the score of 9.0 for patients with early-onset V30M ($p < 0.001$), according to Tukey post hoc tests (figure 2A). Portuguese patients, for whom mean time from symptom onset to NIS measurement was only 1.19 years, made up 54% of the early-onset V30M population. The median NIS score for patients of late-onset V30M genotype was statistically significantly higher than that of patients with the non-V30M genotype ($p < 0.05$).

NIS was positively associated with the PND score (data available for France and Italy only), with median NIS values increasing from 10 (PND score I) to 99 (PND score IV) ($p < 0.0001$ by ANOVA; figure 2B). NIS was also positively associated with FAP stage (data for France, Portugal, and Italy), with median NIS values increasing from 14 for patients with FAP stage 1 to 99 for those with FAP stage 3 ($p < 0.0001$ by ANOVA; figure 2C). Post hoc statistical analyses support both PND and FAP stage as

Table	Patient baseline demographics and disease characteristics				
	France (n = 135)	Italy (n = 31)	Portugal (n = 50)	United States (n = 67)	Total (n = 283)
Age, y	59.3 (48.0–69.9)	65.4 (58.9–71.3)	38.5 (33.3–41.0)	59.6 (50.5–69.0)	56.4 (41.0–69.6)
Time since symptom onset, y	3.19 (1.63–4.33)	5.07 (3.11–6.57)	1.19 (0.5–1.46)	7.03 (2.0–10.0)	3.95 (1.17–5.0)
Male	93 (68.9)	25 (80.6)	29 (58.0)	52 (77.6)	199 (70.3)
Genotype					
Non-V30M ^a	57 (42.2)	19 (61.3)	0 (0)	38 (56.7)	114 (40.3)
Late-onset V30M	45 (33.3)	11 (35.5)	4 (8.0)	18 (26.9)	78 (27.6)
Early-onset V30M	33 (24.4)	1 (3.2)	46 (92.0)	3 (4.5)	83 (29.3)
Unknown	0 (0)	0 (0)	0 (0)	8 (11.9)	8 (2.8)
PND score ^b					
I	40 (30.3)	6 (19.4)	NA	NA	NA
II	41 (31.1)	6 (19.4)	NA	NA	NA
IIIa	32 (24.2)	5 (16.1)	NA	NA	NA
IIIb	14 (10.6)	11 (35.5)	NA	NA	NA
IV	5 (3.8)	3 (9.7)	NA	NA	NA
FAP stage ^c					
1	81 (61.4)	12 (38.7)	50 (100)	NA	NA
2	46 (34.8)	16 (51.6)	0 (0)	NA	NA
3	5 (3.8)	3 (9.7)	0 (0)	NA	NA
On TTR stabilizers at first visit	4 (3)	12 (38.7)	0 (0)	NA	16 (6)

Abbreviations: FAP = familial amyloidotic polyneuropathy; NA = not applicable; PND = polyneuropathy disability; TTR = transthyretin; V30M = Val30Met. Data are mean (interquartile range) or n (%).

^aNon-V30M mutations: A45D (n = 1), A45V (n = 1), A97? (n = 1), A109S (n = 1), A120S (n = 1), C10R (n = 1), D38A (n = 3), D39V (n = 1), E54G (n = 2), E62K (n = 1), F64L (n = 12), G47A (n = 1), G47E (n = 2), G47Q (n = 1), G53Q (n = 1), I107F (n = 2), I107V (n = 8), I68L (n = 1), L58H (n = 1), P24S (n = 2), Q54G (n = 1), Q89G (n = 5), Q89L (n = 1), S77F (n = 6), S77Y (n = 23), S109A (n = 1), T49A (n = 5), T49I (n = 1), T59L (n = 1), T60A (n = 16), V32A (n = 1), V122I (n = 1), Y116S (n = 3), Y78F (n = 5).

^bPND score: I = sensory disturbance but preserved walking capacity; II = impaired walking capacity but ability to walk without stick or crutches; IIIa = walking with help of one stick or crutch; IIIb = walking with help of 2 sticks or crutches; IV = confined to wheelchair or bedridden. One hundred thirty-two of 135 French patients have a valid PND score.

^cFAP stage: 1 = unimpaired ambulation, mostly mild neuropathy in lower limbs; 2 = assistance with ambulation required, mostly moderate neuropathy with progression to lower limbs, upper limbs, and trunk; 3 = wheelchair-bound or bedridden, severe neuropathy of all limbs.

