Genotype–Phenotype Correlation and Course of Transthyretin Familial Amyloid Polyneuropathies in France

Louise-Laure Mariani, MD,[1] Pierre Lozeron, MD, PhD,[1,2,3] Marie Théaudin, MD, PhD,[1,2,4] Zoia Mincheva, PhD,[1,2] Aissatou Signate, MD,[5] Beatrice Ducot, PhD,[6,7,8] Vincent Algalarrondo, MD, PhD,[2,9,10] Christian Denier, MD, PhD,[1,4,9] Clovis Adam, MD,[2,11] Guillaume Nicolas, MD, PhD,[12,13] Didier Samuel, MD, PhD,[14,15] Michel S. Slama, MD,[2,9,10] Catherine Lacroix, MD,[2,11] Micheline Misrahi, MD, PhD,[2,9,16] and David Adams, MD, PhD,[1,2,4,9,17] on behalf of the French Familial Amyloid Polyneuropathies Network (CORNAMYL) Study Group

Objective: To compare the natural history of familial transthyretin amyloid polyneuropathies (FAP) due to the Val30Met, Ser77Tyr, and Ile107Val mutations in France with the classical Portuguese Val30Met FAP.
Methods: We compared 84 French patients with a control group of 110 Portuguese patients carrying the Val30Met mutation also living in France, all referred to and followed at the French National FAP Reference Center from 1988 to 2010. Clinical examination, functional and walking disability scores, nerve conduction studies, and muscle biopsies are reported. We also conducted a comprehensive literature review to further determine the range of phenotypic expression.
Results: By comparison with Portuguese Val30Met FAP, French Ile107Val, Ser77Tyr, and LateVal30Met FAP showed more rapid and severe disease progression; onset of gait disorders was 3 times more rapid ($p < 0.0001$) and the rate of modified Norris test decline was up to 40 times faster in Ile107Val patients ($p < 0.0001$). Median survival was much shorter in Ile107Val and in Val30Met mutation with late onset (>50 years; LateMet30) FAP ($p = 0.0005$). Other distinctive features relative to the Portuguese patients included atypical clinical presentations, demyelination on nerve conduction studies ($p = 0.0005$), and difficult identification of amyloid deposits in nerve and muscle biopsies.
Interpretation: Ile107Val and LateMet30 mutations are associated with the most debilitating and severe FAP ever described, with rapid onset of tetraparesis and shorter median survival. It could be explained by frequent large-fiber involvement and associated demyelination and more severe axonal loss. These findings have major implications for

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Address correspondence to Dr Adams, Department of Neurology, Bicêtre Hospital, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre, France. E-mail: david.adams@bct.aphp.fr

From the [1]Department of Neurology, Bicêtre Hospital, Le Kremlin-Bicêtre;; [2]French National Reference Center for Familial Amyloid Polyneuropathies (NNERf), Le Kremlin-Bicêtre; [3]Department of Neurophysiology, APHP, Lariboisière Hospital, University Paris-Diderot Sorbonne Paris Cité, INSERM UMR-965, Paris, France; [4]National Institute of Health and Medical Research Unit U1191, Le Kremlin-Bicêtre; [5]Department of Neurology, Pierre Zobda-Quitman Hospital, Fort de France; [6]Reproduction and Child Development Team, Center for Research in Epidemiology and Population Health, Le Kremlin-Bicêtre; [7]University of Paris–South, Villejuif; [8]National Institute for Demographic Studies, Paris; [9]University Paris–Sud, Paris; [10]Department of Cardiology, Antoine Béclère Hospital, Clamart; [11]Department of Neuropathology, Bicêtre Hospital, Le Kremlin-Bicêtre; [12]Department of Neurology, Raymond Poincaré Hospital, Garches; [13]University of Versailles Saint-Quentin-en-Yvelines, Versailles; [14]Hepatobiliary Center, Paul Brousse Hospital, Villejuif; [15]National Institute of Health and Medical Research Mixed Unit of Research S785, Villejuif; [16]Department of Molecular Biology, Bicêtre Hospital, Le Kremlin-Bicêtre; and [17]FILNEMUS, Filière nationale de Santé Maladies Rares Neuromusculaires, Marseille, France

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genetic counseling and patient management as new therapeutic options are being assessed in clinical trials (*TTR* gene silencing).

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Familial transthyretin amyloid polyneuropathies (TTR-FAP) are severe high-penetrance autosomal dominant polyneuropathies that are generally fatal within a decade without treatment. They are due to polyvisceral deposits of amyloidogenic transthyretin (TTR) protein, predominating in the endoneurial space of peripheral nerves, heart, bowel, and urogenital tract. Pathological studies of TTR-FAP peripheral nerves show amyloid deposits in endoneurial spaces and axonal degeneration, especially in the distal portion.[1]

TTR is a protein mostly secreted by the liver. The *TTR* gene (Online Mendelian Inheritance in Man database 176300) located in chromosome region 18q11.2–18q12.1 comprises 4 exons. The first pathogenic variant in which a valine (Val) replaced the methionine (Met) at position 30 (Val30Met), due to c.148C>A mutation in exon 2, was identified in Portuguese,[2] Swedish,[3] Japanese,[4] and European patients[5] and remains the most common mutation worldwide. More than 112 missense point mutations and 1 microdeletion in the *TTR* gene have been identified.[3,6] *TTR* gene analysis plays a key role in the diagnosis of European FAP.[5]

Val30Met (Met30) is almost the only variant found in Portugal, where mean age at onset is 33 years, a positive family history is frequent, and penetrance is high.[7–9] In Japan, Met30 families with early onset neuropathy were initially identified in 2 limited areas (Arao district and Ogawa village) with a penetrance of 80%.[10] Late onset (>50 years) TTR-FAP Val30Met (LateMet30) is widely distributed throughout Japan[11] as well as in northern Sweden, where penetrance is lower.[12] FAP patients of French descent are divided into 2 groups depending on their pathogenic *TTR* mutation. LateMet30 accounts for 40% of cases. The remaining patients carry 1 of the 29 known *TTR* mutations in France,[13] leading to different patterns of neuropathy.[14]

The first reports of FAP mentioned purely sensory polyneuropathies predominantly affecting small fibers and leading to dissociated sensory impairment.[8] Initial sensory disturbances mainly affect pain and temperature sensing, and are associated with autonomic dysfunction, weight loss, cardiac disorders, and less frequently renal involvement. Death occurs after a median of 10.8 years, due to wasting, infections, or sudden death.[9] Various patterns of neuropathy have been described more recently.[15,16]

The gold standard curative treatment is liver transplantation (LT), but new therapeutic options are being assessed in clinical trials.[17]

The clinical features and long-term outcome of FAP due to mutations other than Met30 are poorly documented. Here, we assess the clinical and electrophysiological features and natural disease course of TTR-FAP due to the Val30Met (Met30), Ser77Tyr (Tyr77), and Ile107Val (Val107) mutations in France by comparison with a Met30 Portuguese population (PortMet30) also living in France. The patients were recruited during a 22-year period by the French National FAP Reference Center. We also conducted a systematic review of the literature. We show Ile107Val mutation is associated with the most debilitating and severe FAP ever described, with rapid onset of tetraparesis and shorter median survival. LateMet30 and to a lesser extent Tyr77 mutation are also more severe than Portuguese Val30Met FAP.

