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Transthyretin-related familial amyloid polyneuropathy (ATTR-FAP) in Poland — genetic and clinical presentation

Marta Lipowska[1], Hanna Drac[1], Dorota Rowczenio[2], Janet Gilbertson[2], Philip N Hawkins[2], Anetta Lasek-Bal[3], Janusz Szewczuk[4], Jacek Grzybowski[5], Monika Gawor[5], Małgorzata Stępień-Wojno[6], Maria Franaszczyk[7], Joanna Brydak-Godowska[8], Renata Śmierciak[9], Agnieszka Ptasińska-Perkowska[10], Jan Chandoga[11], Robert Petrovic[11], Anna Kostera-Pruszczyk[1]

[1]Department of Neurology, Medical University of Warsaw, Warsaw, Poland
[2]National Amyloidosis Centre, University College London, London, United Kingdom
[3]Department of Neurology, School of Health Sciences, Medical University of Silesia, Katowice, Poland
[4]Department of Neurology, Specialist Hospital, Slupsk, Poland
[5]Department of Cardiomyopathy, Institute of Cardiology, Warsaw, Poland
[6]Unit for Screening Studies in Inherited Cardiovascular Diseases, Institute of Cardiology, Warsaw, Poland
[7]Department of Medical Biology, Institute of Cardiology, Warsaw, Poland
[8]Department of Ophthalmology, Medical University of Warsaw, Warsaw, Poland
[9]Department of Neurology, Specialist Hospital, Nowy Sacz, Poland
[10]Department of Transplantation Medicine, Nephrology, Internal Diseases, T. Orłowski Institute of Transplantation Medical University of Warsaw, Warsaw, Poland
[11]Institute of Medical BiolGenetics and Clinical Genetics, Comenius University, Faculty of Medicine & University Hospital, Bratislava, Slovakia

ABSTRACT

Background. Transthyretin-related familial amyloid polyneuropathy (ATTR-FAP) is a rare, progressive, hereditary, highly disabling multisystem disorder. ATTR-FAP phenotypes differ according to the type of TTR mutation, geographic region and other as yet unidentified factors. The aim of this study was to establish the clinical and genetic characteristics of Polish patients.

Methods and patients. Clinical data and necessary examinations were collected from patients diagnosed with ATTR-FAP at the Department of Neurology of Medical University of Warsaw between 1970 and 2019.

Results. 16 patients from eight unrelated families with five different TTR mutations were identified. The family with Val71Ala TTR mutation presented with early onset severe progressive polyneuropathy, with marked visual symptoms in a few patients. The next family with Ile73Val TTR mutation developed symptoms in middle age, and presented with mixed neuropathic and cardiologic phenotype. Four unrelated families were found to have the Phe33Leu TTR mutation with mixed neuropathic and cardiologic phenotype and late onset of symptoms. Other TTR mutations identified were: Val30Met and Asp38Val, both with late onset sensory, motor and autonomic neuropathy.

Conclusion. Polish ATTR-FAP cases presented with heterogeneity typical for non-endemic areas. Phe33Leu TTR mutation was the most common, found in four unrelated families

Key words: familial amyloid polyneuropathy, amyloidosis, transthyretin, TTR mutations

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Address for correspondence: Marta Lipowska, Department of Neurology, Medical University of Warsaw, Banacha 1a Str., 02-097 Warsaw, Poland, e-mail: mlipowska@wum.edu.pl

Introduction

Transthyretin familial amyloid polyneuropathy (ATTR-FAP) is a rare, progressive and life-threatening systemic disease caused by mutations in the transthyretin gene (*TTR*). It is characterised by an extracellular deposition of transthyretin-derived amyloid fibrils leading to organ dysfunction. Sensorimotor and autonomic neuropathy is the predominant feature of ATTR-FAP, but, depending on the genetic variation, other clinical presentations may include infiltrative cardiomyopathy, visual symptoms such as vitreous opacities; renal impairment and meningeal involvement. The natural course of the disease from onset of symptoms to death is approximately 10 years [1].

ATTR-FAP is an autosomal-dominant disorder and to date more than 100 different TTR mutations have been identified worldwide [2]. The first to be described was the Val30Met (p.Val50Met) mutation, which remains the most common cause of ATTR-FAP in certain endemic areas including Sweden, Portugal and Japan [1]. The prevalence of other TTR mutations varies greatly with regards to ethnicity and geographical region. In ATTR-FAP, different treatment options are available depending on disease stage (i.e. pharmacological treatment, liver transplantation). Therefore, better awareness of this disease is needed among physicians.

