A Novel Variant Mutation of Transthyretin Ile73Val-Related Amyloidotic Polyneuropathy in Taiwanese

Ming-Feng Liao, Hong-Shiu Chang

Abstract-

Purpose: Familial amyloidotic polyneuropathy (FAP) is an inherited disease caused by deposition of mutant amyloid proteins in the peripheral nerves. Abnormal transthyretin (TTR) accounts for protein aggregation in the majority of FAP. Val30Met is the most common *TTR* gene-mutation reported in different ethnic populations. In Taiwan, Ala97Ser mutation is probably a major hot-spot of *TTR* mutations. On the other hand, Ile73Val mutation was only reported in one Bangladeshi family. We reported here the first patient of amyloidotic polyneuropathy with Ile73Val *TTR* mutation in Taiwan.

Case Report: This patient had symptoms and signs of sensory motor polyneuropathy and early gastrointestinal autonomic dysfunction since around 50 years old. A nerve conduction velocity (NCV) study showed typical axonal sensory-motor polyneuropathy. A standard autonomic function test revealed orthostatic hypotension and was compatible with cardiovascular autonomic dysfunction. There was also impaired sudomotor activity. An echocardiogram study suggested amyloidotic restrictive cardiomyopathy. A genetic analysis revealed Ile73Val *TTR*R mutation.

Conclusion: We reported the first patient with Ile73Val *TTR* mutation in Taiwan, who had earlier gastrointestinal dysfunction. Similar to the Bangladeshi patient reported in the previous article, painful neuropathy, a feature typically presented in more common *TTR* gene mutations, is absent.

Key Words: familial amyloid polyneuropathy, transthyretin

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INTRODUCTION

Familial amyloidotic polyneuropathy (FAP) is an inherited disease caused by disposition of abnormal proteins. This protein accumulation most frequently comes from aggregation of denatured transthyretin (TTR). Other uncommon FAP associated proteins include mutants of apolipoprotein AI and gelsolin[1-3]. TTR is a liver-synthesized tetrameric protein which transports thyroxine and retinol-binding protein in serum[1,3]. Among the long list of *TTR* gene mutations, Val30Met is the most common form which accounts for 50% of mutations worldwide across different ethnic populations[1,2,4]. In Taiwan, Ala97Ser mutation is probably a major hot-spot of *TTR* mutations[5,6]. A point mutation of Leu55Pro had also been described in two families[7,8].

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Ile73Val mutation has never been described in Taiwan and had only been reported in one Bangladeshi family in other populations[9]. We here reported the first patient of amyloidotic polyneuropathy with Ile73Val *TTR* mutation in Taiwan.

CASE REPORT

A 52 year-old man had a history of progressive numbness and atrophy in the bilateral feet for 2 years before he visited our outpatient clinic. He was capable of walking independently in spite of mild weakness of the bilateral lower extremities. Before the onset of sensory disturbance, he had intermittent postprandial epigastric fullness for more than 10 years. The gastrointestinal upset including vomiting and constipation along with a poor appetite is becoming more frequent and prominent in the recent 1-2 years. A 20-kg body weight loss in recent half an year was noted. There was no orthostatic dizziness, respiratory distress or urinary sphincter control problems. His mother had amyloid cardiomyopathy which was confirmed by a biopsy and died in her 6th decade. Up to now, the other family members do not have the symptoms or signs suggestive of amyloidosis. The family pedigree is shown in Fig. 1.

On physical examination, there was no cardiac arrhythmia, heart murmurs, breathing sound abnormality or edema. A neurological examination revealed weakness (Medical Research Council Scale: 4) and muscular atrophy in the bilateral tibialis anterior, and gastrocnemius. Areflexia was noted on both knees and ankles. Temperature and pain perceptions were decreased on the bilateral lower legs but there was no painful dysesthesia, hyperalgesia or allodynia. The motor and sensory functions of upper extremities were relatively spared. An ophthalmologic examination showed mild optic atrophy without cataract. The basic blood biochemistry and hemogram were unremarkable. A cerebrospinal fluid study (CSF) showed mildly elevated protein (69.8 mg/dL) without pleocytosis. No proteinuria was found in a urine analysis. The serum levels of thyroid hormones, vitamin B12, cryoglobulin, anti-nuclear antibody, rheumatic factor and tumor markers including cancer antigen 19-9, carcinoembryonic antigen, prostate specific antigen, α-fetoprotein and squamous cell carcinoma associated antigen, were all within the normal limits. No paraproteins were found in a serum protein electrophoresis.