Figure 1 NIS distribution by country and overall

(A) France, (B) Italy, (C) Portugal, (D) United States, and (E) Overall. $\bar{x}$ = mean; $\tilde{x}$ = median; σ = SD. NIS = Neuropathy Impairment Score.

measures that segregate NIS values. For PND scores, all possible pairwise between-stage comparisons were significant ($p < 0.01$) except for stage IV vs stage IIIb. All FAP between-stage comparisons were significant: stage 1 vs 2 ($p < 0.001$), stage 1 vs 3 ($p < 0.001$), and stage 2 vs 3 ($p = 0.03$).

Association of manual grip strength and PND score.

There was an inverse association between right hand manual grip strength and the PND score (data available for France only), with an observed reduction in median grip strength from 30.8 kPa for PND score I to 6.0 for PND score IV ($p < 0.0001$ by ANOVA; figure 3).

Estimation of neuropathy progression rate. Loess Fit and Gompertz Fit models both show a rapid neuropathy progression rate over the initial 3 to 5 years (figure 4, A and B). NIS values range widely from 0 to 140 in this initial phase. Beyond approximately 8 years since symptom onset, a relatively small number of subjects with apparently stable NIS values of <100 have a strong impact on curve fits, yielding asymptotes between 50 and 100 depending on the curve fit method. Linear regression is similarly affected by these points, and results in slow predicted rates of progression. The nonlinear fits illustrated here more

accurately reflect the clinical experience compared with linear models of rapid NIS progression (once measurable) in patients with FAP.

The Gompertz equation $NIS(t) = (57.34367682 \times e)^{[-2.792457 \times e]^{[0.08358818 \times t]}}$ provides a highly significant ($p < 0.0001$) fit to the time since symptom onset vs NIS data (figure 4B). Predicting NIS progression using the inverse of this equation, an example subject with an NIS score of 32 (the median of our dataset, typically at 19 months since symptom onset) would show a change in NIS score over 12 months of +14.3 points. The mNIS+7 system comprises 304 points, as compared with 244 points for NIS (figure e-1).²⁷ Assuming the additional components of mNIS+7 progress at consistent rates, algebraic translation ($244/14.3 = 304/x$) yields an estimated mNIS+7 progression rate of 17.8 points/year.

DISCUSSION This multinational, cross-sectional, natural history study demonstrated that patients with FAP experience rapid progression in NIS, with a strong association of NIS with other functional measures of disease severity (PND and FAP score). Because this international study included patients from different continents, with different FAP

Figure 2 Boxplots of the NIS

NIS vs (A) transthyretin genotype, (B) PND score (France and Italy only), and (C) FAP stage (France, Portugal, and Italy). Median (horizontal line), quartile range (Q1–Q3; box), and lowest/highest data point within $1.5 \times$ interquartile range (vertical line) are presented with individual patient data points. FAP = familial amyloidotic polyneuropathy; NIS = Neuropathy Impairment Score; PND = polyneuropathy disability; V30M = Val30Met.

genotypes and wide ranges of disease duration and neuropathic impairment, it is likely representative of patients with FAP typically encountered in clinical practice in a “real world” setting.

Because this was a retrospective analysis, the projections may be affected by survival bias. Prior treatments may also affect the rate of disease progression, although it should be noted that none of the patients included had received a liver transplant and only 6% were known to be receiving TTR stabilizers. However, the rapid progression of NIS over time estimated in this study is also supported by previous clinical observations, with 13.9 NIS points/year reported for non-V30M patients’ pretreatment in the tafamidis Fx1A-201 study (baseline median NIS score 45.0; $n = 21$).²⁸ Furthermore, the change in NIS of 14.3 points/year for subjects presenting with the median NIS value of 32 estimated in this study is consistent with the rate of 11.6 points/year reported for the placebo arm of the multinational phase III trial of diflunisal, which also included patients with V30M and non-V30M FAP (baseline median NIS score 30.8).¹⁵ In addition to measuring NIS, the diflunisal trial also described neuropathic changes using the composite NIS+7 score in this large heterogeneous FAP population. These data supported the rapid progression of FAP, with an increase in NIS+7 score of 12.5 points at 1 year and 25.0 points at 2 years in the placebo arm. The median (range) duration of FAP symptoms at baseline reported in the tafamidis study was 45.5 (5.2–253.1) months.²⁹