To date, no ATTR-FAP cases from Poland have been published, although there are some reports of ATTR-FAP patients of Polish origin, who were identified in other countries [3–6]. Here, we describe retrospective studies of ATTR-FAP families diagnosed in Poland.

Methods and patients

All patients were diagnosed with ATTR-FAP clinically. All families and most patients were confirmed by genetic testing. Some patients were diagnosed in the past without the possibility of genetic confirmation, but they were included in this study to present a clinical picture of ATTR-FAP. The cohort was assessed between 1970 and 2019 at the Department of Neurology and the Outpatient Neuromuscular Clinic of the Medical University of Warsaw, and some clinical data was provided from other cooperating centres.

Demographics, clinical data, family history and additional examinations were collected in all patients. Available medical documentation of relatives who probably died from ATTR-FAP was also analysed. The study was approved by the Ethics Committee of the Medical University of Warsaw.

Results

We identified 16 patients from eight unrelated families with five different TTR mutations: 11 patients have died in the meantime, five are alive at the time of this publication. The first family has the Val71Ala (p.Val91Ala) mutation and consists of family members from four generations who have been followed up in our Department since 1970. The second family has the Ile73Val (p.Ile93Val) TTR mutation and was diagnosed with ATTR-FAP in 2017 as a result of a retrospective study of three deceased family members and identifying the carrier status among their children. Four unrelated families were found to have the Phe33Leu (p.Phe53Leu) TTR mutation. Other TTR mutations are: Val30Met (p.Val50Met) and Asp38Val (p.Asp58Val).

The first Polish family with the Val71Ala mutation had a genetic diagnosis in the Centre of Medical Genetics, University Hospital, Bratislava, Slovakia. Genetic and histological studies in a patient with Asp38Val TTR mutation were performed at the National Amyloidosis Centre (NAC) in London. One patient with the Phe33Leu TTR mutation was referred by cardiologists and genetic diagnosis was performed in the Institute of Cardiology in Warsaw. Genetic testing in the remaining families was performed at the Centogene Laboratory in Rostock, Germany. All data is set out in Tables 1 and 2 and in the supplementary material (Suppl. Tab. 1–2)

Val71Ala (p.Val91Ala) TTR mutation

The longest follow-up was available for a family with this mutation. Clinical data was collected from six members of this family; in three a TTR-FAP was the most likely diagnosis, but no clinical or genetic study was performed. The index case was a 38-year-old male hospitalised in our Department of Neurology in 1970 with severe sensory, motor and autonomic neuropathy as well as cachexia. Sural nerve biopsy revealed the presence of amyloid and the proband was initially diagnosed with amyloid light-chain (AL) amyloidosis. Only when his two siblings presented with similar symptoms, and amyloid deposits were found in the sural nerve biopsy, was the clinical diagnosis of ATTR-FAP amyloidosis made, although genetic testing was not available at that time to confirm the type of amyloid.

In the next generation, two sisters presented with visual symptoms. Subcutaneous fatty biopsies obtained from both siblings revealed amyloid, which stained positive with antibodies against transthyretin. Eventually in 2013 one of the sisters and her three asymptomatic adult children underwent genetic testing, which revealed heterozygous status for the Val71Ala mutation in the TTR gene in her and in one child. The clinical features in all affected members include severe progressive polyneuropathy with cachexia, and an early disease onset of between 29 and 44 years. The first manifestation of the disease was sensory neuropathy in four cases, autonomic involvement in one, and visual impairment in one. In our family, two sisters presented with marked visual symptoms, connected to large bilateral vitreous opacities, and both underwent vitrectomy [7]. During observations, cataract and secondary glaucoma were diagnosed. No cardiological information is available for this family, but from clinical notes it appears that no marked cardiomyopathy was observed. Eight patients died 4-11 years after disease presentation. The duration of ATTR-FAP in this family, without interventions modifying

