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Genotypic and phenotypic presentation of transthyretin-related familial amyloid polyneuropathy (TTR-FAP) in Turkey

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Abstract

Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is an autosomal dominant disorder caused by mutations of the transthyretin (TTR) gene. The mutant amyloidogenic transthyretin protein causes the systemic accumulation of amyloid fibrils that result in organ dysfunction. TTR-associated FAP is a progressive and fatal disease, if left untreated, and should be considered in the differential diagnosis of any person presenting with a progressive polyneuropathy, particularly with accompanying autonomic involvement. The clinical, electrophysiological, histopathological, and genetic characteristics of 17 patients from Turkey (5 female, 13 male) from nine families with polyneuropathy and mutations in TTR were evaluated. Sequence analysis of the TTR gene revealed five mutations (Val30Met, Glu89Gln, Gly53Glu, Glu54Gly and Gly47Glu). Mean age at disease onset was 40.4 ± 13.9 years (range 21–66 years). The most commonly reported initial complaint was paresthesia in the feet (asymmetric in three patients). Three patients (2 male) with the Glu89Gln mutation presented with carpal tunnel syndrome. Two patients with the Gly53Glu mutation showed episodes of dysarthria and hemiparesis, consistent with this genotype. Seven patients died during the period of follow-up as a result of systemic involvement. Our study suggests that a cohort of patients from Turkey with TTR-FAP exhibits clinical and genetic heterogeneity.

Keywords: Transthyretin-related familial amyloid polyneuropathy; Neuropathy; Progressive; Hereditary; Heterogeneity

1. Introduction

TTR-FAP is a rare autosomal dominant disorder caused by mutations of the TTR gene with variable penetration [1,2]. Transthyretin protein, originally called prealbumin, is mostly produced in the liver and transports vitamin A and thyroxine [3]. Mutant transthyretin protein has been identified as a precursor of amyloid in TTR-FAP. When it dissociates from its native tetrameric form, mutant transthyretin misfolds and aggregates into amyloid fibrils which can accumulate in various organs, particularly the heart, ocular vitreous and kidney. Organ dysfunction is directly related to amyloid deposition [4]. More than 100 different mutations of TTR have been identified worldwide, but the first-described Val30Met mutation remains the most common [5]. The prevalence of different mutations varies according to ethnicity and geographic region. In the three main regions in which TTR-FAP is endemic (Portugal, Sweden and Japan), the Val30Met substitution is the predominant genetic cause, but TTR-FAP cases from non-endemic regions are genetically and clinically heterogeneous. The most common phenotype of TTR-FAP is length-dependent axonal, sensory-motor and autonomic polyneuropathy with differing degrees of other organ involvement [6]. TTR-FAP is a progressive and fatal disease if left untreated and should be considered in the differential diagnosis of any patient presenting with a progressive polyneuropathy, especially when accompanied by autonomic involvement.

To date, a limited number of TTR-FAP cases have been reported from Turkey [7–9], and the genotypic and phenotypic features of TTR-FAP in this population remain unclear. Here, we describe our detailed clinical and molecular genetic findings from 17 patients with TTR-FAP, most of whom are from the Western part of Turkey.

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2. Methods

Seventeen patients followed between 1995 and 2014 at the Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, were included in the study. All patients were diagnosed with TTR-FAP on the basis of clinical and genetic findings. At the beginning of the study, patients underwent a detailed neurological examination. Diagnostic electrophysiological tests included standard electromyography (EMG) and nerve conduction velocity (NCV) studies. Sympathetic skin response and heart rate variability tests were also performed. A verbal pain intensity scale (with outcomes ranging from 'no pain' to 'worst possible pain') was used for the assessment of neuropathic pain. Before the availability of genetic testing, sural nerve biopsies were performed in some patients following written consent, but more recently, salivary gland biopsy was carried out, when necessary. Echocardiogram, electrocardiogram and Holter monitoring (24 h) were performed using standard methodology. Patients were seen regularly by an experienced ophthalmologist and a nephrologist for any finding of ocular and renal involvement.

Genetic test was performed following written informed consent from all participants according to the Declaration of Helsinki. The study protocol was approved by Istanbul University Institutional Review Board for Research with Human Participants.

