Original Paper

Neuro
epidemiology

Neuroepidemiology 2018;51:177–182
DOI: 10.1159/000490553

Received: February 14, 2018
Accepted: June 1, 2018
Published online: August 28, 2018

Epidemiology of Transthyretin Familial Amyloid Polyneuropathy in Portugal: A Nationwide Study

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Keywords
Amyloidosis · Transthyretin familial amyloid polyneuropathy · Prevalence · Incidence · Epidemiology · Portugal

Abstract
Background: Transthyretin-associated familial amyloid polyneuropathy (TTR-FAP) is a rare, hereditary, progressive and neurodegenerative disease. We aimed to study TTR-FAP epidemiology in Portugal. ***Methods:*** National, observational, prospective and retrospective, case identification of adults with TTR-FAP. Countrywide patient multiple identification sources included reference centers registries and centralized medical electronic prescription database. Crude rates were reported per 100,000 adult inhabitants. ***Results:*** Over 2010–2016 period, mean incidence rates was 0.87/100,000 (95% CI 0.68–1.10) corresponding to 71 new patients yearly, that has decreased 31% in the last 7 years. The proportion of late-onset cases (age ≥50 years) among incident cases was 28.7%. Estimated crude 2016 prevalence was 22.93/100,000 adult inhabitants (95% CI 21.90–23.99) corresponding to 1,865 TTR-FAP individuals in Portugal (45.8% male; mean age: 52.3 ± 15.4 years). In 2016, the Portuguese region with the highest TTR-FAP prevalence shows a 16% prevalence increase over the last 25 years. ***Conclusions:*** In Portugal, TTR-FAP affects both genders and mainly young adults. TTR-FAP incidence appears to be decreasing while prevalence is increasing. In comparison to previous studies, there is an increased representativeness of late-onset patients. This epidemiological setting poses future and complex challenges for the social and healthcare system, strengthening the relevance of regular epidemiologic surveillance.

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Introduction

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is an autosomal-dominant, hereditary, adult-onset, progressive and neurodegenerative systemic disease, originally described in 1952 by Corino de Andrade in northern Portugal [1]. More than 120 TTR gene mutations are associated with TTR-FAP being the most common Val-30Met [2]. If untreated, the disease progresses to death usually within the first decade after onset [3]. The global prevalence has been recently estimated by Schmidt et al. [4] to be around 10,000 persons (depicted in Fig. 1), although considerable uncertainty exists (range 5,526–38,468) highlighting the need for increasing epidemiological assessment.

TTR-FAP is a rare disease with endemic populations predominantly in Portugal, Sweden [5] and Japan [6]. Portugal is known to have the largest patients' cohort [4], although previous prevalence studies have more than 25 years old cohorts and are available for regional-level investigations only [3]. Among Portuguese families, women have a late-onset of the disease than men and larger disease anticipation [7]. In Portugal, available disease-modifying treatments include liver transplant (since 1992) and tafamidis (routinely available since 2012 for patients followed at TTR-FAP specialized centers).

Epidemiological studies on TTR-FAP are relevant to improve clinical governance and to better inform health care planning, because of the currently available disease-modifying treatments [8, 9] and potential new promising gene modifying therapy approaches [10] for these patients. This type of evidence nourishes disease awareness, avoiding/reducing misdiagnosis of the disease [11], which can delay disease-modifying treatments, all more effective in early disease stages [9, 12]. This study aims to estimate the incidence and prevalence of TTR-FAP in Portugal and to describe patients' demographic characteristics.

Materials and Methods

We conducted a national, observational, prospective and retrospective case identification of adults (≥18 years of age) with TTR-FAP in Portugal. Currently, once a diagnosis is suspected or established, the patient is referred to one of the 2 national reference centers for follow-up and clinical management. Additionally, any individual with family members diagnosed with TTR-FAP can contact directly these centers. These centers were created in 1960 and 1990 in Porto and Lisbon respectively. Therefore, we assembled the number of new patients with prospective follow-up at these centers in order to estimate TTR-FAP incidence.