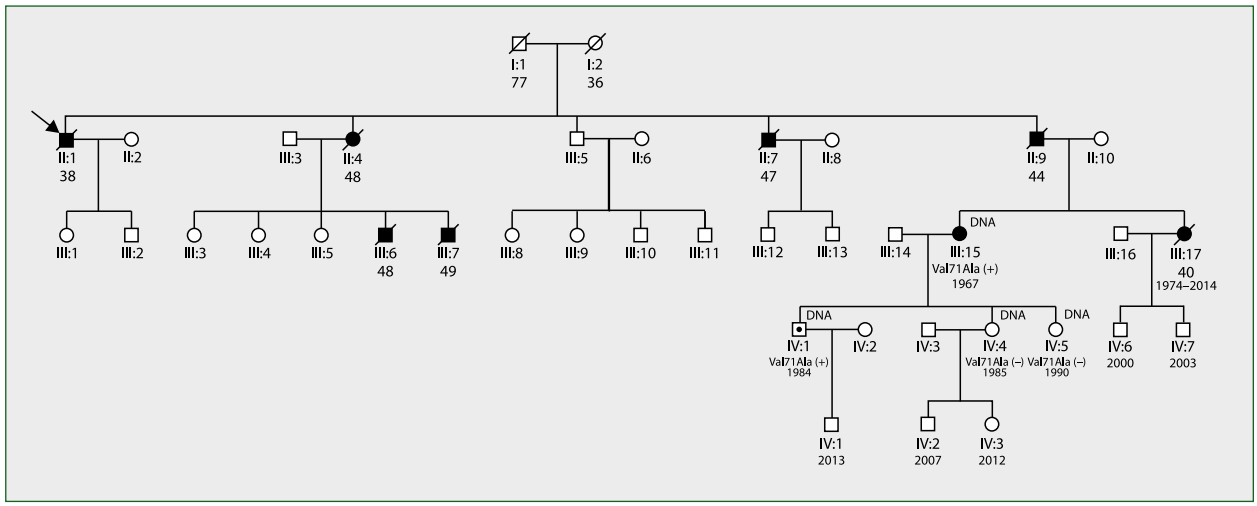

Figure 1. Pedigree of family with Val71Ala TTR mutation. Arrow denotes proband. Darkened square or circle denotes affected individual

disease course, was 4-9 years. Two patients (sisters No. 8 and 9 in Suppl. Tab. 1) who had the longest disease courses underwent liver transplantation four and six years after the initial presentation respectively. Survival after surgery was eight years (still alive) and five years. Currently, only one 34-year-old asymptomatic carrier is known in this family (Fig 1.). See Table 1 in the supplementary material for more information

Ile73Val (p.Ile93Val) TTR mutation

One family with three affected siblings (two brothers and one sister) were discovered to carry this TTR mutation. None of these three patients were diagnosed with TTR FAP during their lifetime. Medical documentation was reviewed, with the conclusion of a clinical course of disease consistent with ATTR-FAP. Clinical data of the patients is set out in the supplementary material — Table 2. The diagnosis of the ATTR-FAP was made when the carrier status for the Ile73Val TTR mutation was established among children of each of these three patients.

The siblings developed symptoms of ATTR-FAP in middle age – between the ages of 45 and 61. Their clinical picture was typical for ATTR-FAP with progressive polyneuropathy with thin fibres affected (pain) and autonomic symptoms.

Patient 1 was misdiagnosed with rheumatoid arthritis and fibromyalgia and treated for rheumatologic disorders. Amyloidosis was suspected a few months before the patient's death, but no diagnosis was reached.

Patient 2 had predominantly cardiac disease. During the last year of his life, he was misdiagnosed as AL amyloidosis and received chemotherapy.

Patient 3 suffered from polyneuropathy and cardiomyopathy. Nevertheless, his clinical course was complicated with comorbidities and the reason for his death was considered to be unrelated to ATTR-FAP. The father of the presented siblings died at the age of 58 from progressive cardiomyopathy and was immobile for a few years before his death, which suggests ATTR-FAP