Proficiency remains a key consideration in the measurement of disease progression, as interpretation of signs and symptoms is subject to variation among physicians.^{21,24} Indeed, ensuring accuracy and

reproducibility is important for both the assessment of clinical signs and nerve tests (e.g., NIS measures), and for assessing acts of daily living, as included in the FAP and PND scores. Test items are therefore highly standardized and most trials use a central reading center. The recently developed mNIS+7 has been adapted from the earlier NIS+7 to more adequately assess sensation somatotopically and to include better measurements of attributes of nerve conduction and autonomic function. The improved approaches to assess neuropathic impairments represented by mNIS+7 have been previously studied.^{18,22} While the NIS+7 has a maximum of 270, the FAP-specific mNIS+7 used in the present study has 304 points maximum.²⁷ The NIS progression rate of 14.3 points/year as observed in this study corresponds to an mNIS+7 progression rate of 17.8 points/year.

The mNIS+7 is being used in the ongoing phase III trials of patisiran (NCT01960348) and ISIS-TTR_{RX} (NCT01737398). Both trials involve patients with FAP with comparable demographics to those in the present study.^{30,31} The results from the present study suggest that the phase III, double-blind, placebo-controlled, global trials of these TTR-lowering agents are robustly powered to show the potential impact of TTR lowering on the mNIS+7 study endpoint. The TRANSCEND observational study, initiated in 2013, is expected in the future to provide further natural history data for patients with FAP.³²

This study also showed the impact of disease on the upper limbs, with progressive reduction of manual grip strength over time and an association with the PND score observed. These data highlight that a reduction in independence in patients with FAP is

Figure 3 Correlation of grip strength and PND score (France only)

PND = polyneuropathy disability.

not only linked to the progressive reduction of locomotion, but is also associated with impairment of major everyday essential movements.

Further analyses of neuropathy may in fact suggest a more rapid rate of disease progression than reported here, as the nonlinear fits used in this study likely underestimate progression rates in patients with advanced NIS; the plateau phase of the curve is

affected by a relatively small number of subjects with low NIS and high time since symptom onset. For patients with a shorter time since symptom onset (<5 years), we used the Gompertz equation, which allows for accurate estimation of progression rate for the majority of subjects (especially those with lower initial NIS values). However, future longitudinal studies of NIS progression rates in a broad range of patients with FAP (e.g., the Alnylam and ISIS pivotal trials) will determine whether the estimation of progression rate in this cross-sectional study and the diflunisal study are accurate.

Progression of FAP through other measures has also been reported in the Transthyretin Amyloidosis Outcomes Survey (THAOS), a multicenter, longitudinal, observational survey that is collecting data on patients with TTR amyloidosis.^{10,33} Scores of the modified PND scale, EuroQol 5-Dimensions (EQ-5D) health scale, EQ-5D health index, and Karnofsky Performance Status progressively decreased over 10 years' disease duration in patients who received no disease-modifying treatment, indicating worsening patient function.³⁴ As in the THAOS, V30M was the most common mutation in the present study; NIS score was higher in patients with late-onset V30M compared with early-onset V30M or non-V30M mutations. Of note, early-onset V30M FAP was common in the Portuguese population assessed, who were typically younger than 40 years at symptom onset and had a low NIS, and as such may not be representative of the overall FAP population. In patients with late-onset V30M FAP, severe

Figure 4 NIS over time

(A) Loess Fit, and (B) Gompertz Fit. CI = confidence interval; NIS = Neuropathy Impairment Score.

polyneuropathy has been previously reported, in agreement with the high NIS scores observed for this population in the present study.^{35,36}

Patients with FAP experience rapid neuropathy progression, as measured by clinical signs and neurophysiologic tests. While FAP-associated polyneuropathy has been previously monitored using the NIS, describing these measures using the FAP-specific mNIS+7 may provide a more detailed insight into the progressive neuropathic burden of this disease.

AUTHOR CONTRIBUTIONS

D.A.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. T.C.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. L.O.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. G.M.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. Z.M.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. N.S.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. B.R.B.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. J.A.G.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. P.J.G.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. W.J.L.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data. P.J.D.: reviewing and revising the manuscript for content, study concept or design, acquisition of data, analysis or interpretation of data.

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