

Different phenotypes of transthyretin-associated familial amyloid polyneuropathy due to a mutation in p.Glu109Gln in members of the same family

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ABSTRACT

Transthyretin-associated familial amyloid polyneuropathy (TTR-FAP) is an unusual but life-threatening disease that is autosomal dominant inherited and involves the mutation of the transthyretin (TTR) gene. A total of 26 patients with TTR-FAP and different mutations, including the p.Glu 109Gln mutation (previously annotated p. Glu89Gln), were previously reported in Turkey. Herein, we reported two patients from the same family who had the same p.Glu 109Gln mutation but had different clinical phenotypes. The clinical picture mainly involved polyneuropathy in one patient and cardiac involvement in the other patient. This case report mentions that TTR-FAP can cause different clinical phenotypes, even due to the same mutation and even in the same family.

Keywords: Familial amyloid polyneuropathy; pGlu109Gln mutation; transthyretin; Turkish family.

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Transthyretin-associated familial amyloid polyneuropathy (TTR-FAP) is an autosomal dominant inherited disorder characterized by a mutation in the gene that encodes the transthyretin (TTR) protein [1]. As a result of the mutation, the tetrameric structure dissociates, and the protein partially unfolds, converts to misfolded monomers, accumulates in tissues, and becomes toxic to the body. The accumulation causes clinical findings in tissues such as the heart, eyes, kidneys, and nervous system [2]. Cardiological, ophthalmological, nephrological, and neurological problems are the prominent outcomes due to the mutation types. Although different types of TTR-FAP mutations are heterogeneously distributed, p.Val50Met (previously annotated p.Val30Met) is the most prevalent TTR-FAP mutation in the world [3].

Although the typical clinical outcome of the disease is generally a sensorimotor neuropathy with autonomic findings, different mutations may cause different clinical manifestations [4]. This difference not only occurs among the different types of mutations but also can be observed in family members with the same mutation [5].

In our cases, the same p.Glu109Gln mutation was detected in two patients, while the clinical outcomes differed among the patients. In one of our cases, the clinical complaints started with carpal tunnel syndrome, and polyneuropathy became prominent overtime. In the other case, which involved the sister of the patient in the first case, the initial findings included symptoms caused by neuropathy, while cardiomyopathy was predominant in the clinical picture.



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CASE REPORT

Case 1 – A 66-year-old female patient presented with numbness in both hands and was diagnosed with carpal tunnel syndrome. As she had a family history of a brother with polyneuropathy who died several years prior, she was followed for a possible polyneuropathic process. Her complaints progressed in the following year, and she defined numbness in both hands and feet, which was followed by weakness in the distal part of all limbs. A neurological examination revealed distal and symmetrical weakness of all four limbs, glove and stocking sensation loss, and diminished Achilles reflexes.

The patient's family history was investigated in detail. In addition to the history of her brother mentioned above, her mother died due to cardiac dysrhythmia in her 60s. The patient also mentioned that her sister was complaining of numbness in the limbs.

An electrophysiological examination revealed motor and sensory axonal neuropathy that was predominant in her lower extremities. In this patient in whom there was a suspicion of familial amyloid polyneuropathy (FAP), a pathologic heterozygous c.325G>C mutation in the TTR gene (NM_000371) located at chromosome 18q12.1, altering the encoded amino acid, p.Glu109Gln, in the TTR protein (NP_000362) was detected. The patient's cardiological, nephrological, and ophthalmological examinations were normal, and the patient was diagnosed with Stage I FAP.

Case 2 – A 67-year-old woman (the sister of the patient in the first case) was referred to our neurology outpatient clinic due to bilateral numbness in her hands and feet. She mainly complained of dyspnea, which was related to effort that began nearly 2 years prior, and she had experienced sensorial loss beginning 1 year prior. Her neurological examination revealed bilateral glove and stocking sensation loss and mild weakness in the limbs. Deep tendon reflexes were absent. The electrophysiological results revealed sensorimotor axonal polyneuropathy. Her genetic analysis revealed a heterozygous p.Glu109Gln mutation. Because of the investigation of the dyspnea etiology, a cardiologist was consulted, and her cardiological examination and echocardiographic findings demonstrated a normal ejection fraction but the left ventricular hypertrophy, Grade 3 diastolic heart failure, and a spotty myocardial view. In addition, due to differential diagnoses for diastolic heart failure, cardiac magnetic resonance imaging (MRI) was performed. The

MRI findings were consistent with myocardial amyloid deposition, a minimal increase in trabeculation in the left ventricle, mild grade pericardial effusion, and moderate thickening of the interventricular septum.

The patient was able to walk without assistance with sensory and motor symptoms and was diagnosed with Stage I TTR-FAP. However, her cardiac complaints were prominent, and she was hospitalized in the cardiology department. Tafamidis treatment was considered for both patients.

We received informed consent from each of the two patients and, thus, did not apply for ethical approval.