Phe33Leu (p.Phe53Leu) TTR mutation

This mutation was identified in four unrelated men, who presented at ages between 54 and 66 (Tab. 1 and Tab. 2, patients 3–6). Two cases presented with predominant polyneuropathy, one with cardiomyopathy, and one with mixed phenotype. The two neuropathic cases had late onset, but rather rapidly progressive motor, sensory and autonomic polyneuropathy accompanied by loss of weight and asymptomatic cardiac involvement. Patient 3 had severe autonomic symptoms with orthostatic hypotension, frequent syncope and diarrhea. Due to the advanced stage of the disease (polyneuropathy stage II, walking on two crutches) the patient had no indications for tafamidis or liver transplantation and was treated with diflunisal. Patient 5 presented with predominant polyneuropathy, and due to a positive family history was diagnosed within one year of disease onset, at stage I of polyneuropathy and started treatment with tafamidis. Despite this, he developed also cardiomyopathy and died suddenly after three years of the disease. Patient 4 presented with late onset predominant cardiomyopathy. He was diagnosed at an advanced stage of cardiac disease and died soon after the genetic diagnosis confirmation. His clinical history included coronary artery bypass grafting (CABG) at age 64 and a minor stroke at age 66. Patient 6 presented with mixed phenotype and initially was diagnosed independently by neurologists and cardiologists. The idea for the diagnosis came from a neurologist (Dr. R. Śmierciak) aware of the clinical picture of ATTR-FAP. The patient was diagnosed at stage II of polyneuropathy; tafamidis was available for him as a compassionate use treatment with indication for cardiomyopathy.

All cases with the Phe33Leu mutation had a positive family history with relatives who died due to a progressive disease

Table 1. Demographic and general data of ATTR-FAP patients with Asp38Val, Val30Met and Phe33Leu TTR mutations

Family/ Patient	Mutation	Age at onset (yrs)	Gender	First manife-station	Delay in diagnosis (yrs)	Duration of disease at time of report (yrs)	Stage of disease at time of diagnosis	Family history	Course of disease and outcome	Treatment of ATTR--FAP
I/1	Asp38Val (p.Asp58Val)	51	M	Loss of wei-ght, numb-ness and paresthesia in feet	5	10	Polyneuropathy stage II[a]	DNA isolated from parents and brother negative, indicating *de novo* mutation. Patient has no children	Slowly progressive polyneuropathy, able to walk with rollator	Enrolled into clinical study with patysiran at age 56, symptomatic treatment (including parenteral feeding)
II/2	Val30Met (p. Val50Met)	50	M	Pain and paresthesia of calves and feet	5	Died	Polyneuropathy stage II[a]	No family history of ATTR-FAP, genetic analysis revealed seven asymptomatic carriers of mutation, including father of patient aged 82	Progressive polyneu-ropathy and devasta-ting diarrhoea; died aged 56 after 6.5 years of disease due to cachexia	Symptomatic treat-ment
III/3	Phe33Leu (pPhe53Leu)	54	M	Numbness of feet and calves	3.5	7.5	Polyneuropathy stage II[a]	Father died suddenly aged 65. Siblings of the patient's father: brother aged 60 and sister aged 70 died in course of devastating disease strongly suggestive of ATTR-FAP, brother of patient aged 58 – bilateral CTS for about ten years, sensory polyneuropathy for a year: **ATTR-FAP confirmed** (awaiting treatment)	Progressed to stage III[a] polyneuropathy, cachexia,	Diflunisal, symptomatic treatment
IV/4	Phe33Leu (pPhe53Leu)	64	M	Cardiac insufficiency	3	Died	Polyneuropathy stage I[a], cardio-myopathy NYHA 3	Sister and brother of patient died in course of disease strongly suggestive of transthyretin amyloidosis (both had polyneuropathy and cardiomyopathy)	Died aged 67 after three years of disease due to cardiomy-opathy	Symptomatic treatment
V/5	Phe33Leu (pPhe53Leu)	57	M	Pain followed by paresthesia of lower limbs, right CTS at age 56	0.5	Died	Polyneuropathy stage I[a]	Two sons of patient's uncle died aged 52 and 53; in both polyneuropathy and amyloidosis were diagnosed. Two sisters aged 56 and 58 carriers of TTR mutation, CTS in both	Progressed to stage II[a] polyneuropathy, died suddenly due to cardiomyopathy after three years of disease	Tafamidis, symptomatic treatment
VI/6	Phe33Leu (pPhe53Leu)	54	M	Pain and paresthesia of calves and feet	4	5	Polyneuropathy stage II[a]	Patient's aunt died aged 62; polyneu-ropathy and renal insufficiency were diagnosed. Two daughters aged 29 and 35 carriers of TTR mutation	Progressed to stage III[a] polyneuropathy,	Tafamidis, symptomatic treatment