Subjects and Methods

We conducted a single center retrospective study of patients referred to the French National FAP Reference Center for diagnosis, follow-up, and treatment. French patients with LateMet30, Tyr77, and Val107 mutations were compared to consecutive Met30 FAP patients of Portuguese origin (PortMet30) until LT, specific oral medication (tafamidis meglumine), or death.

Subjects

We reviewed the records of 208 French FAP patients carrying 3 of the main mutations (Met30, Tyr77, and Val107) referred to our institution between January 1988 and February 2010. The inclusion criteria were (1) clinical manifestations of polyneuropathy; (2) Val30Met, Ser77Tyr, or Ile107Val *TTR* mutation identified by DNA analysis of blood leukocytes; (3) amyloid deposits in non-Portuguese patients with a negative family history; (4) non-Portuguese origin for patients with LateMet30; or (5) Portuguese descent regarding group PortMet30.

Clinical Neurological Assessment

The time between symptom onset and the first neurological examination was assessed, along with the initial symptoms and course of neuropathy.

Clinical data consisted of:

- Age at onset.
- Weight loss and pain at initial examination.
- Personal history of carpal tunnel syndrome (CTS) in patients with nerve conduction study fulfilling the American Association of Electrodiagnostic Medicine criteria for CTS.[18,19]
- Family history of neuropathy or TTR-amyloidosis in at least 1 member of the kindred.
- Two functional questionnaires assessing sensorimotor disability in the 4 limbs, namely the modified Norris test (MNT; best maximum = 75)[20] and the polyneuropathy disability (PND) score for walking capacity.[21]

- Light touch, pinprick, vibratory, joint position sense, and temperature sensation at 4 °C and 40 °C to explore all sensory modalities. Small-fiber polyneuropathy (sensory dissociation) was considered when pain and thermal impairment predominated over light touch and proprioceptive impairment.
- Muscle testing of all 4 limbs according to the Medical Research Council (MRC) scale (5 = normal strength, 0 = no contraction).[22] Proximal strength was evaluated on the quadriceps and/or iliopsoas muscles in the lower limbs, and on the deltoid and/or biceps brachii muscles in the upper limbs. Distal strength was evaluated on the anterior tibialis and/or gastrocnemius muscles in the lower limbs, and on the dorsal interosseus and/or extensor carpi radialis muscles in the upper limbs. Tetraparesis was defined as weakness in all 4 limbs. Proximodistal tetraparesis was defined as both proximal and distal weakness in all 4 limbs.
- Autonomic involvement.[20]
- The rapidity of disease progression, as assessed by the rate of MNT decline ([MNT score maximum - minimum]/disease duration), walking disability, and overall survival (from initial symptoms to initiation of disease-modifying antiamyloid therapy [LT or tafamidis] or death).

Additional final follow-up was based on clinical examination at the reference center or on telephone interview with evaluation of the MNT, autonomic dysfunction, PND score, and/or survival since onset. When patients could not be reached directly, vital status was determined by consulting civil registries.

Electrophysiological Studies

Axonal loss was defined by an amplitude below the lower limit of normal sensory and motor responses. Asymmetry was defined as a ≥50% difference between the left and right recorded amplitudes. Demyelination was defined according to the European Federation of Neurological Societies/Peripheral Nerve Society 2010 criteria.[23] In the Met30 groups, progression of axonal loss was evaluated from the rate of decline in compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes (μV/yr).

SNAP and CMAP amplitudes were measured from baseline to peak in all 4 limbs. Motor conduction velocity was measured in ulnar and peroneal nerves and sensory conduction velocity in ulnar and sural nerves. When performed at our reference center, tests were performed in the same laboratory with KeyPoint equipment (Medtronic, Minneapolis, MN). Skin temperature was maintained at >32 °C. Normal values were obtained from a group of 35 normal volunteers without any sign or symptom of neuropathy.

Histopathology

To confirm amyloid neuropathy and to detect amyloid deposits, biopsies of at least 5cm of clinically affected nerve and/or muscle were performed under local anesthesia with the patients' informed consent, unless there was a family history of histopathologically confirmed TTR-FAP. Other tissues were biopsied when further investigations of amyloid deposits were needed (Supplementary Table 1). Most samples obtained elsewhere were referred to our center for secondary analysis on serial sections.

Nerve samples were fixed at 4 °C in 3.6% glutaraldehyde buffered at pH 7.4. One nerve fragment was embedded in paraffin and cut into 5 μm slices. Four sections were first examined after hematoxylin–eosin (n = 2), Masson trichrome (n = 1), and Congo red (n = 1) staining. Additional serial sections (n = 40 sections) were examined after hematoxylin–eosin (n = 20) and Congo red staining if no amyloid deposits were found on the first sections. Amyloid deposits were characterized by their Congo red affinity and birefringence with thioflavin T under polarized light.

Another fragment was postfixed in 1% osmium tetroxide in buffer for 3 hours at 4 °C and embedded in Epon. One-micrometer-thick cross-sections stained with thionin were used for fiber density assessment. A teased-fiber study was performed in most cases. Immunolabeling of amyloid deposits was performed on paraffin-embedded specimens. In some cases, ultrathin sections were stained with uranyl acetate and lead citrate for electron microscopy to identify amyloid fibrils and lesions of unmyelinated fibers.

Axonal loss was defined as a reduction of nerve fiber density below the 95% confidence interval of normal controls for both small fibers and large fibers. Small fiber count was performed on semithin sections. In selected cases when the quality of the semithin section was not sufficient, small fiber count was performed with electron microscopy.

Segmental demyelination was assessed on teased fiber analysis. More than 10 of 100 teased fibers showing segmental demyelination were necessary for categorization in the "segmental demyelination" group. Control values were based on previous work from our reference center and determined as previously described.[24]

Cardiovascular Evaluation

Signs of cardiac amyloidosis were sought:

- Symptoms of heart failure were evaluated by the New York Heart Association (NYHA) functional classification. Symptomatic cardiomyopathy was diagnosed in patients with a NYHA class > I or in asymptomatic patients with previous heart failure symptoms and with long-term diuretics.
- Characteristic features of myocardial amyloid infiltration on transthoracic echocardiography, including increased interventricular septum thickness, "granular sparkling" myocardial aspect, left ventricular diastolic dysfunction, valve thickening or regurgitation, and pericardial effusion. Interventricular septum thickness was measured by echocardiography (parasternal long axis view, M-mode) and determined as abnormal if ≥12mm.
- Denervation on metaiodobenzylguanidine (MIBG) scintigraphy, response to atropine infusion, and heart rate variability by 24-hour electrocardiogram monitoring.[25] Cardiac denervation was diagnosed if (1) heart/mediastinum ratio was < 1.6 by MIBG scintigraphy, (2) heart rate did not increase after atropine infusion, or (3) the standard deviation of the NN interval was <100 milliseconds.

- Prophylactic cardiac pacing at inclusion or during follow-up performed on the basis of the surface electrocardiogram (ECG) and the electrophysiological study, as previously described.[26] The following parameters were taken into account: PR interval, QRS duration and morphology, the His to ventricle duration (HV interval), and the anterograde Wenckebach point. Prophylactic cardiac pacing was performed if 1 of the following criteria was reached: (1) prolonged HV interval ($\geq$70 milliseconds) or (2) an abnormal HV interval (>55 milliseconds) associated with a fascicular block on ECG (right bundle branch block, left bundle branch block, left anterior hemiblock, left posterior hemiblock), or a first-degree AV block (PR interval $\geq$ 200 milliseconds), or a WA point $\leq$ 100 beats/min.
- Abnormal diastolic ventricular function on cardiac catheterization (mean right atrial pressure > 10mmHg and/or mean pulmonary wedge pressure > 12mmHg in the absence of significant systolic abnormalities, or characteristic "dip and plateau" diastolic pressure defining restrictive cardiomyopathy[27].