For 2016 prevalence estimates, retrospective, countrywide patient multiple identification sources included the 2 reference centers databases and search in the national centralized medical electronic prescription (MEP) database. Data were cross-checked across the reference centers' databases to eliminate duplication and deaths. TTR-FAP cases are identifiable in MEP database, since these patients have access to a specific reimbursement regime under which all medicine prescriptions are 100% funded by the public National Health Service. The municipality where the majority of medicines dispense occurred for each case was set as a proxy for municipality of residence. Patients with an annual unique medical prescription and those without information on the municipality were excluded. Cases were not classified according to the underlying gene mutation because Val30Met accounts for more than 99% of the affected families in Portugal [13]. Asymptomatic carriers were excluded from this study [14].

Statistical data analysis

TTR-FAP is an adult-onset disease. Therefore, population at risk was defined as those aged 18 or more resident in Portugal mainland, comprising 8,133,909 adult inhabitants in 2016 [15]. Crude rates were calculated per 100,000 adult inhabitants. The overall incidence rate was estimated from year 2010 until 2016. The 2016 prevalence rate was estimated by municipality, sex and age-group. Descriptive results were presented as frequencies and proportions. Poisson distribution was assumed to estimate 95% CI for prevalence and crude incidence rates [16]. We used Pearson's chi-square test to compare categorical variables between groups and Wilcoxon rank-sum test for comparisons of continuous variables. Statistical analysis was performed using Stata, version 15.0 (StataCorp). The geographical information system QGIS 2.10.1 Pisa was used to depict prevalence data. The threshold for statistical significance was set at $\alpha = 0.05$.

Ethical Approval

The study protocol was approved by the institutional Ethics Board Committees of the 2 reference centers and by the National Data Protection Committee.

Results

Incidence

There were 500 new cases diagnosed between 2010 and 2016 in the TTR-FAP reference centers. Annual incidence rates estimates (Table 1) varied from 0.97/100,000 adults (95% CI 0.77–1.20) in the early 2010s to 0.66 (95% CI 0.50–0.87) in year 2016. On average, for the period 2010–2016, 71 yearly new TTR-FAP patients were diagnosed corresponding to 0.87/100,000 adults (95% CI 0.68–1.10). Overall, the number of yearly new TTR-FAP patients has decreased by 31% between 2010 and 2016. An artefactual incidence peak was found in 2013 due to the transferal of patients routinely followed in other health services across the country to the TTR-FAP specialized centers to access treatment with tafamidis, as this drug is available only for patients followed at these centers.