CTS — carpal tunnel syndrome; M — male; NYHA — New York Heart Association classification
aClinical staging of TTR-FAP: stage I – walking unaided outside; stage II – walking with aid, stage III – wheelchair-bound or bedridden [1]

Table 2. Neurological data, systemic features and laboratory findings of ATTR-FAP patients with Asp38Val, Val30Met and Phe33Leu mutations at time of diagnosis

Family/ /Patient`s no	Mutation	Neurological findings	Autonomic involvement	NCS	Cardiac involvement	Biopsy	Cachexia	Other organ involvement related to ATTR-FAP
I/1	D38V (p.Asp58Val)	Sensory and motor symmetrical polyneuropathy with wasting of muscles; needs help to stand up, walks with rollator	Progressive diarrhoea, neurogenic bladder with urine retention, erectile dysfunction	Severe sensory and motor axonal polyneuropathy	Clinically mild cardiomyopathy reported on MR and ECHO concentric hypertrophy of left ventricle, NT-pro BNP elevation, ECG – normal	Fat biopsy – amyloid positive, phenotyping for TTR positive	Present BMI 17.5	Vitreous opacities, but with no clinical impact
II/2	Val30Met (p. Val50Met)	Sensory and motor symmetrical polyneuropathy with wasting of muscles, walks with one crutch	Diarrhoea, orthostatic hypotonia with episodes of syncope, urine retention, erectile dysfunction	Severe sensory and motor axonal polyneuropathy	Clinically without symptoms of cardiomyopathy Holter ECG – normal, ECHO – LV mild thickening of wall, NT proBNP elevation	In course of diagnostics gastric and rectal biopsy – no seeking amyloid (no Congo red staining)	Present BMI 17.9	no
III/3	Phe33Leu (p.Phe53Leu)	Sensory and motor symmetrical polyneuropathy with wasting of muscles, needs help to stand up, walks with parapodium	Diarrhoea, severe orthostatic hypotonia with frequent episodes of syncope, erectile dysfunction	Severe sensory and motor axonal polyneuropathy	Clinically mild cardiomyopathy; ECHO – diffuse mild hypokinesis, wall thickening, atrial enlargement, MR sparkling foci in cardiac muscle; Holter ECG – episodes of atrial tachyarrhythmia, NT proBNP elevation, ECG – low QRS voltage	Rectal and abdominal fat biopsy a year before diagnosis – negative for amyloid	Present BMI 16.2	Hoarseness
IV/4	Phe33Leu (p.Phe53Leu)	Motor proximal and distal lower limbs weakness started at age 66, walks independently, limited by cardiac insufficiency	Pin pupils, mild constipation, heartburn, mild nausea	Moderate axonal and demyelinating motor and sensory neuropathy	Severe cardiomyopathy, age 66 CRT-D implantation, NYHA 3, ECHO global hypertrophy NT proBNP elevation, ECG – AF, ventricular pacing	Trepanobiopsy and oral mucosa – amyloid positive, no phenotyping	No, but weight loss 20kg during course of disease BMI 22	Hoarseness, mild creatinine elevation and eGFR decrease, hypothyroidism
V/ 5	Phe33Leu (p.Phe53Leu)	Sensory and motor polyneuropathy with mild to moderate distal < proximal weakness, walking impaired but independent	Mild constipation, erectile dysfunction, heartburn	Moderate sensory and motor axonal polyneuropathy	Without clinical symptoms of cardiomyopathy Holter ECG – episodes of ventricular tachycardia and frequent SVES, ECHO – LV mild thickening, NT proBNP elevation	Not performed	No, but weight loss 20kg during course of disease BMI 20	Hoarseness, mild creatinine elevation and eGFR decrease
VI/6	Phe33Leu (p.Phe53Leu)	Sensory and motor symmetrical polyneuropathy with wasting of muscles, walks with AFO and one crutch; bilateral CTS preceded disease onset for about 10 years	Mild constipation	Severe sensory and motor axonal polyneuropathy	NYHA 2/3, ECHO and MR – restrictive cardiomyopathy typical for amyloidosis, Holter ECG – nsVT, low QRS voltage, NT proBNP elevation	Fat biopsy – amyloid suspicion, rectal biopsy – negative for amyloid	No	Hoarseness