TTR Gene Analysis

All the patients gave their informed consent to genetic studies. DNA was extracted from peripheral mononuclear cells. Direct sequencing of the *TTR* gene full coding region, or a specific exon when a mutation had previously been identified in the family, was performed as previously described.[28]

Statistical Analysis

Patient characteristics are reported as numbers and percentages for categorical variables and medians [range] or mean $\pm$ standard deviation for continuous variables. Quantitative variables were compared using the Kruskal–Wallis test for unpaired variables. In case of significance, groups were compared with one another by using Dunn multiple comparisons test. Repeated measures were compared using 2-way analysis of variance (ANOVA) with Bonferroni post-test to compare replicate means. Categorical variables were compared using the chi-square test or with Fisher exact test when numbers were too small. Overall survival and the median time to onset of walking disability (gait disorder, use of canes, wheelchair-bound) were assessed using the Kaplan–Meier method.

Literature Review

The NIH PubMed database was scanned for reports in English containing detailed clinical descriptions and mutation analysis up to June 2015. Cases purported to be TTR-FAP but with no available DNA analysis or biopsy were discarded, as were case series linked to Val30Met mutation without individualized late and early onset groups. Authors of reports on Japanese and French cases were contacted directly for further information (Haruki Koike and Gen Sobue; Guillaume Nicolas). All reviewed reports are listed in Supplementary Table 2.

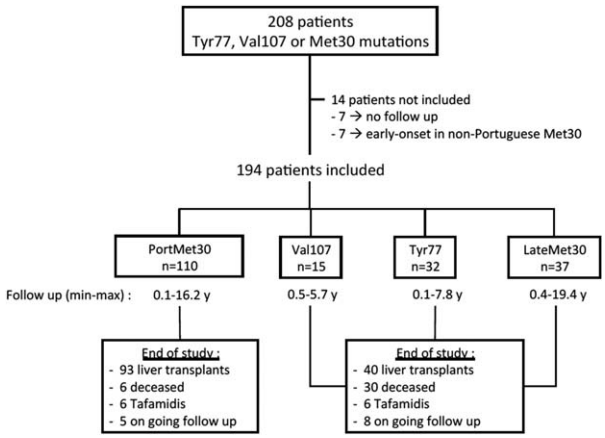

FIGURE 1: Flow chart of patients with familial amyloid polyneuropathy. LateMet30 = Val30Met *TTR* mutation in patients with late onset (>50 years); PortMet30 = Val30Met mutation in patients of Portuguese origin; Tyr77 = Ser77Tyr *TTR* mutation; Val107 = Ile107Val *TTR* mutation.

Results

Patient Inclusion

Between 1988 and 2010, 322 patients were referred to the French National Reference Center for FAP (Supplementary Table 3). Of the 208 records fulfilling the inclusion criteria, 194 patients with TTR-FAP due to heterozygous Met30, Tyr77, and Val107 mutations (118 males, 76 females) were included, and a control group of 110 consecutive patients of Portuguese origin with heterozygous Met30 mutation was defined (Fig 1). The 84 non-Portuguese patients belonged to 63 families. Seven patients were not included because of a lack of follow-up, and 7 non-Portuguese Met30 patients were excluded because of early onset (<50 years; detailed characteristics available in Supplementary Table 4).

Case Demographics

Table 1 describes the case demographics of the Val107, Tyr77, and LateMet30 patients (detailed characteristics in Supplementary Table 1) by comparison with the PortMet30 control group.

In the non-Portuguese groups, 12 patients (15%) originated from outside France. Val107 was the only mutation found in patients from the French West Indies, who represented 60% of all Val107 carriers (see Table 1). A family history of neuropathy or amyloidosis was rare among Val107 and LateMet30 patients at initial examination, and usual in Tyr77 and PortMet30 patients (see Table 1). At last follow-up, a positive family history was significantly more frequent than initially in all the groups but was still less frequent in Val107 and LateMet30 than in Tyr77 and PortMet30 (see Supplementary Table 1). A personal history of CTS, often prior to any other symptom and leading to surgery (Supplementary Table 5), was

TABLE 1. Demographics of Familial Amyloid Polyneuropathies in France

Characteristic	Val107	Tyr77	LateMet30	PortMet30	*p*
No.	15	32	37	110	
Age at onset, yr	64 [52–72][a]	55 [37–79][a]	64 [53–81][a]	32 [22–66]	<0.0001[a]
Sex ratio, M:F	6.5:1	3.6:1	3.1:1	0.9:1	<0.0001
Positive family history	3 (21)	20 (63)	11 (31)	104 (95)	<0.0001
History of CTS	7 (47)	20 (63)	8 (23)	9 (9)	<0.0001
With CTS surgery	5 (71)	11 (79)	5 (71)	1 (11)	<0.0001
Origin					
Portugal	0	0	0	110 (100)	
France	15 (100)	23 (77)	31 (84)	0	
Including French West Indies	9 (60)	0	0	0	
Italy	0	4 (13)	3 (8)	0	
Others	0	3 (10)	2 (5)	0	
Unknown	0	2 (6)	0	0	
Initial symptoms					
Paresthesia, sensory disturbances, pain	11 (73)	23 (74)	34 (94)	86 (79)	0.1145
Dysautonomia	1 (7)	4 (13)	2 (6)	24 (22)	0.073
Weakness	2 (13)	1 (3)	1 (3)	0	0.0326
Gait disorders	1 (7)	7 (23)	0	1 (1)	0.0054
Stiffness and cramps	1 (7)	3 (10)	2 (6)	0	0.0056
Extraneurological	0	0	2 (6)	1 (1)	0.5778
Unknown	0	1 (3)	1 (3)	2 (2)	

Categorical variables are expressed as number (percentage) and continuous variables as median [range]. Quantitative variables were compared using the Kruskal–Wallis test for nonpaired variables. In case of significance, groups were compared to each other using Dunn multiple comparisons test. Categorical variables were compared using the chi-square or Fisher exact test.
CTS surgery percentages are expressed as percentage of the CTS-presenting patients and not the total number of patients.
Other origins: Algeria, Belgium, and Spain (detailed data in Supplementary Table 1). Total percentages of initial symptoms can exceed 100% because multiple symptoms could appear simultaneously.
Extraneurological symptoms: uveitis, arthritis, and retinal hemorrhage in LateMet30 and syncope requiring pacemaker implantation and nephropathy in PortMet30.
[a]Significant differences after Dunn post-test relative to the PortMet30 control group.
CTS = carpal tunnel syndrome; F = female; LateMet30 = Val30Met *TTR* mutation in patients with late onset (>50 years); M = male; PortMet30 = Val30Met mutation in patients of Portuguese origin; Tyr77 = Ser77Tyr *TTR* mutation; Val107 = Ile107Val *TTR* mutation.

more frequent in Tyr77 than in Val107 and LateMet30 and very rare in PortMet30 ($p < 0.0001$; see Table 1).

