Transthyretin-Related Familial Amyloid Polyneuropathy (TTR-FAP): A Single-Center Experience in Sicily, an Italian Endemic Area

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Abstract

Background: Familial amyloid polyneuropathy related to transthyretin gene (TTR-FAP) is a life-threatening disease transmitted as an autosomal dominant trait. Val30Met mutation accounts for the majority of the patients with large endemic foci especially in Portugal, Sweden and Japan. However, more than one hundred other mutations have been described worldwide. A great phenotypic variability among patients with late- and early-onset has been reported.

Objective: To present a detailed report of TTR-FAP patients diagnosed in our tertiary neuromuscular center, in a 20-year period.

Methods: Clinical informations were gathered through the database of our center.

Results: The study involved 76 individuals carrying a TTR-FAP mutation. Three phenotypes were identified, each corresponding to a different TTR variant, homogeneous within and heterogeneous between each other: i) Glu89Gln mutation, characterised by 5th – 6th decade onset, neuropathy as presenting symptoms, early heart dysfunction, cardiomyopathy as major cause of mortality followed by dysautonomia and cachexia; ii) Phe64Leu mutation, marked by familiarity reported in one-half of cases, late onset, severe peripheral neuropathy, moderate dysautonomia and mild cardiomyopathy, death for wasting syndrome; iii) Thr49Ala mutation, distinguished by onset in the 5th decade, autonomic disturbances as inaugural symptoms which may remain isolated for many years, moderate polyneuropathy, cachexia as major cause of mortality followed by cardiomyopathy.

Conclusions: This survey highlighted a prevalence of 8.8/1,000,000 in Sicily Island. Good knowledge of the natural history of the disease according to different TTR mutations allow clinicians to optimise multiprofessional care for patients and to offer carriers a personalized follow-up to reveal first signs of the disease.

Keywords: Familial amyloid polyneuropathy, FAP, transthyretin, TTR, amyloidosis, cardiomyopathy, dysautonomia, epidemiology, Italy

INTRODUCTION

Familial amyloid polyneuropathy (FAP) associated with mutations in the transthyretin (TTR) gene is the most common form of genetic amyloidosis. It is a progressive devastating disease transmitted as an autosomal dominant trait, with fatal outcome occurring within ten years after onset. It accounts several thousand cases worldwide, with Val30Met mutation identified in most patients with endemic foci in Portugal, Sweden and Japan. However, more than one hundred other mutations have been described, with
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of amyloid [1]. Both are associated with variable autonomic disturbances and extra-neurological mani-
festations, especially a cardiomypathy. Some patients
with an early-onset presentation deteriorate quickly
because of autonomic dysfunction and rapid progres-
sion of the sensory-motor deficit. Conversely, in many
patients with a late onset (6th to 8th decade), the
polyneuropathy progresses slowly, often with a car-
diac involvement but with less autonomic dysfunction.
Diagnosis is based on family history, neurographic
evidence of a prevalent axonal polyneuropathy, iden-
tification of amyloid deposits in the tissues, and
detection of TTR mutation. The diagnosis can be
challenging in sporadic cases and when clinical mani-
festations are not typical [7, 8]. Diagnostic pitfalls
include inadequate attention of neurologists to auto-
nomic symptoms, decreased nerve conduction velocity
and increased protein content in the cerebrospinal fluid
leading to a wrong diagnosis of chronic inflammatory
demyelinating polyneuropathy (CIDP), no detection
of amyloid at biopsy, coincident diabetes mellitus or
monoclonal gammapathy [9, 10].

The most typical presentation of TTR-FAP is a progressive length-dependent sensory-motor polyneu-
ropathy, which usually begins with loss of thermal
and pain sensation in the feet and slowly ascends
up the limbs. Another type of clinical appearance
starts with focal deficits resulting from local deposits
of amyloid [1]. Both are associated with variable autonomic disturbances and extra-neurological mani-
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monoclonal gammapathy [9, 10].