His electrocardiography (ECG) showed prolonged PR (208 ms) and QT/QTc (414 ms / 471 ms) intervals (Table 1). An echocardiogram revealed left ventricular failure with global hypokinesia (Ejection fraction = 33.9%), left ventricular diastolic dysfunction, marked left ventricular hypertrophy with a sparkling appearance,

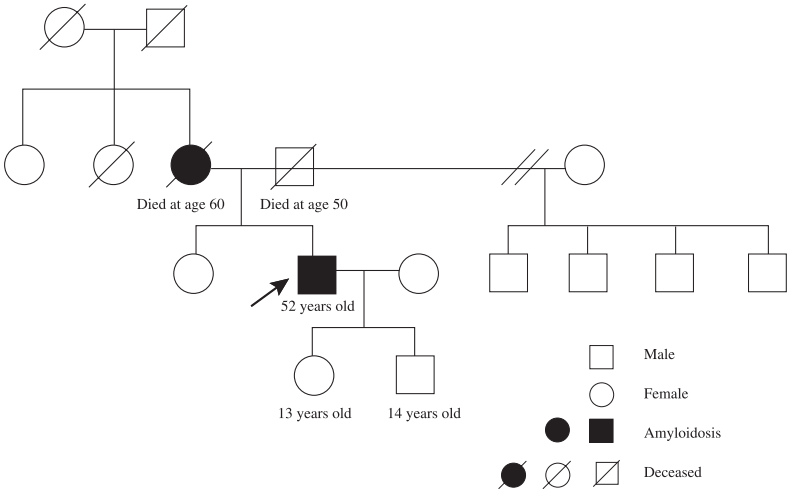

Figure 1. Pedegree of the patient's (arrow) family. The patient's mother had amyloid cardiomyopathy and died in her 6th decade. Other family members do not have the symptoms or signs suggestive of amyloidosis.

Table 1. the Electrocardiography (ECG) study showed prolonged RP and QT intervals in the past 5 years.

EKG date	HR (/min)	PR (ms)	QRS duration (ms)	QT/QTc (ms)
(Normal limit)		(<200ms)	(<160ms)	(<440ms)
200706	78	170	86	414/471
201208	85	208	108	426/506

Table 2. Compared the nerve conduction velocity (NCV) studies in 2001 and 2011. The NCV study in 2001 was normal, and the study in 2011 showed a typical length-dependent sensory-motor polyneuropathy.

Motor NCV	DL (ms)		CMAP (mV)		NCV (m/s)		F-wave (ms)	
	2001	2011	2001	2011	2001	2011	2001	2011
Median (L wrist)	3.5	5.4	7.4	3.5	N/A	48	N/A	34
Ulnar (L wrist)	2.4	3.1	10.0	5.3	N/A	54	N/A	33
Peroneal (L ankle)	3.9	NR	4.5	NR	N/A	NR	N/A	NR
Tibial (L ankle)	4.0	4.6	12.0	0.4	N/A	36	N/A	NR

Sensory NCV	DL		SNAP (uV)		NCV (m/s)		H-reflex (ms)	
	2001	2011	2001	2011	2001	2011	2001	2011
Median (L wrist)	2.3	4.3	42.8	9.9	63	41	N/A	NR
Ulnar (L wrist)	1.8	2.8	27.7	4.8	54.6	41		
Sural (L ankle)	2.9	NR	18	NR	48.3	NR		

DL: distal latency. CMAP: compound motor action potential. SNAP: sensory nerve action potential. NR: no response. N/A: not available. L wrist: stimulation on the left wrist region. L ankle: stimulation on the left ankle.

increased left ventricular mass (461.6 gm) and interventricular septal thickness (24 mm), of which all these features were compatible with amyloidotic restrictive cardiomyopathy. An endoscopy study showed mild chronic gastritis. A further endoscopic retrograde cholangiopancreatography (ERCP) suspected Oddi sphincter dysfunction without organic lesions.