Presenting Symptoms

The first disease manifestations were sensory disturbances (see Table 1 and Supplementary Table 1). Initial autonomic dysfunction tended to be less frequent in the non-PortMet30 than in the PortMet30 group (see Table 1), consisting mostly of diarrhea and vomiting (21 of 110 PortMet30 patients).

Atypical initial symptoms in non-Portuguese patients included weakness, gait disorders, stiffness, and onset in the upper limbs. Weakness was more frequent in Val107 ($p = 0.0326$), gait disorders in Tyr77 and Val107 ($p = 0.0054$), and stiffness and cramps in Tyr77, Val107, and LateMet30 ($p = 0.0056$); only 1 PortMet30 patient had gait disorders at onset.

In 22 non-Portuguese patients (26%), symptoms started in the upper limbs, asynchronously in the lower limbs, or in a single limb. Extraneurological disorders were extremely rarely the first symptoms (see Table 1). Apart from the 4 patients with a history of CTS (see Supplementary Table 5), none of the PortMet30 patients presented with upper limb symptoms as initial manifestation.

Neurological Findings at Referral

The impact of the neuropathy on functional disability and ambulation was major in non-Portuguese patients. Walking difficulties were already present at referral in most Val107 and LateMet30 patients, many Tyr77 patients, and fewer PortMet30 patients ($p < 0.0001$). The median MNT was significantly lower in Val107 and LateMet30 than in PortMet30 (Table 2).

Initial neurological examination at our center showed neuropathy in every case, with superficial sensory impairment (91–100%), weakness (37–80%), deep tendon reflex loss (59–100%), autonomic dysfunction (72–76%), pain (73–83%), and major weight loss (48–79%; see Table 2 and Supplementary Table 1).

Predominant and early large-fiber sensory dysfunction was significantly more frequent in non-Portuguese patients than in PortMet30 patients, marked by deep sensory impairment, deep tendon reflex loss, and weakness (see Table 1). Small-fiber involvement (sensory dissociation) was more frequent in PortMet30 (59%) than in the other groups ($p = 0.012$; see Table 2 and Supplementary Table 1).

Initial weakness was significantly more frequent and more severe in Val107 and LateMet30 than in the other groups (see Table 2). Upper limb weakness was more frequent in Val107 (73%) and LateMet30 (57%) than in Tyr77 (25%) and PortMet30 (24%; $p < 0.0001$). Proximal deficits were mainly found in Val107 (67%; $p < 0.0001$; see Table 2 and Supplementary Table 1). Paresis was limited to toe extensors in 7 PortMet30 patients.

Nerve Conduction Studies

Nerve conduction studies showed signs of severe axonal neuropathy and frequent features of demyelination in non-Portuguese patients (Table 3). Eight PortMet30 patients showed normal findings.

Axonal loss was found in all 4 limbs (86–100%), and was asymmetric in almost all Val107 patients and about half the patients in the other groups (see Table 3). Ninety-six percent of non-Portuguese patients had a reduced amplitude of either CMAP or SNAP. In all 4 groups, sensory nerves seemed to be more severely affected than motor nerves, with at least 1 action potential not elicited in either an upper or a lower limb (see Table 3).

Signs of demyelination, excluding common compression sites, were frequent in non-Portuguese patients (52–86%). Definite electrophysiological demyelination was found in half the Val107 and LateMet30 patients, and in significantly fewer Tyr77 and PortMet30 patients (see Table 3). Final clinical and electrophysiological criteria of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) were met by 6 (40%) Val107, 9 (24%) LatMet30, and 2 (6%) Tyr77, whereas no PortMet30 patients met these criteria.

Cerebrospinal Fluid Analysis

Cerebrospinal fluid analysis was performed in 28 of 77 (36%) non-Portuguese patients (see Table 3), showing increased protein level in 20 of 28 (71%) of them.

Histopathological Findings in Non-Portuguese Patients

Biopsies were performed in 117 patients, comprising 14 (93%) Val107, 20 (63%) Tyr77, 32 (87%) LateMet30, and 51 (46%) PortMet30 patients. Both nerve and muscle specimens were collected in respectively 11 (73%), 7 (22%), 25 (68%), and 28 (25%) cases. Biopsy was less commonly performed in Tyr77 and PortMet30 patients because of more frequent positive family history (see Tables 1 and 3).

Amyloid deposits were found in most patients in all the groups after examination of serial sections at our reference center (see Table 3). They were located within or around endoneurial or perineurial vessel walls in 67% of Val107, 67% of Tyr77, and 46% of LateMet30 patients. Axonal loss was present in 10 (91%) Val107, 5 (71%) Tyr77, and 24 (96%) LateMet30 patients, and was severe in respectively 73%, 57%, and 80%, predominating on small fibers in 24 to 40% and large fibers in 20 to 40%. Signs of segmental demyelination $\pm$ remyelination (thinly myelinated fibers or segmental demyelination $\pm$ remyelination on teased fiber preparations) were found in 29% of non-Portuguese patients.

Cardiovascular Evaluation

All Val107, Tyr77, and LateMet30 patients investigated developed cardiac manifestations of amyloidosis during the study, compared to 81% of PortMet30 patients ($p = 0.0018$). A total of 13 of 15 (87%) Val107, 31 of 32 (97%) Tyr77, 34 of 37 (92%) LateMet30, and 87 of 110 (79%) PortMet30 patients were investigated.

On electrocardiogram, conduction abnormalities were less frequent in Val107 (33%) than in Tyr77 (64%) and LateMet30 (75%). Cardiac electrophysiological studies revealed conduction disorders, indicating pacemaker implantation in significantly more Tyr77 (55%) and LateMet30 (58%) patients than Val107 (22%) and PortMet30 patients (22%, $p = 0.0002$).

Echocardiography showed cardiac infiltration in 83 to 92% of non-Portuguese patients, with increased echogenicity (granular sparkling) in 71% of Tyr77, 57% of LateMet30, and only 22% of Val107 patients, and increased wall thickness in 83 to 91% of non-Portuguese