Following acquisition of written, informed consent, blood was taken for DNA extraction and DNA was isolated from a 10 ml whole blood sample using a commercially available kit (QIAamp DNA Blood Maxi Kit [QIAGEN]). For the detection of variants in the TTR gene, exon 2 (e2F3′-CTTGTTTCGCTCCAGATTTC-5′; e2R3′-TGAGCCT CTCTCTACCAAGTG-5′), exon 3 (e3F3′-TGTTTCCTCCAT GCGTAACT-5′; e3R3′-TAGGACATTTCTGTGGTACACTG-5′), and exon 4 (e4F3′-GGACTTCCGGTGGTCAGT-5′; e4R3′-TGCCTGGACTTCTAACATAGC-5′) fragments were amplified and Sanger sequencing was performed (Macrogene). Chromatograms were analyzed with the aid of Chromas and CLC Main Workbench 5.5 programs. The resultant sequences were aligned with the human reference sequence NG_009490. Detected variants were searched and confirmed in public databases including the *Single Nucleotide Polymorphism database* (*dbSNP*) (http://www.ncbi.nlm.nih.gov/SNP/) and *Mutations in Hereditary Amyloidosis* (http://amyloidosismutations.com/cdna-attr.html). Amino acid changes in TTR were numbered according to the beginning of the mature protein, as described historically, rather than including the 20 amino acid signal sequence.

3. Results

We studied the clinical and genetic characteristics of TTR-FAP in 17 patients (5 female, 12 male) from nine unrelated families. While the mean age at disease onset in the entire cohort was 40.4 ± 13.9 years (range 21–66 years), the mean age at disease onset for patients with the Val30Met mutation was 54.5 ± 10.4 years (range 44–66 years). Two patients had no family history of TTR-FAP and were considered as sporadic cases, and the remainders showed an inheritance pattern compatible with an autosomal dominant trait (Table 1). Five different mutations in TTR were identified in our cohort. Four patients from unrelated families carried the Val30Met mutation and two of these patients were homozygous for the mutation. The second most common mutation was Glu89Gln, which was identified in two unrelated families (five patients). The remaining three families were carrying the Gly53Glu (three patients), Gly47Glu (three patients), and Glu54Gly (one patient) mutations. With the exception of the patient with the Glu54Gly mutation who came from Southeast of Turkey, all the other participants originated from Western Turkey.

The most common presenting symptom was paresthesia in the feet, affecting six of the 17 patients (Table 1). In three patients, paresthesia was asymmetric at the time of presentation. Four other cases had paresthesia in the hands and feet, accompanied, to a varying degree, by autonomic symptoms. Interestingly, for two male and one female patients with the Glu89Gln mutation, the presenting symptom was paresthesia in the hands due to carpal tunnel syndrome. Isolated autonomic involvement was apparent as a presenting symptom in two patients with the Gly47Glu and in one with a homozygous Val30Met mutation. Cardiac involvement was rare in our cohort at the time of first presentation, only one patient with the Gly47Glu mutation presented with isolated cardiac symptoms.

Length-dependent polyneuropathy was detected in all patients at clinical examination. Motor impairment followed sensory loss in all participants after 4–12 months (mean duration 7 ± 2.12 months). One patient with a TTR-FAP disease duration of nine years was bedridden due to marked weakness at their last evaluation. Of those people with disease duration of 9–12 years, four needed unilateral or bilateral walking aids.

With the exception of one, most patients complained of mild-to-severe neuropathic pain, according to the verbal neuropathic pain scale, in the very early stages of disease. Only two people with Gly47Glu and Glu89Gln mutations reported severe neuropathic pain. All participants responded well to first-line neuropathic pain treatment.

Hypophonia due to vocal cord involvement was detected in two patients carrying the Val30Met and Glu89Gln mutations. In the patient with a Glu89Gln mutation, vocal cord paralysis caused severe obstructive sleep apnea which was treated successfully with bilevel positive airway pressure (BIPAP) ventilation.

In six patients, findings from electrophysiological studies undertaken at presentation were compatible with sensory-motor axonal polyneuropathy and autonomic neuropathy. EMG showed sensory-motor axonal polyneuropathy without autonomic neuropathy in six, carpal tunnel syndrome in only three, sensory axonal polyneuropathy in one and autonomic neuropathy in another patient (Table 2).