His motor nerve conduction velocity (NCV) study showed no response in the bilateral peroneal nerves and decreased amplitude of the compound motor action potentials (CMAP) with normal NCV in the bilateral tibial nerves. The motor NCV study on the upper extremities revealed mildly prolonged distal latency (DL), decreased amplitude of CMAP and slow NCV in the bilateral median nerves. The sensory NCV study showed absence of sensory nerve action potentials (SNAP) in the bilateral sural nerves, and mildly decreased amplitude of SNAP and slow sensory NCV in the bilateral median and ulnar nerves. An electromyography study demonstrated active denervation and chronic reinnervation changes in the tibialis anterior and gastrocnemius. These electrophysiological studies were comparable with typical length-dependent, predominantly axonal sensory-motor polyneuropathy. Similar NCV studies in a health examination 10 years ago were normal (Table 2). A standard battery of autonomic function tests was carried out. It included arithmetic, cold, and exercise pressor tests, an orthostatic stress test, R-R interval variability, and sympathetic skin response tests. The result showed orthostatic hypotension and was compatible with cardiovascular, both sympathetic and parasympathetic, dysfunction. There was also impairment of sudomotor activity in the four limbs.

A rectal biopsy was suggested but the patient refused this procedure. A genetic analysis by sequencing the whole *TTR* gene showed a heterozygous A-to-G mutation on exon 3 at codon 277, which changed 73th amino acid from isoleucine (coded by ATA) to Valine (coded by GTA) (Fig. 2). Other family members declined further genetic analysis.

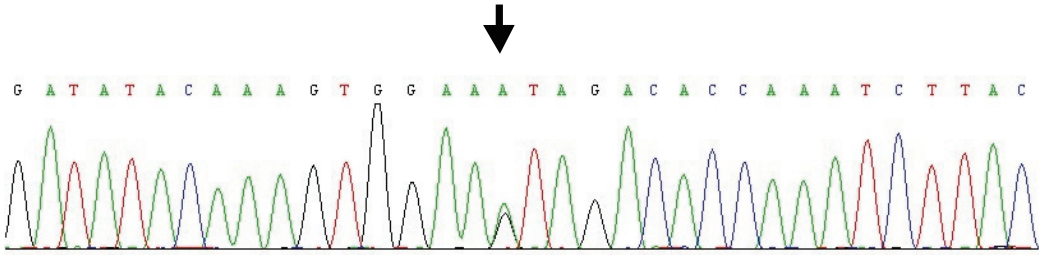

Figure 2. The sequence of the *TTR* gene showed heterozygous mutation on exon 3 at codon 277, from wild-type ATA (Ile) to mutant GTA (Val) (arrow).

DISCUSSION

We reported the first case of FAP with Ile73Val *TTR* mutation in Taiwan. This conclusion is supported by the characteristic clinical manifestations, the laboratory tests, a positive familial history and the genetic analysis. The key clinical presentations of this patient are axonal sensory-motor polyenuropathy and autonomic dysfunction which are typical of FAP. Restrictive cardiomyopathy revealed by the echocardiography was compatible with a diagnosis of amyloid cardiomypathy, a feature of which was shared by his mother. The genetic study showing an Ile73Val missense mutation in the *TTR* gene provided a genetic basis for his disease and further substantiated the diagnosis of FAP. The missense *TTR* point mutation is possibly inherited form his mother who was also affected with amyloidosis.

Ile73Val *TTR* gene mutation had only been reported in one Bangladeshi family[9]. The patient of the Bangladeshi family had similar clinical presentations as those of our patient. She developed severe sensory-motor polyneuropathy, and cardiomyopathy around the age of 55. These were also preceded by gastrointestinal disturbances including nausea, gastroparesis and diarrhea[9].