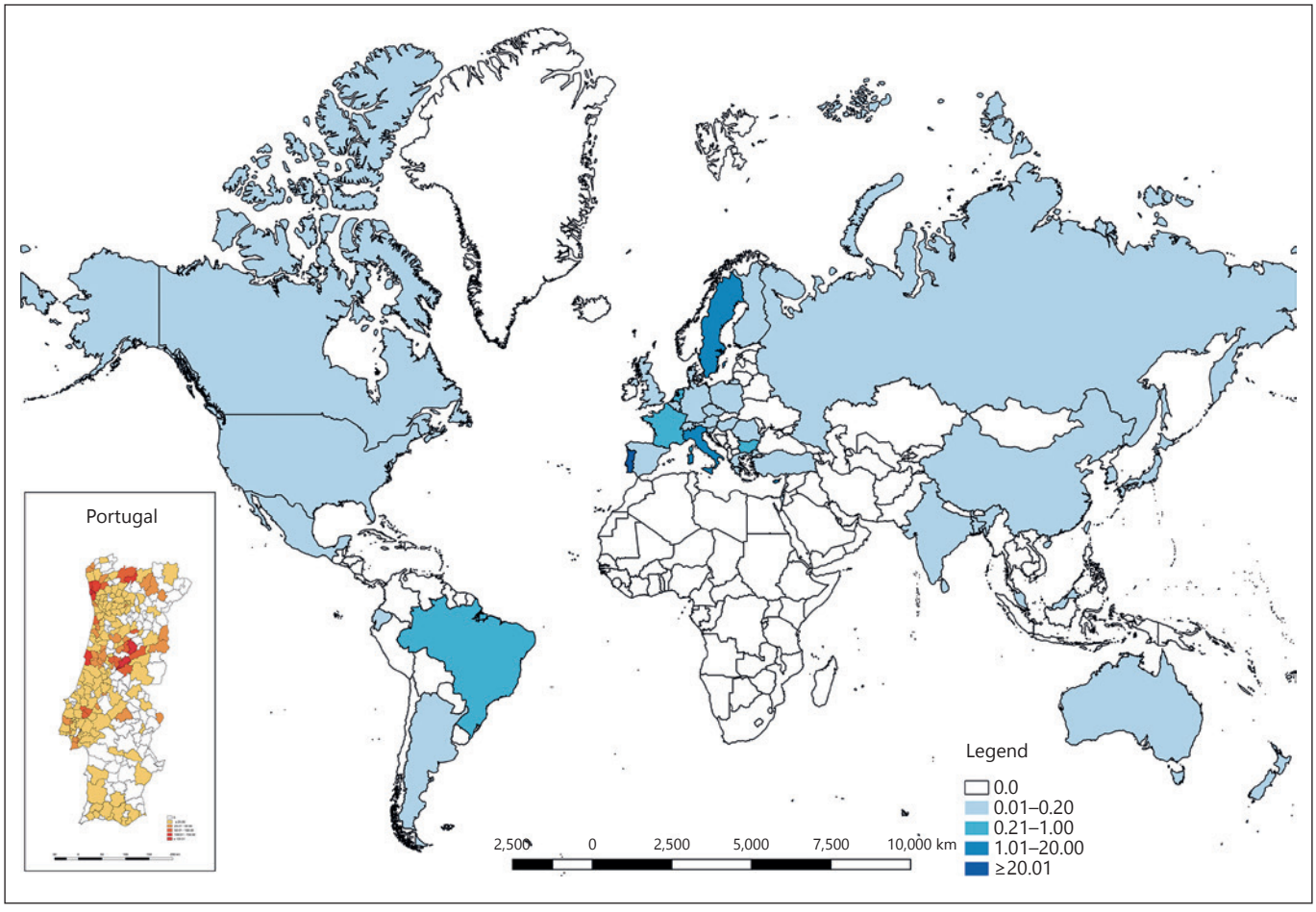

Fig. 1. TTR-FAP worldwide prevalence according to Schmidt et al. [4]. Portugal prevalence estimated in this study is shown in the box, per 100,000 adult inhabitants, by municipality.

Table 1. TTR-FAP incidence per 100,000 adult inhabitants, by year

Year	Number of new patients	Adult population	New patients per 100,000 adult inhabitants (95% CI)
2010	80	8,273,321	0.97 (0.77–1.20)
2011	74	8,251,086	0.90 (0.70–1.13)
2012	74	8,206,405	0.90 (0.71–1.13)
2013	82	8,158,614	1.01 (0.80–1.25)
2014	67	8,118,501	0.83 (0.64–1.05)
2015	69	8,093,296	0.85 (0.66–1.08)
2016	54	8,133,909	0.66 (0.50–0.87)
7-Year*	71	8,176,447	0.87 (0.68–1.10)

* 7-Yr denotes 7 years average (2010–2016).
TTR-FAP, transthyretin familial amyloid polyneuropathy.

The mean age of onset of the incident cases was 42.8 ± 15.0 years, 56.0% of which were male (Table 2). A higher age-of-onset and a higher proportion of late-onset (age ≥50 years) cases were found in more recent years ($p < 0.01$, for both comparisons). No significant differences were found for sex distribution across the years ($p = 0.643$).

Prevalence

In Portugal, a total of 2,348 potential cases were identified through MEP database, 482 of which were excluded (421 cases with 1 unique medical prescription and 62 without municipality of dispense data). Estimated crude TTR-FAP 2016 prevalence was 22.93/100,000 adult inhabitants (95% CI 21.9–23.99) corresponding to 1,865 individuals with TTR-FAP in Portugal (45.79% men; mean age: 52.34 ± 15.38 years). TTR-FAP men patients were significantly younger than women (50.10 ± 14.37 vs.

Table 2. Characteristics of incident TTR-FAP patients, by year of diagnosis

Year	Male, %	Late-onset†, %	Age-of-onset†, years	
			mean ± SD	median (IQR)
2010	53.8	22.4	39.3±13.1	35 (30–47)
2011	47.3	23.6	41.0±14.1	35 (31–49)
2012	59.5	16.4	39.4±11.8	35 (31–46)
2013	53.7	28.8	42.6±15.2	38 (31–52)
2014	59.7	32.8	43.8±15.5	42 (29–55)
2015	60.9	37.7	46.1±15.8	41 (33–59)
2016	59.3	44.4	49.3±17.6	47 (34–66)
7-Year*	56.0	28.7	42.8±15.0	38 (31–53)

* 7-Yr, 7 years period (2010–2016).