TABLE 2. Neuropathy Characteristics at First Neurological Examination

Characteristic	Val107	Tyr77	LateMet30	PortMet30	*p*
No.	15	32	37	110	
Time to first examination, yr	3.0 [0.6–10.4]	2.1 [0–10.4]	2.8 [0–10.9]	1.8 [0–14.6]	0.1273
Symptoms					
Functional disability					
Gait disorders	13 (87)	14 (44)	25 (68)	26 (23)	<0.0001
MNT score, best max = 75	64 [33–74][a]	67 [30–75]	59 [9–75][b]	74 [11–75]	<0.001,[a] <0.0001[b]
Pain	11 (73)	24 (83)	24 (75)	NS	0.6955
Weight loss {kg}	11 (79) {12.9}	13 (48) {9.6}	17 (49) {10.2}	63 (66) {11}	0.0512
Physical examination					
Autonomic manifestations	11 (73)	22 (69)	24 (65)	62 (74)	0.7519
Postural hypotension	7 (47)	10 (31)	18 (49)	60 (65)	0.0071
Nausea/vomiting	7 (47)	8 (25)	3 (8)	55 (59)	0.0001
Diarrhea/constipation	8 (57)	18 (56)	16 (43)	72 (77)	0.0022
Sphincter dysfunction	4 (27)	9 (28)	7 (19)	47 (50)	0.0034
Erectile dysfunction	8 (62)	16 (64)	16 (57)	8 (16)	0.8349
Sensory impairment					
Deep	14 (93)	21 (68)	28 (80)	35 (38)	<0.0001
Superficial	15 (100)	29 (91)	36 (97)	104 (100)	0.2812
Sensory dissociation	7 (47)	8 (25)	17 (46)	55 (59)	0.012
DTR					
Normal	0	6 (24)	0	40 (41)	0.0035
Lower limb loss	2 (20)	10 (40)	2 (20)	49 (50)	0.0993
Diffuse loss	8 (80)	9 (36)	8 (80)	9 (9)	<0.0001
Weakness	12 (80)	13 (41)	24 (65)	38 (37)	0.0013
Distal deficit	12 (80)	13 (41)	24 (65)	30 (30)	<0.0001
Lower limbs	11 (73)	7 (22)	22 (59)	28 (28)	<0.0001
Upper limbs	11 (73)	8 (25)	21 (57)	21 (21)	<0.0001
Proximal deficit	10 (67)	3 (9)	6 (16)	13 (13)	<0.0001
Lower limbs	10 (67)	3 (9)	3 (8)	11 (11)	<0.0001
Upper limbs	6 (40)	1 (3)	6 (16)	3 (3)	<0.0001
Tetraparesis	12 (80)	3 (9)	19 (51)	19 (19)	<0.0001
Mean MRC score	4.4 [2.6–5][b]	5 [3.25–5]	4.8 [2.8–5][a]	5 [2.6–5]	<0.001,[a] <0.0001[b]
Distal	4.3 [1.8–5][a]	5 [2.5–5]	4.5 [1–5][a]	5 [1.3–5]	<0.001[a]
Proximal	4.8 [3–5][c]	5 [4–5]	5 [4–5]	5 [4.0–5]	<0.0001[c]

Unless otherwise specified, categorical variables are expressed as number (percentage) and continuous variables as median [range].
[a,b]Significant differences versus PortMet30 control group after Dunn post-test.
[c]Significant differences between Val107 and each other group after Dunn post-test.
Dissociation is defined as predominant small-fiber impairment with more superficial than deep sensory loss (pain and thermal sensation impaired more than vibration and joint position sensation).
DTR = deep tendon reflexes; LateMet30 = Val30Met *TTR* mutation in patients with late onset (>50 years); MNT = modified Norris test score; MRC = Medical Research Council score; NS = not specified in this study; PortMet30 = Val30Met mutation in patients of Portuguese origin; Tyr77 = Ser77Tyr *TTR* mutation; Val107 = Ile107Val *TTR* mutation.

TABLE 3. Investigations: Nerve Conduction, Cerebrospinal Fluid, and Amyloid Deposits

Investigation	Val107	Tyr77	LateMet30	PortMet30	Normal	*p*
Nerve conduction studies, No.	14/15	31/32	32/37	83/110		
Lower limbs						
Peroneal						
CMAP, mV	1.1 ± 1.1	3.4 ± 2.8[a]	1.3 ± 1.4	2.4 ± 2.9	3	<0.01[a]
MCV, m/s	38.0 ± 4.8	40.0 ± 6.0	38.9 ± 6.2	41.8 ± 7.5	43	0.0116
DML, ms	5.9 ± 1.5	5.3 ± 1.7	5.7 ± 1.9	5.4 ± 2.4	5	0.1590
F wave, ms	55.0 ± 11.2	49.3 ± 8.0	49.8 ± 18.3	44.4 ± 16.8	53	0.1040
Not elicited	6 (21)	1 (2)	4 (9)	42 (31)		<0.0001
Sural						
SNAP, μV	2.0 ± 2.9[b]	5.2 ± 7.4	4.1 ± 3.9	12.4 ± 16.0	7	<0.01[b]
SCV, m/s	35.2 ± 6.0[d]	41.1 ± 8.8	42.1 ± 7.2	41.3 ± 8.3	44	<0.05[c]
Not elicited	12 (46)	16 (31)	10 (26)	44 (30)		0.3551
Upper limbs						
Ulnar						
Motor						
CMAP, mV	5.5 ± 3.2	8.0 ± 4.6	5.8 ± 3.9[b]	8.5 ± 5.6	7	<0.05[b]
MCV, m/s	47.8 ± 6.8	52.7 ± 10.6	49.6 ± 9.1	52.9 ± 9.7	61	0.0235
DML, ms	3.5 ± 0.8	3.5 ± 1.0	3.4 ± 1.1	3.5 ± 1.8	3.1	0.3428
F wave, ms	34.2 ± 3.2***	34.4 ± 12.4	33.7 ± 10.9[c]	28.2 ± 5.2	31	<0.01,[c] < 0.001***
Not elicited	0	0	0	2 (2)		
Sensory						
SNAP, μV	5.5 ± 9.8	7.8 ± 9.0	4.3 ± 5.8	7.4 ± 7.4	8	0.0273
SCV, m/s	37.2 ± 9.9	44.3 ± 10.8	46.6 ± 10.8	45.4 ± 6.6	46	0.0602
Not elicited	5 (24)	5 (11)	10 (29)	16 (14)		0.1090

TABLE 3: Continued

Investigation	Val107	Tyr77	LateMet30	PortMet30	Normal	*p*
Pattern						
Axonal loss	14 (100)	30 (97)	30 (94)	71 (86)		0.1261
Upper limbs	14 (100)	24 (77)	30 (94)	64 (77)		0.0460
Lower limbs	12 (86)	26 (84)	22 (69)	48 (58)		0.0237
Asymmetric	13 (93)	15 (48)	19 (59)	43 (52)		0.0268
Demyelination	12 (86)	16 (52)	20 (63)	29 (35)		0.0009
Definite	8 (57)	8 (26)	15 (47)	21 (25)		0.0235
Possible	4 (29)	8 (26)	5 (16)	8 (10)		0.0907
Search for amyloid deposits						
No.	14/15	20/32	32/37	51/110		
Nerve or muscle examination	11 (73)	7 (22)	25 (68)	28 (25)		<0.0001
Other tissues examination	6 (40)	14 (44)	11 (30)	25 (29)		0.4064
Total deposits identification, including after second look	13/14 (93)	15/20 (75)	28/32 (88)	47/51 (92)		0.4374
Cerebrospinal fluid						
No.	9/15	6/28	13/34	5/110		
Protein, g/l	0.49 [0.25–1]	0.48 [0.36–0.74]	0.6 [0.5–0.76]	0.55 [0.31–0.63]		
Cells	0 [0–1]	0 [0–1]	0 [0–2]	0 [0–3]		

Axonal loss and demyelination were assessed by studying the median, ulnar, tibial, and peroneal motor nerves and the median, ulnar, tibial, sural, and peroneal sensory nerves. Other biopsies were performed on accessory salivary glands, the gastrointestinal tract, urinary tract, skin, synovium, abdominal fat, or respiratory tract.
[a]Significant differences between Tyr77 and each other group after Dunn post-test.
[b,c]Significant differences versus PortMet30 control group after Dunn post-test.
[d]Significant differences between Val107 and each other group after Dunn post-test.
LateMet30 = Val30Met *TTR* mutation in patients with late onset (>50 years); PortMet30 = Val30Met mutation in patients of Portuguese origin; Tyr77 = Ser77Tyr *TTR* mutation; Val107 = Ile107Val *TTR* mutation; CMAP = compound muscle action potential amplitude; MCV = motor nerve conduction velocity; DML = distal motor latency; SNAP = sensory nerve action potential amplitude; SCV = sensory nerve conduction velocity.