Treatment often requires a multidisciplinary
approach for symptomatic management of ortho-
static hypotension, cardiac failure, gastrointestinal
disorders, malnutrition, neuropathic pain. Liver
transplantation (LT) provides a specific therapy by
allowing for the suppression of the main source
of mutant TTR [11]. However, its effectiveness is
higher in Val30Met versus non-Val30Met patients,
is influenced by nutritional status, age, severity of

neuropathy and cardiac involvement, and is associated
to surgery risks and unending use of immunsup-
pressants. Tafamidis meglumine (Vyndaqel, Pfizer),
a selective TTR kinetic stabilizer that inhibits the
amyloid cascade, has been approved by European
Medicines Agency in 2011, and it seems promising
[12–16]. Very recently, antisense technology and
interfering RNA therapeutics have been developed,
respectively by Isis Pharmaceutical Inc. and Alnylam
Pharmaceuticals Inc. Both treatments displayed potent
dose-dependent suppression of mutant and normal
TTR levels in humans and randomized, double-blind,
placebo controlled phase 3 studies are ongoing [17].

In the common Val30Met mutation, a consider-
able phenotypic variation with late- and early-onset
has been reported in endemic areas, suggesting that
unknown genetic or environmental factors are impor-
 tant in the clinical expression [18, 19]. Some other
mutations are thought to be associated with partic-
ular phenotypes, although a great variability among
patients carrying the same mutation has also been
described [20]. In Northern Italy, Val30Met is carried
by roughly one fourth of the patients with non-endemic
distribution [20]. In South Italy, according to our expe-
rience in a tertiary neuromuscular center, Val30Met
mutation is absent, and only three mutations are found
with an endemic distribution. The three cohorts are
quite homogeneous but different from each other in
age of onset, phenotype, severity, diagnostic difficulty
and management. We report here their clinical and
laboratory characteristics and phenotype-to-genotype
correlations.

MATERIALS AND METHODS

A retrospective, observational study was performed
involving 76 individuals (36 M; 40 F) carrying a
TTR mutation, all of Sicilian origin, and followed
longitudinally at Neuromuscular Center of the AOU
Policlinico Hospital, Messina, Italy in a 20-year period
(1995–2015). Our Center is the only neuromuscular
center in a wide area including Sicily and the near
Calabria Region. The study included living symp-
tomatic patients (n. 34), deceased patients (n. 23) and
asymptomatic carriers (n. 19). The latter were rela-
tive in the clinical expression [18, 19]. Some other
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tives of patients, alive or dead, who had asked for a
genetic testing because of 50% risk for TTR-FAP and
had received a positive DNA result [21]. Two sym-
tomatic patients carrying a TTR mutation (Glu89Gln
n. 1 and Phe64Leu n. 1) with associated other cause of
peripheral neuropathy (diabetes mellitus and mul-
The autonomic score was the presence of a definite autonomic dysfunction if the score was in the range of 2–3 [27, 28]. Continuous variables were analyzed using Student’s t-test or one-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc test. A level of significance of p < 0.05 was considered.

RESULTS

Glu89Gln mutation

Forty subjects carried a heterozygous Glu89Gln mutation, 38/40 (95%) referred a positive family history. They belonged to 8 apparently unrelated families,
all located in the South-East of Sicily (Syracuse and Catania provinces) and of Sicilian descent (Fig. 1). 17 were males (42.5%) and 23 were females (57.5%). 12 subjects are asymptomatic carriers (age range: 21–47 years), 20 living symptomatic patients (age range: 39–63 years) and 8 deceased (Table 1).

The asymptomatic carriers had a follow-up of 4.5 ± 3.7 years (range: 1–10) since the time of genetic test result. When investigated with neurographic, autonomic and cardiological tests, all had normal results at last follow-up.

Age of onset was 49 ± 7.9 years (range: 37–66; n. 28). Male patients had a mean age of onset of 47.2 ± 5.2 years, whereas females 50.4 ± 9.3 (no significant difference). Presenting symptoms were distal paraesthesia (n. 14), carpal tunnel syndrome (CTS) (n. 7 monolateral and n. 1 bilateral), gait and balance disorder (n. 3), orthostatic hypotension (n. 2), stipped/diarrhoea (n. 1). Age at diagnosis in 8 probands was 56.3 ± 5.3 years (range: 46–63) versus age at onset of 50.5 ± 7.1 years (range: 38–60). Therefore, the interval between onset and diagnosis was 5.8 ± 3.8 years (range: 1–10). Previous wrong diagnosis were lumbar radiculopathy, lumbar stenosis, spastic colitis.