† Age-of-onset calculated only for those with data available ($n = 491$).

TTR-FAP, transthyretin familial amyloid polyneuropathy; IQR, interquartile range.

54.23 ± 15.95 years; $p < 0.001$). Those aged 35–44 years had the highest prevalence (35.55/100,000 adult inhabitants; 95% CI 32.56–38.75). Overall, men/women ratio was 0.97, documenting a similar prevalence among genders (Table 3).

During 2016, TTR-FAP was identified in 174 of the 278 Portuguese mainland municipalities (62.6%; online suppl. Table 1, see www.karger.com/doi/10.1159/000490553). In 19 of these 174 municipalities TTR-FAP exceeded the European threshold for rare disease (any disease affecting 5 or less in 10,000 persons in the community; Fig. 1, box).

Discussion

The overall number of new TTR-FAP cases is decreasing. Interestingly, the mean age of onset significantly increased in more recent years. The proportion of late-onset incident cases almost doubled between 2010 and 2016, from 22.4 to 44.4%. The reported mean age of onset for prevalent cases in 1991 was 33.5 ± 9.4 years, about 10 years lower than the mean age of onset found among incident cases in the last years (42.8 ± 15.0 years). Similarly, the proportion of late-onset cases increased more than threefold from 7.4% [3] in 1991 (prevalent cases) to 28.7% in the last years (incident cases).

Although these figures are not directly comparable, the current findings clearly show an increased representativeness of late-onset patients, probably reflecting a

Table 3. TTR-FAP prevalence per 100,000 adult inhabitants, 2016, by sex and age group

Age group	Number of patients			Adult population			Patients per 100,000 adult inhabitants (95% CI)			Sex ratio*
	males	females	all	males	females	all	males	females	all	
18–24	7	13	20	366,202	356,375	722,577	1.91 (0.77–3.94)	3.65 (1.94–6.24)	2.77 (1.69–4.27)	0.52
25–34	82	69	151	542,366	556,566	1,098,932	15.12 (12.02–18.77)	12.40 (9.65–15.69)	13.74 (11.64–16.12)	1.22
35–44	286	234	520	699,165	763,399	1,462,564	40.91 (36.30–45.93)	30.65 (26.85–34.84)	35.55 (32.56–38.75)	1.33
45–54	188	263	451	685,737	755,217	1,440,954	27.42 (23.64–31.63)	34.82 (30.74–39.3)	31.30 (28.48–34.33)	0.79
55–64	124	169	293	613,401	693,485	1,306,886	20.22 (16.81–24.1)	24.37 (20.83–28.33)	22.42 (19.93–25.14)	0.83
65–74	112	111	223	485,431	590,654	1,076,085	23.07 (19.00–27.76)	18.79 (15.46–22.63)	20.72 (18.09–23.63)	1.23
≥75	55	152	207	393,600	632,311	1,025,911	13.97 (10.53–18.19)	24.04 (20.37–28.18)	20.18 (17.52–23.12)	0.58
Total	854	1,011	1,865	3,785,902	4,348,007	8,133,909	22.56 (21.07-24.12)	23.25 (21.84-24.73)	22.93 (21.9–23.99)	0.97

* sex ratio calculation: male/female prevalence.
TTR-FAP, Transthyretin familial amyloid polyneuropathy.

trend towards more ascertainment of these cases, due to increased disease awareness and improvement in the health care services, including availability of a new treatment. This epidemiological trend poses additional challenges to the clinical governance of this population because the phenotype of late-onset TTR-FAP patients is characterized by a more frequent organ involvement, in particular, cardiologic and renal involvement, probably leading to an increase in the burden of the disease. Furthermore, late-onset patients are not usually eligible for liver transplant.

Genetic counselling programs to at-risk families and medical-assisted techniques of reproduction [17] were progressively implemented in the last 30 years aiming to diminish the number of carriers. Considering that the mean age of disease onset in Portugal in the last years is higher than 40 years, these public health policies were not likely the main reason responsible for the decreased incidence here observed. Portugal has one of the lowest birth rates of developed nations [15], with a fertility rate decline of more than 50% over the last 4 decades (from 2.81 births per female in 1976 to 1.36 births per female in 2016). These changes in overall fertility rate can, at least partially, explain the decrease in the absolute number of TTR-FAP incident cases.