Sural nerve biopsy was performed in eight patients. Of these, seven showed findings compatible with severe axonal neuropathy with endoneural and perivascular amyloid accumulation. In the remaining patient, abdominal fat pad biopsy confirmed the presence of amyloid (Table 2).

Severe bilateral carpal tunnel syndrome was observed in three patients with Glu89Gln mutations. For two study patients,

Table 1
Demographic and clinical characteristics of study cohort (n = 17).

Family/ patient	Age at onset of neuropathy (years)/gender	Disease duration at last examination	Age at death (years)/cause of death	Mutation	Family history	Presenting symptom	Neurological findings at last examination	Autonomic involvement
I/1	66/M	8	–	Heterozygous Val30Met	–	Paresthesia in the feet	Hypophonia. Distal and LL prominent weakness of limbs, DTRs abolished. S-G type hypoesthesia, decreased vibration sensation. Walks with bilateral assistance.	Impotence (early), OH, ADC
II/2	48/M	6	54/unknown – sudden death	Homozygous Val30Met	+	Autonomic –impotence	Distal and LL prominent weakness of limbs, DTRs abolished. S-G type hypoesthesia, decreased vibration sensation.	Impotence (early), ADC, urinary incontinence (late)
III/3	44/F	6	–	Heterozygous Val30Met	+	Paresthesia in the hands and feet	S-G type hypoesthesia, decreased vibration sensation	OH
IV/4	60/M	3	–	Homozygous Val30Met	+	Paresthesia in the feet	Distal and LL prominent weakness of limbs, DTRs abolished. S-G type hypoesthesia, decreased vibration sensation. Walks with bilateral assistance.	Impotence
V/5	53/M	7	60 / cardiac failure	Heterozygous Glu89Gln	+	Paresthesia in the hands due to bilateral CTS (36 years)	Hypophonia. Distal and LL prominent weakness of limbs, DTRs abolished. S-G type hypoesthesia, decreased vibration sensation. Bedridden due to weakness and orthostatic hypotension.	Impotence (early), ADC, OH urinary incontinence
V/6	62/F	5	–		+	Paresthesia in the feet and constipation	Mild distal weakness in LLs, DTRs hypoactive or abolished. S-G type hypoesthesia, decreased vibration sensation in LLs.	Constipation (early), urinary incontinence (early), OH
V/7	55/M	11	–		+	Paresthesia in the feet, especially on the left side	Distal and LL prominent weakness of limbs, DTRs abolished. S-G type hypoesthesia, decreased vibration sensation in LLs. Walks with unilateral assistance.	OH (only mild symptoms)
V/8	37/M	4	–		+	Paresthesia in the right hand	Bilateral CTS	None
VI/9	52/M	5	57/cardiac and renal failure	Heterozygous Glu89Gln	–	Paresthesia in the feet, especially on the right side	Distal and LL prominent weakness of all limbs, DTRs abolished, S-G type hypoesthesia, decreased vibration sensation.	Impotence (early), ADC (3 years later)
VII/10	33/M	4	37/cardiac failure	Heterozygous Gly53Glu	+	Paresthesia in the feet, dry mouth, weight loss	Distal and LL prominent weakness of all limbs, DTRs abolished in LLs, S-G type hypoesthesia, decreased vibration sensation in LLs. Bedridden because of severe autonomic involvement.	Severe OH, impotence, ADC (early), 2 years later urinary incontinence
VII/11	22/F	2	–		+	Paresthesia in the feet	Mild S-G type hypoesthesia	None
VII/12	31/M	4	35/cardiac failure		+	Dizziness, diarrhea, paresthesia	Distal and LL prominent weakness of all limbs, DTRs abolished in LLs. S-G type hypoesthesia, decreased vibration sensation in LLs. Bedridden because of severe autonomic involvement.	OH, ADC (early)
VIII/13	21/M	2	–	Heterozygous Glu54Gly	+	Paresthesia in the hands, cramps in lower extremities, constipation	Mild S-G type hypoesthesia	OH, ADC(early)
IX/14	39/F	6	46/cardiac failure	Heterozygous Gly47Glu	+	Fatigue, autonomic symptoms	Distal and LL prominent weakness of limbs, DTRs abolished. S-G type hypoesthesia, decreased vibration sensation.	OH, ADC (early), urinary incontinence
IX/15	25/M	2	–		+	Paresthesia	Mild S-G type hypoesthesia, decreased vibration sensation	Impotence
IX/16	26/M	2	–		+	Nausea and vomiting	Mild S-G type hypoesthesia, decreased vibration sensation, decreased vibration sensation	Severe vomiting, ADC
IX/17	25/F	8	33/cardiac failure		+	Nausea and vomiting	Mild S-G type hypoesthesia, distal and LL prominent weakness of limbs, DTRs abolished	Severe vomiting, ADC