TABLE 4. Clinical Outcomes and Functional Disability in Familial Transthyretin Amyloid Polyneuropathy

Characteristic	Val107	Tyr77	LateMet30	PortMet30	*p*
No.	15	32	37	110	
Follow-up	2.2 [0.5–5.7]	1.2 [0.1–7.8]	2.7 [0.4–19.4]	1 [0.0–16.2]	<0.0001
MNT, No.	11/15	28/32	31/37	107/110	
Initial score	64 [33–74][a]	67[30–75]	59 [9–75][a]	74 [11–75]	<0.0001[a]
MNT rate of decline	13 [3–80][a]	8 [0–126][a]	9 [0–66][a]	0.3 [0–27]	<0.0001[a]
Gait impairment, median time to onset, yr					
Delay to PND score ≥ II	2.1	2.8	3	5.6	<0.0001
Delay to PND score ≥ IIIa	3.1	4.5	3.8	10	<0.0001
Delay to PND score = IV	5.6	11.5	7	18	<0.0001
Median time to death, yr	6.8	12.5	7.6	16.9	0.0005
Liver transplant	5 (33)	24 (75)	11 (30)	93 (84)	<0.0001

Categorical variables are expressed as number (percentage) and continuous variables as median [range]. Median times to onset of gait disturbances and assisted walking, and median time to death, were calculated by the Kaplan–Meier method.
The MNT rate of decline (points per year), defined as MNT score (maximum - minimum)/disease duration, is an index of disease progression.
[a]Significant differences compared to the PortMet30 control group after Dunn post-test.
LateMet30 = Val30Met *TTR* mutation in patients with late onset (>50 years); MNT = modified Norris test (best max = 75); PND score = polyneuropathy disability score. A score of II indicates difficulties in walking but without the need for a walking stick, a score of IIIa indicates 1 stick or 1 crutch required for walking, a score of IIIb indicates 2 sticks or 2 crutches required for walking, and a score of IV indicates a patient confined to a wheelchair or to bed; PortMet30 = Val30Met mutation in patients of Portuguese origin; Tyr77 = Ser77Tyr *TTR* mutation; Val107 = Ile107Val *TTR* mutation.

patients. Restrictive cardiomyopathy was found on cardiac catheterization in 88 to 100% of non-Portuguese patients and seemed to be more frequently symptomatic in Tyr77 patients (35%) as compared to Val107 (20%) and LateMet30 (29%) patients. Cardiac denervation, when sought, was also very frequent (83–100% of non-Portuguese patients).

Disease Course

DISEASE PROGRESSION. The disease progressed more rapidly and more severely in Val107, Tyr77, and LateMet30 than in PortMet30. In the non-Portuguese groups, functional disability (rate of MNT decline) progressed up to 40 times more rapidly in Val107 patients ($p < 0.0001$); the median times to onset of gait disorders and assisted walking were significantly shorter than in PortMet30 patients (Table 4, Fig 2A, B).

Weakness was present in most patients at the final examination, after 3 to 5 years of follow-up (93% Val107, 65% Tyr77, 86% LateMet30). Tetraparesis affected 87% of Val107, 73% of LateMet30, and only 35% of Tyr77 patients, both proximally and distally in respectively 80%, 54%, and 19% of patients. Mean MRC scores for all tested muscles (see Subjects and Methods) declined over time, with lower scores in Val107 and LateMet30 than in Tyr77 ($p < 0.0001$), but a significant time interaction was found by 2-way ANOVA (see Fig 2D).

Axonal loss over time could only be reliably evaluated in Met30 patients, who had less severe initial axonal loss. A trend toward more severe progression of sensory loss assessed in the sural nerve was found in LateMet30 by comparison with PortMet30 (mean = 3.3 μV/yr vs 1.5 μV/yr; $p = 0.08$). The mean annual axonal loss of peroneal motor nerve was 0.26mV for LateMet30 versus 0.63mV for PortMet30 ($p = 0.12$).

SURVIVAL. Median survival was significantly shorter among Val107 (6.8 years) and LateMet30 (7.6 years) patients than among Tyr77 and PortMet30 patients (see Table 4 and Fig 2C). More Tyr77 and PortMet30 patients than Val107 and LateMet30 patients underwent LT, a study endpoint ($p < 0.0001$). Nine Val107, 4 Tyr77, 17 LateMet30, and 6 PortMet30 patients died during the study.

Literature Review

We analyzed 150 reports of Val107, Tyr77, and late onset Met30 FAP. Thirty-nine reports met the inclusion

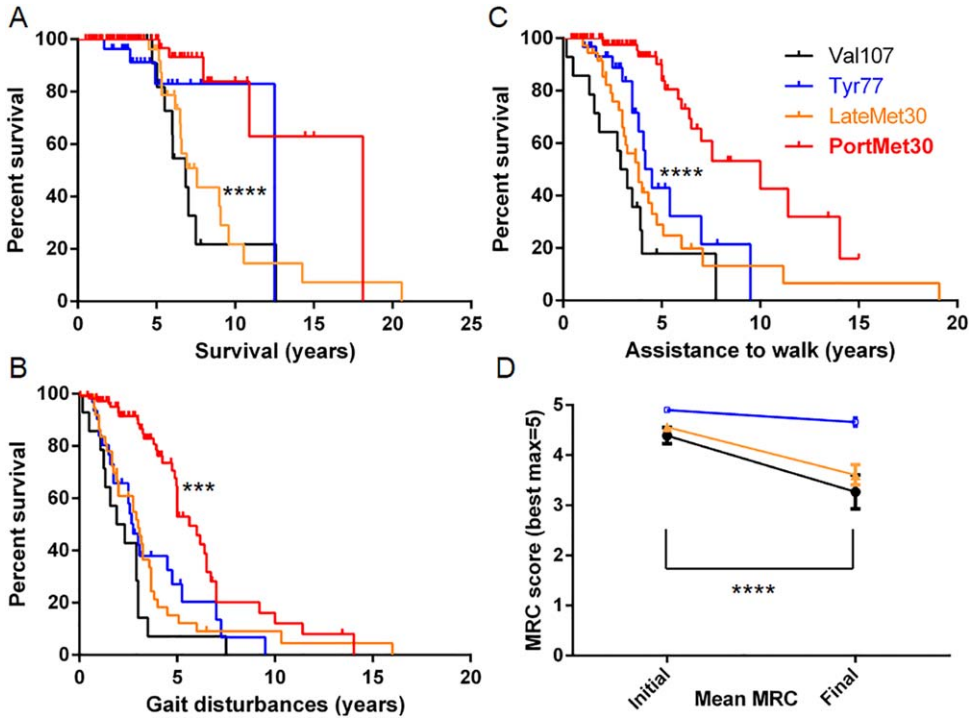

FIGURE 2: Survival curves (Kaplan–Meier) of overall survival (A), gait disorders (B), and need for assistance to walk (C) for Ile107Val *TTR* mutation (Val107), Ser77Tyr *TTR* mutation (Tyr77), Val30Met *TTR* mutation in patients with late onset (>50 years; LateMet30), and Val30Met mutation in patients of Portuguese origin (PortMet30) patients, in years after disease onset. Changes in the mean Medical Research Council (MRC) score (best maximum = 5) in the Val107, Tyr77, and LateMet30 groups (D) were compared by 2-way analysis of variance. ***$p < 0.0005$ and ****$p < 0.0001$ significant curve differences and significant MRC score differences.

criteria and were included in the review. Only 8 cases of individualized Swedish LateMet30 were reported, the other cases belonging to mixed late and early onset cohorts (see Supplementary Table 2). Most previous reports concerned case series. Only Japanese reports of LateMet30 concerned controlled studies. Table 5 gives an overview of the specific phenotypes of Val107, Tyr77, and Met30 FAP delineated by both our study results and previous case reports in the literature.