AF — atrial fibrillation; AFO — ankle foot orthosis; BMI — body mass index; CRT-D — cardiac resynchronisation therapy defibrillator; CTS — carpal tunnel syndrome; ECG — electrocardiogram; ECHO — echocardiogram; eGFR — estimated glomerular filtration rate; EMG — electromyography; LV — left ventricle; MR — magnetic resonance; NCS — nerve conduction studies; NTproBNP — N-terminal pro brain natriuretic peptide; NYHA — New York Heart Association classification; nsVT — non-sustained ventricular tachycardia; SVES — supraventricular extrasystole

suggestive of TTR-FAP. At present, one brother of patient No. 3 has developed sensory polyneuropathy at age 57 and has been included in the number of patients affected by ATTR-FAP

Asp38Val (p.Asp58Val) TTR mutation

A 51-year-old male developed the typical clinical picture of ATTR-FAP with predominant sensory, motor and autonomic neuropathic symptoms (Tab. 1 and Tab. 2). Before admission to the Department of Neurology, Medical University of Warsaw, with symptoms of progressive polyneuropathy, the patient underwent six different biopsy procedures with inconclusive results. As the patient`s symptoms were highly suggestive of ATTR-FAP, and because genetic testing was not then available in Poland, his blood sample and fat biopsy were sent to the National Amyloidosis Centre (NAC) in London for genetic and histopathological studies. Amyloid deposits were identified on fat biopsy by pathognomonic green birefringence when stained with Congo red and viewed under crossed polarised light. The amyloid stained specifically with antibodies to transthyretin. Genetic analysis demonstrated that the patient was heterozygous for the Asp38Val (p.Asp58Val) TTR mutation. DNA isolated from the patient's parents and brother was negative, indicating a *de novo* mutation, which is uncommon in ATTR-FAP. Due to the advanced stage of the disease (polyneuropathy stage II – walking on two crutches), the patient had no indications for tafamidis or liver transplantation. He was enrolled into a randomised clinical trial and continues to take part

Val30Met (p.Val50Met) TTR mutation

Only one patient was found with the Val30Met mutation. No affected family members have been identified so far, although asymptomatic carriers were found (Tab. 2). The patient developed symptoms at 50 years of age and presented with the typical clinical picture of progressive sensory, motor and autonomic polyneuropathy, with severe, devastating diarrhoea, which immobilised him at home. Due to the advanced stage of the disease at diagnosis (polyneuropathy stage II – walking on two crutches), the patient had no indications for tafamidis or liver transplantation and due to severe gastrointestinal problems we did not introduce diflunisal. The patient died six years after disease onset at the age of 56, due to severe complications from cachexia

Discussion

We present here a retrospective study of ATTR-FAP in Poland. Finding only 16 individuals among 38 million people, the current population of Poland, with ATTR-FAP suggests that Poland is a non-endemic region with a very low frequency of ATTR-FAP. Nevertheless, awareness of this disease among neurologists and other specialists in Poland is low and we believe that this is why ATTR-FAP is underdiagnosed; all families except one were only diagnosed after 2014.

As the clinical picture of ATTR-FAP depends on the type of mutation, ethnicity and geographical region, we have discussed each TTR mutation separately. Despite the limited number of cases, we observed differences in the clinical features depending on the type of mutation. We observed that the Val71Ala mutation was associated with early onset, severe course, and marked ocular symptoms. Patients with other TTR mutations presented with a similar clinical picture of late onset progressive sensory and motor polyneuropathy with autonomic features and mild cardiomyopathy, with the exception of one case with the Phe33Leu mutation, who had predominant cardiomyopathy.

Val71Ala (p.Val91Ala) TTR mutation

The Val71Ala *TTR* mutation has been identified in families from several different countries (France, Spain, Netherlands, UK, Australia, Slovakia) [8–12], [Jan Chandoga – personal communication]. In the Netherlands, the Val71Ala mutation was responsible for 25% of cases [13]. In all reported families, visual symptoms were noted, which sometimes preceded polyneuropathy. Some of these patients underwent vitrectomy [10, 11]. In our family, two sisters presented with marked visual symptoms, connected to large bilateral vitreous opacities, and both of them underwent vitrectomy [7].