DTR, deep tendon reflexes; F, female; LL, lower limb; M, male; S-G type hypoesthesia, stocking-glove type; ADC, alternating diarrhea-constipation; OH, orthostatic hypotension.

Table 2
Clinical and laboratory findings from study cohort (n = 17).

Family/ patient	Mutation	Electrodiagnostic tests* at presentation	Biopsy	Bilateral CTS	Cardiac involvement	Renal involvement	Eye	Neuropathic pain
I/1	Heterozygous Val30Met	Sensory and motor PNP	SN – amyloid deposition	–	+ (RC, AF)	+	–	Moderate
II/2	Homozygous Val30Met	Sensory and motor PNP and autonomic involvement	SN – amyloid deposition	–	+ (RC)	–	Vitreous opacities	Moderate
III/3	Heterozygous Val30Met	Sensory and motor PNP and autonomic involvement	–	–	–	–	–	Moderate
IV/4	Homozygous Val30Met	Sensory and motor PNP and autonomic involvement	SN – amyloid deposition	–	–	–	–	Mild
V/5	Heterozygous Glu89Gln	Sensory and motor PNP, bilateral CTS	SN – amyloid deposition	+	+ (RC, severe CI, AV block)	–	–	Mild
V/6	Heterozygous Glu89Gln	Sensory and motor PNP, autonomic involvement, bilateral CTS	–	+	+ (RC, moderate CI, AV block)	–	–	Mild
V/7	Heterozygous Glu89Gln	Sensory and motor PNP	SN – amyloid deposition	–	+ (RC, mild CI)	–	–	Mild
V/8	Heterozygous Glu89Gln	Bilateral CTS	ND	+	–	–	–	–
VI/9	Heterozygous Glu89Gln	Sensory and motor PNP	SN – amyloid deposition	–	+ (RC, AV block)	–	–	Severe
VII/10	Heterozygous Gly53Glu	Sensory and motor PNP	SN – amyloid deposition	–	+ (RC)	–	–	Mild
VII/11	Heterozygous Gly53Glu	Mild sensory PNP	ND	–	–	–	–	Mild
VII/12	Heterozygous Gly53Glu	Sensory and motor PNP	AF = amyloid deposition	–	+ (RC)	–	–	Mild
VIII/13	Heterozygous Glu54Gly	Autonomic PNP	ND	–	–	–	–	Mild
IX/14	Heterozygous Gly47Glu	Sensory and motor PNP	SN – amyloid deposition	–	+ (RC)	–	–	Mild
IX/15	Heterozygous Gly47Glu	Sensory and motor PNP, autonomic involvement	ND	–	+ (RC)	–	–	Moderate/ severe
IX/16	Heterozygous Gly47Glu	Sensory and motor PNP, autonomic involvement	ND	–	+ (RC)	–	–	Mild
IX/17	Heterozygous Gly47Glu	Sensory and motor PNP, autonomic involvement	ND	–	+ (RC)	–	–	Mild

F, abdominal fat pad biopsy; CTS, carpal tunnel syndrome; ND, not done; PNP, polyneuropathy; SN, sural nerve biopsy; RC, restrictive cardiomyopathy; CI, cardiac insufficiency; AV block, atrioventricular block; AF, atrial fibrillation.
* ENG/EMG and sympathetic skin response and R-R interval.

carpal tunnel syndrome findings were present 10 and 16 years before the full-blown neuropathic symptoms emerged. Spinal stenosis due to amyloid accumulation in the spinal canal was observed in one person with the Glu89Gln mutation (Patient V/5).