Discussion

We compared the clinical phenotypes and disease course of FAP due to 3 of the main *TTR* mutations found in France (Met30, Tyr77, and Val107) in a series of 84 patients referred to our reference center from 1988 to 2010, by comparison with a control group of 110 Portuguese Met30 patients followed in the same center. Val107 was associated with the most debilitating and severe FAP ever described, with rapid onset of gait disturbances due to tetraparesis and shorter median survival. LateMet30 and to a lesser extent Tyr77 were also more severe than Portuguese Met30 (see Table 5).

This is among the largest series reported to date. Only 9 Val107 cases and 23 Tyr77 cases have been previously reported, with a relatively short follow-up. Our series is the first to compare non-Portuguese LateMet30 patients with early onset Met30 patients of Portuguese origin living in a similar environment (France).

The shorter survival of Val107 and LateMet30 patients compared to Tyr77 and PortMet30 patients underlines the exceptional severity of these forms and confirms a recent report concerning late onset Met30 in Japan.[29] The excellent survival among PortMet30 patients followed at the French Reference Center is mainly due to the large proportion of patients whose follow-up was censored because they initiated a disease-modifying therapy (LT) in our institution.

Functional disability and its progression were more severe in the non-Portuguese patients. The MNT rate of decline, with a yearly decline up to 40 times faster in Val107 FAP, was far higher in non-Portuguese than in PortMet30 patients. This was mostly due to repercussions of motor impairment on gait but also to the consequences of cardiomyopathy in non-Portuguese patients.[26] Gait impairment and the need for walking assistance occurred earlier in non-Portuguese patients than in our PortMet30 patients and in previously reported PortMet30 patients.[9] This rapid course has previously been noted in a Japanese series of LateMet30 FAP[11] and some other variants.[15,30] Apart from these studies, patient

TABLE 5. Overview of Phenotypes of Val107, Tyr77, and Met30 Familial Amyloid Polyneuropathies Based on This Study and Previous Reports

Characteristic	Val107	Tyr77	LateMet30	PortMet30
Age at onset, yr	65	60	62	30
Sex ratio, M/F	7/1	3/1	4/1	1/1
Positive family history	+	++	+	+++
Weight loss	+++	++	++	+++
Neuropathy				
Sensory dissociation	++	+	+/++	+++
Deep sensory impairment	+++	++	+++	+
Weakness	+++	++	+++	+
Autonomic dysfunction	+	+	++	+++
Nerve conduction pattern				
Axonal	+++	++	++	+++
Demyelinating	+++	++	++	+
Positive amyloid deposits	++	++	++	+++
Pacemaker implantation	+	++	++	+
Outcome				
Gait impairment	+++	+	++	+/++
Median time to death, yr	7	10	8	11

Semiquantitative overview of item frequency: + is uncommon or mild, + + is average or moderate; + + + is frequent or intense. F = female; LateMet30 = Val30Met *TTR* mutation in patients with late onset (>50 years); M = male; PortMet30 = Val30Met mutation in patients of Portuguese origin; Tyr77 = Ser77Tyr *TTR* mutation; Val107 = Ile107Val *TTR* mutation.

disability has rarely been documented, especially with respect to gait disorders and overall survival, ruling out any direct statistical comparison of times to onset. This may explain discrepancies in the severity of Tyr77 and LateMet30 FAP in previous reports[31–33] and in our series, in which the median times to assisted walking were longer in Tyr77 than in LateMet30 FAP.

Weakness occurred early and was severe and extensive in Val107 and LateMet30 FAP, some patients presenting with upper limb involvement or tetraparesis with a proximodistal distribution at the first examination, whereas weakness occurs late and remains limited to the lower limbs in early Met30.[8,9,33]

The Val107 mutation led to the most severe and debilitating form of TTR-FAP, characterized by rapidly progressive tetraparesis and a proximodistal distribution mimicking chronic inflammatory demyelinating polyneuropathy, which is quite unusual in FAP. Most of these patients were of French West Indian origin, which suggests a founder effect. Correlation studies of the genotype and TTR protein function are needed to explain this phenotype. Imaging of proximal nerves in the limbs by magnetic resonance neurography could help to identify clinical–pathological correlations in patients with these severe phenotypes.[34]

Initial symptoms such as weakness in Val107 FAP and gait disorders in both Tyr77 and Val107 FAP were never seen in PortMet30 FAP, reflecting the early initial severity of these forms, as previously reported in LateMet30 FAP.[33] In the literature, initial symptoms consist mostly of sensory disorders or sometimes weakness, autonomic symptoms, or cardiomyopathy, especially in LateMet30. In our series, initial autonomic dysfunction tended to be more frequent in PortMet30 FAP. A few non-Portuguese patients had upper-limb onset, asynchronous lower-limb onset, or focal involvement of 1 limb. These atypical presentations must be borne in mind when assessing patients referred for atypical focal neuropathies.

Sensory dissociation was less frequent in the non-Portuguese patients, as previously reported,[33] particularly in those with Tyr77 FAP (see Table 2). In most cases, all fibers were involved at the first examination. Detailed descriptions of the severity of these deficits are only available in individual case reports. Despite large studies of the main clinical features of LateMet30 FAP,[11,35] no

controlled studies have focused on the clinical features of FAP neuropathies in Val107 and Tyr77 carriers. Almost all our patients exhibited autonomic dysfunction, as previously reported. Autonomic symptoms are less severe in LateMet30 FAP, accounting less for disability than tetraparesis or cardiomyopathy, as previously reported.[31,33,36] These differences could be explained by less abundant amyloid deposits and less severe neuron loss in sympathetic than dorsal root ganglia, as previously suggested by a histopathological study of Japanese LateMet30 FAP.[36]

Diagnosis of TTR-FAP in non-Portuguese patients may be complicated by misleading presentations, including atypical clinical manifestations at onset, definite electrophysiological features of demyelination (European Federation of Neurological Societies/Peripheral Nerve Society), and lack of amyloid deposits at initial biopsy.

Because of the lower penetrance in non-Portuguese patients, a positive family history of FAP is less frequent than in PortMet30 patients. It is initially underestimated; parents and siblings may still be asymptomatic carriers, as the proportion of probands with a positive family history increased over time. Genetic counseling of family members should be systematic, particularly for asymptomatic patients, as anticipation has been shown to exist in FAP.[37] Variations were noted across the non-Portuguese groups, as a family history of neuropathy was more frequent in Tyr77 patients, as previously reported (see Supplementary Table 2). Symptomatic CTS, a nonspecific feature of FAP, is frequently reported in non-Portuguese patients and can be an early disease manifestation[19] (see Supplementary Table 2), as in our cohort (see Supplementary Table 5). Systematic histopathological assessment in case of CTS surgery could help in earlier diagnosis of FAP in those cases.