Val30Met, Leu55Pro and Ala97Ser mutations usually have different clinical manifestations[2,4-8]. Patients of Val30Met mutation typically have sensory and autonomic polyneuropathy around the age of 30, and the disease progressed slowly to the terminal stage for more than 10 years[2,4]. The disease of the patients with Leu55Pro mutation started at younger age and progressed with a precipitating clinical course[7,8]. The patients usually began to have postural dizziness, syncope, gastrointestinal symptoms, and length-dependent sensory-motor polyneuropathy around the age of 20. The condition rapidly deteriorated and the patient became bedridden and died within the next 1-2 years[7,8]. By contrast, the onset of neurological manifestations in patients with Ala97Ser mutation is similar to that of our patient. The symptoms or signs of polyneuropathy, autonomic dysfunction, and cardiac involvement usually began around the age of 50~60[5,6]. On the other hand, the clinical course of Ala97Ser *TTR* mutation usually progressed more rapidly compared to those of Val30Met mutation in other ethnic populations[4-6]. The patients usually required a wheelchair for ambulation within 2.5-8.4 years[5,6]. The nature course of our patient is currently unknown and long-term observation is indicated.

Another interesting feature is the absence of painful neuropathy in our patient and the Bangladeshi case. FAP is an important differential diagnosis of painful neuropathy[10]. Painful dysesthesia or allodynia have been reported to 73% patients with Val30Met mutation[4,5]. Neuropathic pain has also been reported in case series with Ala97Ser mutation[5].

The autonomic dysfunction of our patient preceded the manifestations of sensory-motor polyneuropathy. Gastrointestinal disturbances including epigastric fullness, anorexia, constipation, and diarrhea were common in patients with FAP[1,2,6,11]. Some *TTR* point mutations, such as Cys10Arg, Pro24Ser, Val30Met, et al[11], were

Table 3. Clinical presentations of the patients with Ile73Val, Ala97Ser, and Val30Met mutations of *TTR* gene.

Mutation	Ile73Val (Our patient)	Ile73Val (Jacobson)[9]	Ala97Ser (Hsieh)[5] (n=19)	Ala97Ser (Liu)[6] (n=5)	Val30Met (Ando) [2,4] (n=169)
Age of initial symptoms (y/o)	50	50	N/A	51.2	34.8
Age of diagnosis (y/o)	52	55	59.5	59.8	N/A
Sensory symptoms (%)					
Carpal tunnel syndrome	-	N/A	N/A	80%	25%
Paresthesia	+	+	100%	100%	100%
Pain (Allodynia)	-	-	57.9%	0%	73%
Autonomic dysfunction (%)					
Orthostatic hypotension	+	N/A	73.7%	40%	82%
Gastrointestinal symptoms	+	+	94.7%	100%	88%
Genital urinary symptoms	-	N/A	31.6%	20%	92%
Cardiac involvement (%)					
Heart failure symptoms	-	N/A	N/A	40%	60%
Cardiac hypertrophy	+	+	N/A	60%	N/A
Arrhythmia	-	-	N/A	60%	64%
Peace marker dependent	-	-	N/A	40%	N/A
Renal involvement (%)	-	+	N/A	20%	5%

N/A: not available. +: with the symptoms. -: without the symptoms.

more susceptible to gastrointestinal involvement. The gastrointestinal involvement in FAP is likely due to amyloid protein deposition in the nerves innervating the gastrointestinal tract rather in the mucosa[11]. Some reports emphasized that some patients had earlier gastrointestinal symptoms than sensory disturbance[1-3,6]. The early gastrointestinal symptoms suggest earlier involvement of the autonomic nerves in the gastrointestinal tracts than the peripheral nerves in FAP. Clinical presentations of the patients with Ile73Val, Ala97Ser, and Val30Met *TTR* mutation were summarized on Table 3.

In summary, we reported the first patient with FAP carrying Ile73Val *TTR* mutation in Taiwan. The clinical presentations were typical of FAP. These symptoms and signs included axonal sensory-motor polyneuropathy, early autonomic dysfunction involving gastrointestinal systems, and cardiomyopathy. The onset of the neurological manifestations associated with polyneuropathy was at the age of 50, which is a little younger compared to that of FAP with Ala97Ser mutation previously reported in Taiwan. The absence of painful neuropathy in our patient and the case with the same Ile73Val mutation in the Bangladeshi family is different from those of FAP associated with other common TTR mutations.

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