In 2016 in Portugal, 1,865 persons living with TTR-FAP were identified, accounting for nearly 20% of worldwide patients. The prevalence found in this study is the highest country estimate (22.93/100,000 adult inhabitants) reported to date. According to a recently published synthesis of the epidemiological evidence, the countries showing the highest prevalence per 100,000 inhabitants, following Portugal (19.9; corresponding to our previous estimates for 2014 [18]), were Cyprus (4.25), Sweden (2.58), Italy (0.90) and France (0.75).

The disease affects both genders equally and mainly young adults. The conjoint prevalence reported more than 2 decades ago [3] for the municipalities with the highest prevalence (Póvoa de Varzim/Vila do Conde) was 151/100,000 adult inhabitants. In 2016, the corresponding estimate for these municipalities is 176.01/100,000 adult inhabitants (95% CI 152.69–201.89), which represents a 16% increase over the last 25 years. Both studies used the reference centers databases as source for prevalence estimates. TTR-FAP is currently more distributed across the country and prevalence exceeds the rare disease cut-off in 19 Portuguese municipalities. Overall, TTR-FAP prevalence has increased in the last decades, which is probably explained by the survival benefits of the currently available disease-modifying treatments [19], as well as better generalized healthcare services, which increased disease duration.

We are aware that some ATTR-FAP patients are followed outside the reference centers, which can be a limitation towards overall ascertainment of cases. We attempted to minimize this bias by using complementary patient identification sources. We also acknowledge some degree of uncertainty regarding geographical distribution within the country, since the pharmacy municipality most used by the patient to receive their medicines was used as a proxy for residence, which is not always the case.

The prevalence estimate reported in this study is a conservative value, as we have not included asymptomatic carriers. Although TTR-FAP penetrance is not complete, most people carrying Val30Met mutation will develop symptoms through their lives [20]. Therefore, including asymptomatic carriers would have considerably increased TTR-FAP prevalence.

Conclusion

Our findings reinforce the relevance of TTR-FAP epidemiologic surveillance from a public health and policy perspective. This research can be used for conducting comparative analysis across different countries and regions and establishes a useful framework for health service planning and resource allocation.

Acknowledgements and Funding

The authors are grateful to the Central Administration of the Health System (ACSS) and Serviços Partilhados do Ministério da Saúde (SPMS) for access to the national Medical Electronic Prescription (MEP) database, to Isaura Vieira and Rita Mendes for MEP database clarifications, to Marta Santos and Margarida Fernandes for reference centers databases queries resolution and to Rui Alves for support with the geographical information system. Our thanks are also due to Ordem dos Farmacêuticos, which scientifically awarded this research with the *Prémio de Investigação Científica Professora Doutora Maria Odette Santos-Ferreira*. No funding or sponsorship was received for this study.

Disclosure Statement

This study was conducted under the PhD dissertation program of M.I. This dissertation is supervised by J.C. and M.C., both professors at the Faculty of Medicine of the University of Lisbon and

co-authors of the paper. M.I. is full-time employee of Pfizer and hold stock and/or stock options. T.C. received financial support from Alnylam, IONIS, and Pfizer to attend scientific meetings and personal fees from Alnylam and Pfizer to provide scientific lectures. I.C. acknowledges financial support as primary investigator of clinical studies from FoldRx Pharmaceuticals/Pfizer Inc., Alnylam Pharmaceuticals and IONIS Pharmaceuticals. She also received research support from Pfizer and serves on the THAOS scientific advisory board, financially supported from Pfizer. I.C. also participates in Medical Advisory Boards promoted by Alnylam and Pfizer. F.D.-R. received financial support from Pfizer to provide scientific lectures. M.C. reports no disclosures. J.C. is the Associated Director of the Evidence Based Medicine (EBM) center at Faculty of Medicine, University of Lisbon, Portugal. This research center is devoted to pre- and postgraduate medical education. Since 2002, the Lisbon EBM center has undertaken several research projects, which had unrestricted funding (paid to the institution) from over 20 different pharmaceutical companies. One of those companies was Pfizer. The center has not received any direct or indirect payment or other types of benefit related to this study.

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