Living patients had a follow-up ranging from 0.5 to 10 years. At last follow-up, autonomic involvement (orthostatic hypotension, diastolic/bradycardia, erectile dysfunction, urinary incontinence, xerostomia) paralleled sensory and motor dysfunction in 12/20 cases; 4 patients had only sensory disturbances, 1 sensory-motor dysfunction, and 3 had yet only CTS.

Heart involvement with an increased IVS thickness ranging 15 to 24 mm (NYHA class II to IV) was found in 10/20 symptomatic patients. Its severity was proportional to both sensory-motor peripheral neuropathy and dysautonomia. One patient had a borderline IVS thickness of 14 mm (NYHA class II), one 13 mm (NYHA class I) and one 12 mm (NYHA class I). The former had mild muscle weakness at upper limbs, mild pinprick at upper and lower limbs, styphisis and xerostomia; the second had only mild pinprick at upper limbs; the latter had CTS.

Whereas most of the symptomatic patients referred as first symptoms those indicative of a peripheral neuropathy, among non-symptomatic subjects who had received a positive DNA results and were followed with neurographic, autonomic and cardiological tests once every one (two) year(s), the heart resulted to be firstly affected, even though without symp-

**Table 1**

| Glu89Gln | Phe64Leu | Thr49Ala | p value |
|----------|----------|----------|---------|
| Patients (n.) | | | |
| asymptomatic carrier | 12 | 6 | 4 | 0.0001 |
| living symptomatic | 20 | 10 | 4 | |
| deceased | 8 | 12 | 3 | |
| Familial cases | 38/40 (95%) | 15/28 (54%) | 7/8 (88%) | |
| Ratio M/F | 17/23 | 16/12 | 5/5 | |
| Age of onset (years) | 49 ± 7.9 (37–66) | 64.1 ± 7.4 (44–75) | 43.7 ± 7.5 (33–55) | n.s. |
| Prevalent symptoms at onset | distal paraesthesias | distal paraesthesias | autonomic disturbances | 0.0001 |
| Age at diagnosis in probands (years) | 36.3 ± 5.3 (46–63) | 72.4 ± 4.8 (64–78) | 46.5 ± 6.9 (41–66) | |
| Interval between onset and diagnosis (years) | 5.8 ± 3.8 (1–10) | 6.1 ± 3.7 (1–11) | 4.5 ± 3.9 (1–10) | n.s. |
| Involvement | | | |
| peripheral neuropathy | moderate | severe | moderate | |
| dysautonomia | moderate | moderate | severe | |
| heart dysfunction | mild | | moderate | |
| Age at death (years) | 63.4 ± 5.1 (58–71) | 77.6 ± 3.8 (69–82) | 55 ± 6.5 (49–62) | 0.0001 |
| Life expectancy (years) | 7.6 ± 3.7 (3–13) | 11.5 ± 5.1 (3–20) | 10.7 ± 2.5 (8–12) | n.s. |
| Prevalent cause of death | cardiomyopathy | cachexia, dysautonomia | cachexia | |

*by ANOVA. Mean ± standard deviation (range).*
Fig. 2. Clinical findings in an asymptomatic Glu89Gln carrier, showing higher sensitivity of 99mTc-DPD scintigraphy in detecting heart involvement. She was followed every two years with neurographic, autonomic and cardiological tests. Asterisk indicates a pathological result. At first control in 2006, at 46 years of age, Charcot-Marie-Tooth neuropathy score (CMTNS), compound autonomic dysfunction test (CADT), inter-ventricular septum thickness (IVST) and ejection fraction (EF) were normal; cardiac MRI and 99mTc-DPD scintigraphy were also normal; the latter showed no significant cardiac uptake (score 0) and normal indexes of semi-quantitative analysis (HR, WBR, H/WB ratio; see Materials and Methods). In 2008, CMTNS, CADT, IVST, EF and cardiac MRI were still normal. On the contrary, 99mTc-DPD scan showed a mild cardiac uptake (score 1) confirmed by some pathological semiquantitative indexes.

At last follow-up, heart involvement with an increased IVS thickness ranging 12 to 16.5 mm (NYHA class I to II) was found only in 5/10 symptomatic patients.

Age at death was 77.6 ± 3.8 years (range: 69–82) often in a severe tetraparetic status with a disease duration of 11.3 ± 5.1 years (range: 3–20). The main cause of death was wasting syndrome, followed by dysautonomia and then heart failure.