A high proportion of our non-Portuguese patients met the electrophysiological criteria for demyelination in keeping with recent observations of histological demyelination in peripheral nerves.[38] Misleading CIDP presentations have been occasionally reported in TTR-FAP[14,38]; we found 20% of our cohort of French ancestry fulfilling CIDP criteria. This is to our knowledge the first study able to estimate the prevalence of pseudo-CIDP presentation in a large cohort of non-Portuguese FAP patients. However, FAP is mostly an axonal neuropathy. Myelinated fiber density was severely decreased in most Val107, Tyr77, and LateMet30 nerve biopsies. This matches clinical observations of predominantly myelinated fiber loss, more severe motor impairment, and less frequent sensory dissociation. Electrophysiological features of only early onset[39–41] and LateMet30 have previously been reported. In a Japanese controlled study by H. Koike and colleagues in 2008 (see Supplementary Table 2), the reductions in CMAP and especially SNAP amplitude were more profound in LateMet30 and more frequently predominated in the lower limbs than in early onset Met30. Electrophysiological indices worsened with clinical duration in both the early onset and the LateMet30 patients as previously described for LateMet30.[11] Sensory axonal loss was faster in LateMet30 in line with predominance of large-fiber involvement found in previous series of late onset Met 30.[36] Conduction velocity slowing and increased distal latency suggestive of demyelination have occasionally been reported.[38]

Amyloid deposition is a major diagnostic clue to FAP. Histopathological examination of nerve and muscle biopsies frequently identifies amyloid deposits but requires sampling of long nerve fragments and serial sections. The deposits are mainly located within or around endoneurial or perineurial vessel walls, especially in Val107 patients in our study, in keeping with previous reports.[42] Contrary to early onset Met30 patients,[36,43] amyloid deposits are sparse in non-Portuguese patients, necessitating careful histopathological examination in reference centers with examination of all sections. As in our series, amyloid deposits were found in most reported cases, often after second-look examination, repeat biopsy, or necropsy (see Supplementary Table 2). A Japanese study[36] compared 11 LateMet30 patients to 11 early onset Met30 patients. LateMet30 FAP was characterized by depletion of myelinated fibers, axonal sprouting, relatively preserved unmyelinated fibers, and scarce or absent amyloid deposition. Early onset Met30 showed predominantly small-fiber loss and more abundant amyloid deposits. Early onset Met30 autopsy studies showed more severe amyloid deposition in sympathetic than dorsal root ganglia, with the opposite pattern in LateMet30. Another study[35] compared sural nerves biopsies from early onset to late onset Met30 patients and found predominantly small-fiber loss for the first. Scarce amyloid deposition casts doubt on the pathogenicity of these deposits. Axonal degeneration starts long before the first deposits, which are composed of both mutant and wild-type TTR protein.[43] Nonfibrillary mutant and wild-type TTR appear to lead to inflammation and oxidative stress, followed by axonal degeneration and neuronal loss even before deposits appear.[6,44] Demyelinating features found on nerve biopsy were most often associated with electrophysiological signs of demyelination, suggesting its responsibility for the patients' deficits.

As previously reported, cardiac involvement seemed more frequent and severe in non-Portuguese patients. Most often they have increased left ventricle thickness and restrictive cardiomyopathy. Symptomatic cardiomyopathy was more frequent in our Tyr77 FAP patients, in

agreement with previous reports.[45] Amyloid deposition in conduction pathways requiring pacemaker implantation was also more frequent in non-Portuguese than PortMet30 patients (see Table 3). A higher prevalence of severe cardiac infiltration in LateMet30 may reflect more diffuse myocardial amyloid deposition, leading to frequent pacemaker requirement.[36,43,46]

Our data have major therapeutic implications. First, LT may halt the progression of neuropathy in PortMet30[47] and markedly increase survival,[48] but neuropathy and cardiomyopathy may still progress in LateMet30 and forms due to other mutations, because of wild-type TTR deposition.[49] TTR kinetic stabilizers such as tafamidis[17] and diflunisal[50] may slow disease progression, and RNAi[51] and antisense oligonucleotides[52] inhibit hepatic production of TTR by post-transcriptional gene silencing. These approaches are currently in phase 3 clinical trials. Another possible strategy is to enhance clearance of amyloid deposits by using monoclonal antibodies to human serum amyloid P component.[53]

Conclusion

Patients with the 3 most common TTR-FAP genotypes in France have distinct clinical and electrophysiological features relative to classical early onset Met30 TTR-FAP. Despite its later onset, Val107 FAP is the most debilitating and severe form (early onset of tetraparesis and short survival), followed by LateMet30 and to a lesser extent Tyr77. Our results show the existence of misleading phenotypic variations that may delay diagnosis and treatment. The severity of these phenotypes is associated with more severe axonal loss and a demyelinating pattern easily misleading for a CIDP in one-fifth of patients. Epigenetic studies could be useful to further explain these differences.

These specific patterns of progression have major implications for genetic counselling and treatment. Our findings of these more aggressive phenotypes should help to identify better primary outcomes for clinical trials and candidate populations for specific treatments.

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Authorship

Concept and study design: L.-L.M., P.L., D.A. Data acquisition and analysis: L.-L.M., P.L., D.A., M.T., Z.M., A.S., B.D., V.A., C.D., C.A., G.N., D.S., M.S.S., C.L., M.M. Drafting the manuscript or figures: L.-L.M., P.L., D.A., M.T., Z.M., A.S., B.D., V.A., C.D., C.A., G.N., D.S., M.S.S., C.L., M.M.

Members of the French FAP Network (CORNAMYL) Study Group and their affiliations: Thierry Maisonobe (Pitié-Salpêtrière Hospital, Paris), Jean Marc Leger (Pitié-Salpêtrière Hospital, Paris), Tanya Stojkovic (Pitié-Salpêtrière Hospital, Paris), Karine Viala (Pitié-Salpêtrière Hospital, Paris), Timothée Lenglet (Pitié-Salpêtrière Hospital, Paris), Jean Christophe Antoine (Saint-Étienne), Jean Philippe Camdessanche (Saint-Étienne), Christophe Vial (Lyon), Philippe Petiot (Lyon), Laurent Magy (Limoges), Jean Michel Vallat (Limoges), Jean Pouget (Marseille), Shahram Attarian (Marseille), Jérôme Franques (Marseille), Claude Desnuelle (Nice), Emilien Delmont (Marseille), Arnaud Lacour (Lille), Eric Hachulla (Lille), Gwendal le Masson (Bordeaux), Guilhem Sole (Bordeaux), Yann Pereon (Nantes), Andoni Echaniz-Laguna (Strasbourg), Christine Tranchant (Strasbourg), Pierre Labauge (Montpellier), Raul Juntas Morales (Montpellier), Philippe Corcia (Tours), Remi Bellance (Fort of France), Claude Mignard (Réunion), Pierre Clavelou (Clermont-Ferrand), Christophe Guiraud-Chaumeil (Albi), Antoine Guegen (Rothschild Foundation, Paris).

Potential Conflicts of Interest

P.L.: personal fees, Fold-RX Pharmaceuticals. M.T.: travel expenses, Pfizer. Z.M.: consultancy, Pfizer. A.S.: nonfinancial support, Pfizer. C.D.: consultancy, Biogen Idec, Serono, Novartis, Sanofi, Boehringer, Bayer, BMS. C.A.: personal fees, Pfizer. D.S.: consultancy, Astellas, BMS, Gilead, LFB, MSD, Novartis, Roche, Biotest. D.A.: travel expenses, Pfizer, Alnylam; speaking fees, Pfizer.

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