DISCUSSION

TTR-FAP develops as a result of amyloid fibrils in the mutant TTR protein collapsing into the various tissues and organs, primarily the peripheral nerve cells. The result of mutations in the TTR gene is a loss-of-function protein, which is converted to insoluble amyloid fibrils. This autosomal dominant disease includes more than 120 mutation types [4]. The most common symptom, as in our patient, is numbness and paresthesia in the feet. Different types of mutations may cause different clinical findings. In patients with p.Glu109Gln (p.Glu89Gln) mutations, carpal tunnel syndrome and neuropathy could be the presenting clinical symptom [6]. First, amyloid affects small nerve fibers, especially those in the lower limbs, and pain and temperature sensation loss occur in the feet. Overtime, involvement spreads to the upper limbs, and loss of light and deep touch sensation, muscle strength, and imbalances occur. Amyloid may accumulate locally in the peripheral nervous system in places such as the cranial nerves and nerve trunk or plexus. In some cases, the initial symptom can be carpal tunnel syndrome, such as in our case 1. Peripheral neuropathy reveals autonomic nerve system dysfunction. Related autonomic dysfunction, anhidrosis, sexual impotence, disturbances in gastrointestinal motility (most commonly diarrhea alternating with constipation but nausea and vomiting as well), orthostatic hypotension, and neurogenic bladder also occur. Cardiac, gastrointestinal, urinary, and ophthalmological problems can also be observed during the course of the illness [7].

The diagnosis of cardiac involvement requires cardiac tissue biopsy, but because this procedure is invasive, electrocardiography, echocardiography, and cardiac MRI are also useful. There are many different signs of cardi-

ac amyloidosis. Dysrhythmias are one of the findings, and atrial fibrillation is the most common. The mother of our patients died from dysrhythmia. According to the echocardiographic signs, a thick-walled ventricle with a speckled appearance of the myocardium, small left ventricular chamber volume, valve thickening, atrial enlargement, pericardial effusion, pleural effusions, and dilated vena cava can be observed [8]. Although cardiac MRI is a more precise and detailed technique than echocardiography, its use is limited due to its high cost. Late gadolinium enhancement imaging is identified in cardiac amyloidosis related to myocardial injury. Late gadolinium enhancement imaging with global sub-endocardial, diffuse, and focal foci notes differences from the other causes of myocardial injury [9].

Ocular manifestations include vitreous opacities, which can cause gradual vision loss, trabecular obstruction, which is responsible for chronic open-angle glaucoma, and scalloped pupils. Nephritic syndrome and progressive renal failure may be associated with renal abnormalities. Other systemic problems are cachexia related to gastrointestinal dysautonomia, bed sores, venous thrombosis, pulmonary embolism related to immobility, and mortality. Different clinical presentations due to different mutations in familial amyloid neuropathy have been reported. The most common mutation in the world is p.Val30Met (p.Val50Met), and the second most common mutation is p.Glu109Gln (p.Glu89Gln). Previously, 26 individuals from Turkey with heterozygous and homozygous p.Val30Met (p.Val50Met), heterozygous p.Glu89Gln (p.Gly109Gln), p.Gly53Glu (p.Gly73Glu), p.Glu54Gly (p.Glu74Gly), and p.Gly47Glu (p.Gly67Glu) mutations have been reported [6, 10]. Our patients also had heterozygous Glu89Gln (p.Glu109Gln) mutations. The clinical glove and stocking sensation loss, carpal tunnel syndrome, distal muscle weakness, loss of deep tendon reflexes, and cardiac involvement in our patients were compatible with the clinical presentation of familial amyloid neuropathy in previously reported families [6]. In addition, the same mutation may rarely cause different clinical pictures [5].

Herein, we presented two individuals with the same mutation from the same family. One of our patients had polyneuropathy as the main clinical manifestation, while the other additionally had neuropathy; nevertheless, cardiac involvement was the predominant finding.

At present, approaches to treatment are determined according to the disease stages, and treatment is recom-

mended in Stage I [11]. Since both of our patients were symptomatic but could walk without assistance, their disease stages were consistent with Stage I according to Coutinho et al. [12], and treatment with tafamidis was appropriate. In Stage 0, patients are asymptomatic but have a variant form of the TTR gene and amyloid deposits; in Stage I (mild), patients are ambulatory; in Stage II (moderate), patients are ambulatory but require assistance; and finally, in Stage III (severe), patients are bedridden or depend on a wheelchair [12]. Tafamidis stabilizes the TTR gene by restricting the transformation of native TTR tetramers into monomers, and this restriction is a critical step for inhibiting TTR amyloid fibril formation [13]. The use of this treatment is only recommended in Stage I due to the lack of data supporting the treatment in patients with Stages II and III disease.

Conclusion

TTR-FAP is a life-threatening disease, and early diagnosis and initiation of treatment is important. Therefore, patients who are admitted to the neurology department with complaints of neuropathy or neuropathic pain should be questioned for autonomic findings and about their family history, and a detailed systemic examination should be performed. It also should be kept in mind that the same mutation may cause different phenotypes, so members of the same family can present with different clinical pictures.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report.

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