TTR is produced in the liver, choroid plexus and the eye, probably in the retinal pigment epithelium [1, 12]. In FAP patients with the common TTR mutation Val30Met, vitreous opacities are an infrequent and late feature [1]. An explanation for the high prevalence and early occurrence of vitreal opacities associated with Val71Ala is unavailable. It is possible that in the microenvironment of the eye, certain TTR variants may be unstable and are therefore more likely to be amyloidogenic [12]. Thus, ophthalmological examination could provide important clues in the diagnosis of ATTR-FAP in patients with the Val71Ala mutation.

Our family presented with an early onset between the ages of 29 and 44 and somewhat rapid progression – in four of nine affected family members, disease duration was no longer than six years and all patients died before the age of 50, with the exception of one patient who had a liver transplantation (LT) and is alive at the age of 51. In other reported families with this mutation, early and late onsets were observed between the ages of 32 and 56. Disease duration was rarely reported. Based on available descriptions, the Val71Ala TTR mutation appears to be associated with a severe form of TTR-FAP, with progressive wasting, polyneuropathy, autonomic dysfunction and vitreous opacities that may lead to blindness, but no marked cardiomyopathy has been observed [7–12]. Dutch investigators observed the development of cardiac symptoms, with NT proBNP elevation in 11% of their patients with the Va71Ala mutation, but milder than in Val30Met mutation patients [14].

The clinical course in our family without and with LT shows a slower course of disease in the latter, suggesting the

effectiveness of LT in ATTR-FAP caused by the Val71Ala mutation, although it does not stop disease progression. This procedure was performed in our patients before pharmacological treatment was available. These two sisters had the longest course of disease in the family (one sister died 11 years after the onset of symptoms, the other is still alive after 12 years of disease). In the FAP World Transplant Registry, the Val71Ala mutation, represented by 13 cases, showed the best 10-year survival rate after LT (85%) among the nine most common nonVal30Met mutations [15]. The data from our family is consistent with these results.

A clinical course with an emphasis on ocular symptoms, as in these two sisters, has been described in another publication; TTR mutation was not confirmed at the time of that report [7]

Ile73Val (p. Ile93Val) TTR mutation

So far, only two families with the Ile73Val mutation have been reported: in Taiwan and Bangladesh [16, 17]. The Taiwanese patient was a man who began symptoms of sensory and motor neuropathy with early gastrointestinal autonomic dysfunction around the age of 50. He also presented with weight loss, and echocardiogram revealed left ventricular failure with global hypokinesia. His mother had amyloid cardiomyopathy, which was confirmed by a biopsy, and died in her sixth decade [17]. The female patient reported from Bangladesh had a very similar presentation as well as her father and two siblings. They all had onsets in their fifth decade [16].

In both the Taiwanese and the Bangladeshi patient, pain was not a significant feature of the neuropathy. [17]. However, in our family patient 1 suffered from severe pain for a few years without aproper diagnosis, perhaps related to small nerve fibere involvement. Based on our cases and previous reports, the Ile73Val TTR mutation seems to cause mixed neuropathic and cardiologic phenotype with onset in the 5–6th decade of life.

Phe33Leu (p.Phe53Leu) TTR mutation

Phe33Leu is a rare mutation, only ever reported in families from the Baltic regions (unrelated Polish-American patients) [3–5, 18] Sweden [19], Taiwan [20], China [21] and Israel [22].

Typical clinical features associated with the Phe33Leu TTR mutation include axonal polyneuropathy with marked autonomic involvement and cardiomyopathy with the onset of symptoms in middle age. Bilateral carpal tunnel syndrome (CTS) was also reported [3, 19]. The clinical features in our families were consistent with previous reports. The patient reported by Myers et al. [3] initially presented at the age of 65 with symptomatic ascites, mild peripheral neuropathy, carpal tunnel syndrome and mild cardiomyopathy. The FAP World Transplant Registry reported two LT and two combined liver and heart transplantations in patients with this mutation who had cardiac and neuropathic phenotype [15]. Reports of the Phe33Leu mutation in patients from the Baltic regions, including families of Polish descent [3–5, 18], together with our cases, may suggest a common origin of this mutation in this region.