Thr49Ala mutation

Eight subjects carried the Thr49Ala mutation (all heterozygous). 7/8 (88%) referred a positive family history. They belonged to 4 apparently unrelated families, located in the South Center of Sicily (Agrigento province) and of Sicilian descent (Fig. 1). 3 were males (37.5%) and 5 were females (62.5%). One 35-year-old female is an asymptomatic carrier, 4 subjects are living symptomatic patients (age range: 41–58 years) and 3 deceased (Table 1).

Age of onset was 43.7 ± 7.7 years (range: 33–55; n. 7). Male patients had a mean age of onset of 64.9 ± 7.2 years, whereas females 62.2 ± 8.5 (not significant). Presenting symptoms were distal paraesthesia (n. 10, 2/10 had also diarrrhoea), CTS (n. 10 monolateral), gait and balance disorder with orthostatic hypotension or diarrrhoea and weight loss (n. 2). Age at diagnosis in 19 probands was 72.4 ± 4.8 years (range: 64–78) versus age at onset of 66.3 ± 4.9 years (range: 54–76). Therefore, the interval between onset and diagnosis was 6.1 ± 3.7 years (range: 1–11). Previous wrong diagnosis included compressive radiculopathy, hemibul-sclerosis, CIDP.

While autonomic disturbances were not present in most patients when seen the first time, orthostatic hypotension, diarrrhoea/stypsis, erectile dysfunction, urinary incontinence, xerostomia occurred in all of them approximately within 4 years from the onset.

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Age of onset was 43.7 ± 7.7 years (range: 33–55; n. 7). Male patients had a mean age of onset of
44.7 ± 11 years, whereas females 43 ± 6 (not significant). Presenting symptoms were autonomic disturbances (syncpe, orthostatic hypotension, stypsis, weight loss, impotence) in 4 patients, distal paraesthesia in 2, and CTS in one. Age at diagnosis in 4 probands was 46.5 ± 6.9 years (range: 41–56) versus age at onset of 42 ± 4.7 years (range: 37–46). The interval between onset and diagnosis was 4.5 ± 3.9 years (range: 1–10). Previous wrong diagnosis was vasovagal syncope in an already reported 46-year-old man [37]. He had recurrent episodes of syncope for 4 years as an overt and isolated symptom. Later, he experienced paresthesia in the hands and impotence, and clinical and neurophysiological signs of axonal polyneuropathy and mixed parasympathetic and sympathetic dysfunction were detected.

Autonomic disturbances paralleled sensory/motor dysfunction in 5 patients, and were more severe in 2. At last follow-up, heart involvement with an increased IVS thickness ranging from 13 to 20 mm (NYHA class I to III) was found in all four symptomatic patients with a long disease duration.

Age of death was 55 ± 6.6 years (range: 49–62) with a disease duration of 10.7 ± 2.3 years (range: 8–12). The first cause of death was dysautonomia and cachexia due to diarrhoea and malnutrition syndrome, followed by cardiomyopathy.

**Statistics among different mutations**

Table 1 summarizes clinical features according to mutation in our cohort and statistics. Age of onset resulted significantly higher in Phe64Leu than in both Glu89Gln (Δ: 15.1 years; p < 0.001) and Thr49Ala mutation (Δ: 20.4 years; p < 0.001). Moreover, Thr49Ala had an earlier onset of 5.3 years than Glu89Gln (p < 0.05). Fig. 3 shows estimated penetrance curve according to mutation. Similarly, diagnosis in probands occurred later in Phe64Leu than in both Glu89Gln (Δ: 16.1 years; p < 0.001) and Thr49Ala mutation (Δ: 25.9 years; p < 0.001). In Thr49Ala, age at diagnosis was lower than in Glu89Gln (Δ: 9.8 years; p < 0.05). Interval between onset of symptoms and TTR-FAP diagnosis was similar in the three mutations.

Life expectancy was not different among patients carrying the three mutations, with a high range from 3 to 20 years. Consequently, age at death in the different mutations corresponded to differences in age at onset. It was significantly higher in Phe64Leu than in both Glu89Gln (Δ: 14.2 years; p < 0.001) and Thr49Ala mutation (Δ: 22.6 years; p < 0.001). Moreover, in Thr49Ala mutation, death occurred earlier than in Glu89Gln (Δ: 8.4 years; p < 0.05).