Central nervous system involvement was observed in two patients with the Gly53Glu mutation (Patients VII/10 and VII/12). Both patients presented with transient ischemic attack-like episodes of dysarthria and hemihypoesthesia. Cranial magnetic resonance imaging revealed gadolinium enhancement of leptomeningeal vessels in one patient and mild generalized cortical atrophy in the other. For one participant who complained of progressive forgetfulness, neuropsychological test results were compatible with frontal dysexecutive syndrome with reduced verbal fluency and vigilance, mild impairment in abstract thinking and naming.

Autonomic involvement was observed in all but two patients. Participants without autonomic symptoms had disease duration of 1 or 2 years only. Impotence was the first sign of autonomic involvement in men, with onset typically within six months of the emergence of neuropathic symptoms. In men, urinary incontinence was a late autonomic symptom (Stage 3 only), whereas women with Val30Met and Glu89Gln mutations experienced urinary incontinence and constipation early in the disease process. Early and severe gastrointestinal manifestations (nausea and vomiting, episodic attacks of constipation and diarrhea) and orthostatism were associated with Gly47Glu and Glu54Gly mutations. Orthostatism was typically very disabling, two people with the Gly53Glu mutation were unable to walk or stand due to severe orthostatic hypotension after 4 years of the disease. Among the remaining patients, gastrointestinal manifestations and orthostatism were mild and developed 3–6 years after neuropathic symptoms (Table 2).

Twelve study patiens showed signs of cardiac involvement. Age at onset of cardiomyopathy was heterogeneous. People carrying the Gly47Glu and Glu54Gly mutations developed cardiomyopathy within five years of disease onset. Among patients with other mutations, the onset of cardiac involvement varied, even between family members (3–12 years later after the emergence of the first neuropathic symptoms).

Ophthalmologic examinations revealed vitreous opacities in one patient with a homozygous Val30Met mutation.

Renal involvement was suspected in two cases with Val30Met and Glu89Gln mutations because of low creatinine clearance and proteinuria without any other explanation, but kidney biopsy could not be performed.

Seven patients died during the follow-up period. Mean age at the point of death was 47.71 ± 12.03 years (range 33–60 years) and the mean disease duration was 7.43 ± 2.12 years (range 4–12 years). The most common cause of death was cardiac failure (five patients), one patient died due to combined cardiac and renal dysfunction and one patient died suddenly due to an unknown cause.

4. Discussion

TTR-FAP is a rare, yet disabling neurological disorder with high genotypic and phenotypic variability. Length-dependent sensory-motor axonal polyneuropathy and autonomic neuropathy are characteristic features of TTR-FAP, but cardiovascular, renal, ocular and central nervous system involvement contributes to mobility and mortality. Here we report the largest cohort of TTR-FAP patients from Turkey published to date.

TTR-FAP was first described in Portugal in 1952 [1], where the disease has reached endemic proportions. Two other endemic regions, Sweden [10] and Japan [11], were identified subsequently. Within endemic regions, the first-identified Val30Met mutation is almost the only genetic cause of TTR-FAP, but cases from the rest of the world are genetically and clinically heterogeneous. Turkey is a non-endemic region for TTR-FAP. Interestingly, most of the patients in our cohort come from the West or Northwest part of the country, a Thracian area, where Turkish people who descended from immigrants who entered the country as a result of people exchange with other Balkan countries following the First World War have settled. We identified 17 patients from nine unrelated families carrying five different genetic mutations (Val30Met, Glu89Gln, Gly53Glu, Glu54Gly, and Gly47Glu). The most common mutations were Val30Met and Glu89Gln. Two patients, symptomatic individuals aged 48 and 60 years, were homozygous for the Val30Met mutation. Both presented with length-dependent sensory-motor axonal polyneuropathy and autonomic neuropathy and one displayed vitreous opacity. From this we can conclude that homozygosity of the mutant gene does not affect the clinical phenotype of the disease, except for the high occurrence of vitreous opacity [12].