Asp38Val (p.Asp58Val) TTR mutation

This rare mutation was found in one case and probably occurred *de novo*, which is uncommon in ATTR-FAP. To the best of our knowledge, this variant has previously been identified only in a Ghanaian male and in one large Spanish family [5, 23]. The Ghanaian male presented with predominant polyneuropathy, but also heart and spleen involvement at age 58 , which is similar to our patient [5]. The phenotype in the Spanish kindred was associated with late-onset amyloidosis and predominant heart involvement with variable degree of peripheral and autonomic polyneuropathy. Two affected members were described. A 61-year-old male who had cardiomyopathy and required a pacemaker, at the age of 66 developed severe axonal motor and sensory polyneuropathy and autonomic symptoms, and at the age of 71 was diagnosed with advanced heart failure secondary to amyloid cardiac infiltration. The other affected family member presented with significant heart involvement at the age of 66 and some autonomic symptoms (orthostatic hypotension, diarrhoea) but no motor and sensory polyneuropathy. Thus, unlike our patient, the previously reported cases with this mutation had more advanced cardiac features.

Val30Met (p.Val50Met) TTR mutation

One patient had the Val30Met mutation, with no family history. The patient developed symptoms at age 50, which is in between early and late onset described for the Val30Met TTR mutation. Our patient presented with the typical clinical picture of progressive sensory, motor and autonomic polyneuropathy [24, 25]. Similar to Swedish patients from endemic areas for the Val30Met TTR mutation who present late in life, we also observed incomplete penetrance as the probands` father, who is now 82, is an asymptomatic carrier [26]. Non-endemic area, rather rapid disease progression, and incomplete penetrance is more characteristic for a late onset Val30Met TTR mutation [27].

Conclusion

ATTR-FAP is a heterogeneous disease with substantial variations in age at onset, organ involvement, and variable penetrance, depending on the pathogenic TTR mutation and other unknown genetic and environmental factors. TTR-FAP is frequently diagnosed late, especially in non-endemic areas, because the disease is difficult to recognise due to phenotypic heterogeneity, systemic presentation and low awareness of this entity among physicians [25].

Polish cases with ATTR-FAP described here presented with heterogeneity which is typical for non-endemic areas. The Phe33Leu TTR mutation was the most common, found in four unrelated families. This mutation was also described in patients of Polish descent [3–5, 18]. The previously reported patient of Polish origin by Hagenacker et al. [6] had the p.Glu81Lys TTR mutation, which was not identified in our

study. Difficulties in determining the presence of amyloid deposits in a biopsy material in many of our patients shows how vital is the expertise of highly specialist centres dedicated to the diagnostics of amyloidosis.

Despite better diagnosis of Polish families since 2014, the long period from the onset of symptoms to diagnosis, and in some patients the absence of a correct diagnosis before death, highlight the need for education about this rare disease among physicians.

In recent years, new pharmacological therapies have been developed for ATTR amyloidosis, making a great advance in the treatment of this disease. Since TTR is mainly produced by the liver, the first therapeutic approach was liver transplantation to inhibit mutated TTR production and amyloid formation. Pharmacological therapies act either as kinetic TTR stabilisers or gene-silencing drugs. TTR stabilisers prevent the circulating protein from dissociating and conformational changes that lead to its aggregation as amyloid. Tafamidis is the first oral kinetic stabiliser, approved in 2011 in Europe for the treatment of hATTR in adults with early stage of polyneuropathy. Recently, tafamidis received approval also for transthyretin cardiomypathy treatment. Another agent acting as TTR stabiliser is diflusinal, a nonsteroidal anti-inflammatory drug the efficacy of which has been proven in clinical trials. However, its benefit is limited by side effects, and it is used off-label [1, 28].

New gene-silencing drugs, inhibiting TTR synthesis: inotersen, antisense oligonucleotide therapy, and patisiran, a small interfering RNA therapy, received approval in Europe in 2018. These therapies have demonstrated efficacy in patients with early stage and also more advanced disease, leading to delayed or halted progression of neurological manifestations.

Disease-modifying therapies should be initiated at the early stages of disease, because they may inhibit or slow the progression of neuropathy, while improvement is minimal. In the case of tafamidis or liver transplantation, patients who received treatment later (stage II polyneuropathy) did not benefit from treatment, while with therapies that inhibit transthyretin synthesis, the improvement was less than in patients who started treatment earlier [28, 29].

The fact that new pharmacological therapies with a good chance of changing the natural course of the disease are available constitutes a strong argument for the early recognition of ATTR-FAP.

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