**Carpal tunnel syndrome**

When considering all the patients together, CTS alone was recorded as inaugural symptom in 19/57 patients (33%). 4/19 still have no other complaints for a mean period of 5.6 years. In 15/19 CTS remained the only symptom for a period ranging from 1 to 12 years (mean, 4.6 years), before another clinical manifestation occurred. The latter was: distal paraesthesias in 6, muscle weakness in 3, walking difficulty, orthostatic hypotension and constipation in 2 each. There
was no significant association between type of second symptom or length of time interval and any of the three mutations.

Nerve biopsy

A nerve biopsy was performed in sixteen sporadic or doubtful cases, all limited to the period 1995–2005. It showed a severe fibre loss in all patients. Deposits of Congo red-positive amyloid were found in 13/16.

Treatment

23 patients had symptomatic treatment for neuropathic pain with gabapentin or pregabalin. 15 patients received midodrine or fludrocortisone acetate for orthostatic hypotension. Symptoms of irritable bowel syndrome were alleviated in 36. 6 patients had LT and 2/6 died. In none of them, LT modified the course of the disease. In the last two years, 17 patients started treatment with tafamidis meglumine. They have been enrolled in an Italian multicenter observational study of 61 patients, most of them with non-Met30 mutation and in all disease stages, followed by a homogenous protocol for 24 months. Preliminary results have shown: stabilization of nutritional status; 30–35% of responders’ rate independently from disease severity; few and minor adverse events. However, all neurological and cardiological outcome measures significantly worsened [16].

Prevalence

On 31st December 2014, 36 symptomatic patients with TTR-FAP were living in Sicily region. The prevalence of the disease was 7.1/1,000,000. We asked two major reference centers for TTR-FAP, one in North Italy, Pavia, and one in Center Italy, Rome, to provide us the number of living patients of Sicilian origin and with Sicilian residency, who were followed by them. Individuals who had moved from Sicily to another Italian city for study or work reasons were excluded. Other nine living symptomatic patients, 8 with Gln89Gln mutation and 1 with Phe64Leu mutation, were identified, leading to a total prevalence rate of 8.8/1,000,000.

DISCUSSION

Although TTR-FAP is a seemingly monogenic disease, literature highlights the considerable phenotypic heterogeneity in patients with either the hereditary or sporadic form, in endemic and non-endemic areas. Val30Met is the most studied mutation, in which similarities as well differences in age at onset, system/organ involvement and complications have been reported in diverse or even the same geographical areas [18, 38–40]. Mean age of onset ranges from 32–35 years in endemic areas of Brasil, Portugal and Japan to 56.7 years in Sweden [41]. An even later age of onset (61 years) has been reported in sporadic cases in a series from a non-endemic area [7, 42]. In the same mutation, gender analysis reported a later age of onset in women in Portugal and Brasil, whereas no difference in Sweden, Cyprus and Majorca [41]. Possible factors contributing to the differences among populations, but also within populations, include associate polymorphisms, mitochondrial function, environmental or external causes as diet influencing amyloid deposition, and are now under investigation [19, 43]. On the contrary, very few reports examined other mutations in details, but often they described small numbers of cases, or miscellanea of mutations all together [20, 44]. Differences in natural history among mutations and within mutations may have a number of important consequences in planning measures to overcome diagnostic difficulty and therapeutic management. With the promise of new disease-modifying gene/RNA therapies on the horizon, it has become increasingly important to have a good knowledge of the natural history of the disease, according to different mutations.