Age at the onset of TTR-FAP symptoms varied between families and between family members in our cohort. The mean age at symptom onset was 40.4 ± 13.9 years (range 21–66 years), younger than expected for a non-endemic area, in which disease-related symptoms tend to occur later in life, after the fifth decade [13,14]. In our cohort, the mean age of onset for patients with the Val30Met mutation was 54.5 ± 10.4 years (range 44–66 years). The age at disease onset for patients with Gly47Glu, Glu54Gly and Gly53Glu mutations was particularly young, and ranged between 22 and 39 years. Glu54Gly and Gly47Glu mutations have previously been associated with an aggressive form of TTR-FAP with early onset and rapid progression [15,16]. Genetic anticipation in the age at onset of the disease was observed in the family with the Gly47Glu mutation. Pelo et al. made a similar observation in an Italian family with the same mutation [17]. A male predominance (male/female: 2.4) was observed in our cohort, consistent with other non-endemic regions [18].

The most common initial complaint was paresthesia in the feet, which progressed to the hands. Motor impairment followed sensory loss for all patients after 4–12 months. Presentation with isolated autonomic or cardiac symptoms was rare in our cohort. Bilateral carpal tunnel syndrome was an early finding in patients with Glu89Gln mutations. TTR-FAP should be considered in young male patients with bilateral carpal tunnel syndrome without any other explanation. In one patient with a Glu89Gln mutation, spinal stenosis due to amyloid accumulation, which was not reported previously, was observed. Recent research suggests that senile systemic amyloidosis could be a common cause for lumbar spinal stenosis [19]. Whether there is an increased risk of amyloid-generated spinal stenosis in familial TTR-FAP should be further investigated. With the exception of carpal tunnel syndrome, symptoms related to focal amyloid depositions are rare in TTR-FAP [20]. Vocal cord involvement was identified in two patients of our cohort (Table 1), not surprisingly, one of them was carrying the Glu89Gln mutation. Focal amyloid depositions may represent a key feature of this mutation.

Autonomic involvement is one of the characteristic features of TTR-FAP and was observed in almost all study participants [21]. Sensory-motor axonal polyneuropathy of unknown origin accompanying autonomic involvement should raise suspicion of TTR-FAP. Impotence in male participants and urinary dysfunction and constipation in female participants were early signs of autonomic involvement in our cohort. Early and severe disturbances of gastrointestinal motility due to autonomic neuropathy and orthostatism were observed, particularly in people carrying Gly47Glu and Glu54Gly mutations. Orthostatism was very disabling and difficult to manage, and two of our participants with the Gly53Glu mutation were unable to walk or stand up due to severe orthostatic hypotension after four years of disease.

Neuropathic pain was a common complaint within our cohort but it was usually not severe enough to interfere with daily activities and easily controlled with first-line treatments.

Two patients with a Gly53Glu mutation showed episodes of dysarthria and hemiparesis which have previously been associated with this genotype [22]. One of these patients developed progressive symptoms of dementia at age 35 (Patient VII/10). Patients carrying mutations associated with CNS involvement should be observed carefully for signs of cognitive impairment, even if conventional imaging studies prove normal.

Seven patients died during the follow-up period. Mean disease duration at the time of death was 7.43 ± 2.12 years (range 4–12 years). The major cause of death was cardiac involvement and these participants died before new disease-modifying drugs became available [5]. Liver transplantation was considered, but could not be performed, given the challenges still associated with organ transplantation in Turkey.

Infiltrative cardiomyopathy was observed in 76% of the cohort, and cardiac involvement was one of the major causes of mortality and morbidity. We endorse the recommendation that patients with TTR-FAP should be closely followed up by an experienced cardiologist [18]. One patient carrying the Gly47Glu mutation presented with cardiomyopathy. Cardiologists should be aware of the risk of cardiomyopathy associated with TTR-FAP and genetic testing should be performed in patients with cardiomyopathy and unexplained sensory-motor polyneuropathy or bilateral carpal tunnel syndrome.

Kidney involvement was rare in the cohort, with only two patients with Val30Met and Glu89Gln mutations showing possible evidence of this. Ocular involvement was also unusual and was observed in only one participant with a homozygous Val30Met mutation.

5. Conclusion

TTR-associated FAP is a progressive and fatal disease if left untreated and should be considered in the differential diagnosis of progressive polyneuropathy, especially if accompanied by autonomic involvement. TTR-FAP should also be considered in people diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) who are not responding to standard immune therapy. Our study suggests that patients from Turkey with TTR-FAP exhibit clinical and genetic heterogeneity.

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References

[1] Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain 1952;75:408–27.
[2] Sasaki H, Yoshioka N, Takagi Y, Sakaki Y. Structure of the chromosomal gene for human serum prealbumin. Gene 1985;37:191–7.
[3] Costa PP, Figueira AS, Bravo FR. Amyloid fibril protein related to prealbumin in familial amyloidotic polyneuropathy. Proc Natl Acad Sci USA 1978;75:4499–503.
[4] Plante-Bordeneuve V, Kerschen P. Transthyretin familial amyloid polyneuropathy. Handb Clin Neurol 2013;115:643–58.
[5] Plante-Bordeneuve V. Update in the diagnosis and management of transthyretin familial amyloid polyneuropathy. J Neurol 2014;261: 1227–33.
[6] Hund E. Familial amyloidotic polyneuropathy: current and emerging treatment options for transthyretin-mediated amyloidosis. Appl Clin Genet 2012;5:37–41.
[7] Skare J, Yazici H, Erken E, et al. Homozygosity for the met30 transthyretin gene in a Turkish kindred with familial amyloidotic polyneuropathy. Hum Genet 1990;86:89–90.
[8] Schanzer A, Kimmich C, Rocken C, et al. A woman with a rare p.Glu74Gly transthyretin mutation presenting exclusively with a rapidly progressive neuropathy: a case report. J Med Case Rep 2014;8:403.
[9] Bekircan-Kurt CE, Gunes N, Yilmaz A, Erdem-Ozdamar S, Tan E. Three Turkish families with different transthyretin mutations. Neuromuscul Disord 2015;25:686–92.
[10] Andersson R. Familial amyloidosis with polyneuropathy. A clinical study based on patients living in northern Sweden. Acta Med Scand Suppl 1976;590:1–64.
[11] Araki S, Mawatari S, Ohta M, Nakajima A, Kuroiwa Y. Polyneuritic amyloidosis in a Japanese family. Arch Neurol 1968;18:593–602.
[12] Sandgren O, Holmgren G, Lundgren E. Vitreous amyloidosis associated with homozygosity for the transthyretin methionine-30 gene. Arch Ophthalmol 1990;108:1584–6.
[13] Holmgren G, Costa PM, Andersson C, et al. Geographical distribution of TTR met30 carriers in northern Sweden: discrepancy between carrier frequency and prevalence rate. J Med Genet 1994;31:351–4.
[14] Sousa A, Andersson R, Drugge U, Holmgren G, Sandgren O. Familial amyloidotic polyneuropathy in Sweden: geographical distribution, age of onset, and prevalence. Hum Hered 1993;43:288–94.
[15] Kim HS, Kim SM, Kang SW, et al. An aggressive form of familial amyloid polyneuropathy caused by a Glu54Gly mutation in the transthyretin gene. Eur J Neurol 2005;12:657–9.
[16] Haagsma EB, Hawkins PN, Benson MD, Lachmann HJ, Bybee A, Hazenberg BP. Familial amyloidotic polyneuropathy with severe renal involvement in association with transthyretin Gly47Glu in Dutch, British and American-Finnish families. Amyloid 2004;11:44–9.
[17] Pelo E, Da Prato L, Ciaccheri M, et al. Familial amyloid polyneuropathy with genetic anticipation associated to a gly47glu transthyretin variant in an Italian kindred. Amyloid 2002;9:35–41.
[18] Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis 2013;8: 31.
[19] Westermark P, Westermark GT, Suhr OB, Berg S. Transthyretin-derived amyloidosis: probably a common cause of lumbar spinal stenosis. Ups J Med Sci 2014;119:223–8.
[20] Ikeda S, Nakazato M, Ando Y, Sobue G. Familial transthyretin-type amyloid polyneuropathy in Japan: clinical and genetic heterogeneity. Neurology 2002;58:1001–7.
[21] Adams D, Theaudin M, Cauquil C, Algalarrondo V, Slama M. FAP neuropathy and emerging treatments. Curr Neurol Neurosci Rep 2014;14:435.
[22] Ellie E, Camou F, Vital A, et al. Recurrent subarachnoid hemorrhage associated with a new transthyretin variant (Gly53Glu). Neurology 2001;57:135–7.