Our findings, which are based on a relatively large series of patients followed in the only tertiary neuromuscular center in Sicily, provide additional informations on three non-Val30Met mutations, so far described in some isolated patients, most of which of Sicilian origin [44–48]. The present study is the first epidemiological survey of TTR-FAP in an Italian area. We estimated its prevalence in Sicily Region to be 8.8/1,000,000. It is lower than the prevalence of 151, 104 and 3.72/100,000 in endemic areas as North Portugal, North Sweden and Cyprus, respectively [39, 49, 50], but higher than that of 0.87–1.1/1,000,000 in an even endemic area as Japan (having Nagano prefecture the highest prevalence of 11–15.5) [19] and that of approx. 3-4/1,000,000 in France [51] (David Adams, personal communication). We can assume that the prevalence is underestimated because of possible late onset, isolated cases and diagnostic pitfalls. A major challenge is to create a national registry to know the distribution of the disease in all Italian territory and to plan adequate multidisciplinary care for the patients.
This survey reported phenotype-to-genotype correlations in 76 patients belonging to 31 Sicilian families, carrying three different TTR mutations (Glu89Gln, Phe64Leu, Thr49Ala) geographically distributed in three major areas of the island. They could be inherited from three common ancestors, and haplotype analyses should be performed to confirm this hypothesis. It is summarized that there are three phenotypes of FAP in Sicily, each corresponding to a different TTR variant, which are homogeneous within and heterogeneous between each other: i) Glu89Gln mutation, characterised by onset in the 5th – 6th decade, prevalence distal paraesthesias/CTS as presenting symptoms, early heart dysfunction but with fatigue, palpitation, dyspnea appearing later, heart failure and sudden death as major cause of mortality followed by dysautonomia and cachexia; ii) Phe64Leu mutation, marked by familiarity reported in one-half of cases, late onset from 5th to 8th decade, prevailing distal paraesthesias/CTS at onset, organ involvement with severe peripheral neuropathy, moderate dysautonomia and mild cardiomyopathy, death from 7th to 9th decade for wasting syndrome followed by dysautonomia; iii) Thr49Ala mutation, distinguished by an earlier onset in the 5th decade, autonomic disturbances as inaugural symptoms which may remain isolated for many years, moderate polyneuropathy, dysautonomia and cachexia as major causes of mortality followed by cardiomyopathy. In contrast, comparison among the three mutations revealed no sex predominance, no sex difference in age of onset, same interval between onset and diagnosis from 1 to 11 years, same life expectancy from 3 to 20 years. However, duration of the disease appeared shorter in Glu89Gln patients (7.6 years), most likely due to the cardiomyopathy which represents the first cause of death. Although the disease profile associated with mutations with an exclusively/predominantly cardiac involvement has been little defined, patients with non-endemic Val30Met or with non-Val30Met mutations display a more frequent and severe heart phenotype [10, 20, 52]. The only large prospectively followed cohort of patients with one of the so-called “cardiac” mutations, Thr60Ala, showed in sixty patients that: i) clinical presentation was cardiac in 42% but 96% of the patients had echocardiographic evidence of amyloidosis at diagnosis; ii) the median age of onset of symptoms was 63 years; iii) prognosis was poor, reflecting frequency and severity of cardiac involvement [53]. Our experience on asymptomatic carriers of Glu89Gln mutation followed with periodic check-ups suggests that heart involvement occurs in their forties and before that of nervous system.

Unfortunately, the absence of neurological symptoms and indolent course of cardiomyopathy may cause the patient to seek medical attention far along. The present survey is one of the most numerous on non-Val30Met patients reporting phenotype-to-genotype correlations. Studies regarding epidemiological data from different countries are very important worldwide and should be encouraged.

CTS alone was the first symptom/sign in one third of our cohort, occurring bilaterally only in one patient. CTS remained the only manifestation for a period of 1–12 years. The occurrence of a short interval supports, as postulated by some authors, that the electrophysiological abnormality at the distal portion of the median nerve may be the consequence of polynuropathy rather than an entrapment injury [54]. On the other hand, occurrence of a long interval between CTS signs and appearance of other complaints could suggest a coincidental presence of an idiopathic CTS, because of the high CTS prevalence of 7.8% in working populations [55]. However, life expectancy in our cohort should be misleadingly lengthened when considering CTS as presenting symptom. This is not the case since the mean values of 7.6 – 11.3 years in our study are in accordance with the known mean duration of the disease of 10 years [10].

In conclusion, TTR-FAP is a progressive and fatal disease that is increasingly diagnosed worldwide. This analysis of data in Sicily Region highlighted a prevalence of 8.8/1,000,000, absence of the common Val30Met mutation, and presence of only three TTR variants (Glu89Gln, Phe64Leu, Thr49Ala) with homogeneous within and heterogeneous clinical characteristics between each other. Neurologists must be aware of diagnostic pitfalls of TTR-FAP and gene sequencing should be done in all suspected cases. Genetic testing should be also encouraged in relatives of diagnosed cases when they are able to understand its medical, social and psychological consequences. Good knowledge of the natural history of the disease according to different TTR mutations allow clinicians to optimise multiprofessional care for patients and to offer carriers a personalized follow-up to reveal first signs of the disease.

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DISCLOSURES

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