Hereditary ATTR Amyloidosis with Cardiomyopathy Caused by the Novel Variant Transthyretin Y114S (p.Y134S)

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Abstract:
We report the clinical features of a patient with hereditary ATTR amyloidosis associated with a novel mutation (Y114S, p.Y134S). A 65-year-old Japanese man was admitted to our hospital after a 3-year history of progressive dyspnea on exertion. Five years previously, he presented dysesthesia in both hands caused by carpal tunnel syndrome. A genetic analysis revealed a base pair substitution of adenine to cytosine in the second codon of exon 4, residue 114, in the TTR gene (c.401A>C). The clinical characteristics were progressive cardiomyopathy with a poor vital prognosis, late onset, sporadic case, bilateral carpal tunnel syndrome, hypothyroidism, and small fiber neuropathy.

Key words: amyloid, transthyretin, mutation, cardiomyopathy, tafamidis

Introduction
Hereditary transthyretin (ATTR) amyloidosis, a life-threatening, autosomal-dominant systemic amyloidosis that is caused by mutant transthyretin (TTR), includes the following syndromes: familial amyloid polyneuropathy (FAP), familial amyloid cardiomyopathy, and familial oculoleptomeningeal amyloidosis/cerebral amyloid angiopathy (1-4).

In addition to patients with ATTR V30M mutations who show early-onset symptoms in endemic areas, patients with ATTR V30M mutations who show late-onset symptoms and patients with non-V30M ATTR mutations are now considered to be prevalent in non-endemic areas (5). More than 140 TTR variants have been described so far, with various geographic distributions and degrees of amyloidogenicity and organ involvement (6, 7). Recently, disease modifying therapies such as liver transplantation and gene silencing to reduce the production of mutated TTR from the liver, and TTR stabilizer to reduce amyloid formation have come into clinical use in the treatment of hereditary ATTR amyloidosis (8-11). We herein describe a case of hereditary ATTR amyloidosis with cardiomyopathy that was associated with a novel mutation: ATTR Y114S (p.Y134S).

Case Report
A 65-year-old Japanese man was admitted to our hospital after a 3-year history of progressive dyspnea on exertion. Five years previously, he had had dysesthesia in both hands caused by mild carpal tunnel syndrome and the dysesthesia had improved naturally. One year earlier, he had hypothyroidism, and a thyroid biopsy revealed amyloid deposition (Congo red staining). Immunohistochemical staining was performed to identify amyloid fibril protein with specific antibodies (anti-TTR antibody, anti-amyloid A antibody, anti-
kappa light chain antibody, and anti-lambda light chain antibody). The deposited amyloid reacted with anti-TTR antibody without a positive reaction to other antibodies. He had no family history of heart disorder or neuromuscular disease and no relation to endemic areas of hereditary ATTR amyloidosis.

On admission of the patient to our hospital, a physical examination revealed numbness and reduced pain and temperature sensation in both feet. The patient had decreased bilateral Achilles’ tendon reflexes. The patient demonstrated no muscle weakness or atrophy, and his touch, vibration sense, joint position sense, and autonomic function were normal. A fundus examination showed no vitreous opacity.

Laboratory studies revealed a reduced TTR level (7.0 mg/dL, normal range: 22-34 mg/dL), increased serum brain natriuretic peptide level (732.4 pg/mL, normal value: <18.4 pg/mL), elevated protein in cerebrospinal fluid (81.8 mg/dL, normal range: 22-34 mg/dL), increased serum brain natriuretic peptide level (732.4 pg/mL, normal value: <18.4 pg/mL), and hypothyroidism. Nerve conduction studies revealed carpal tunnel syndrome and mild sensory axonopathy of the sural nerve (Table). Anti-PGP9.5 antibody staining of a skin biopsy specimen revealed reduction studies revealed carpal tunnel syndrome and mild sensory axonopathy of the sural nerve (FigureD).

An electrocardiogram indicated low voltage and first-degree atrioventricular block. Echocardiography showed concentric ventricular hypertrophy, atrial dilatation, and dys-telectasis (aortic diameter: 35.1 mm, mean left atrial diameter: 50.8 mm, left ventricular end-diastolic diameter at end-diastole: 41.4 mm, interventricular septal thickness: 15.1 mm, posterior wall thickness: 15.2 mm, fractional shortening: 40%, E/e’: 18.3), with a granular sparkling pattern (FigureA). 

Liver transplantation in patients with the non-V30M mutation or cardiomyopathy is usually less effective than that in patients with hereditary ATTR V30M amyloidosis (11). We therefore treated the patient with tafamidis to stabilize the TTR and reduce amyloid deposition (10, 13). The patient died of heart failure 5 years after the disease onset with carpal tunnel syndrome.

**Discussion**

Amyloid cardiomyopathy and carpal tunnel syndrome were the primary and initial clinical manifestation in this patient with the ATTR Y114S mutation, respectively. The survival time of this case was shorter in comparison to patients with ATTR V30M mutations in endemic areas (10.6 years), as well as that in non-endemic areas (7.3 years) (11, 14). In addition to wild-type ATTR amyloidosis (senile systemic amyloidosis), physicians should consider hereditary ATTR amyloidosis when elderly patients present with heart failure and carpal tunnel syndrome (15). A genetic analysis should be performed, especially for patients with polyneuropathy and hypothyroidism.

The TTR Y114C and Y114H mutation, which are mutations in the same position in TTR also produce a low conformational change in the second codon of exon 4, residue 114, in the TTR gene (c.401A>C) (FigureF). This substitution resulted in heterozygosity for normal tyrosine and variant serine (ATTR Y114S, p.Y134S).

We performed a duodenal mucosa biopsy that showed ATTR amyloid deposition. Laser capture microdissection with liquid chromatography-tandem mass spectrometry of amyloid deposits revealed that TTR (25.3%) was the most abundant protein in the amyloid deposits.

We therefore treated the patient with tafamidis to stabilize the TTR and reduce amyloid deposition (10, 13). The patient died of heart failure 5 years after the disease onset with carpal tunnel syndrome.

**Table. Data of Nerve Conduction Studies of This Case Examined in the Left Side. Upper or Lower Limits of Reference Values were Described in the Parenthesis.**

| Nerve          | DL (ms)  | CMAP (mV) | MCV (m/s) | F latency (ms) | SNAP (μV) | SCV (m/s) |
|----------------|----------|-----------|-----------|----------------|-----------|-----------|
| Median nerve   | 5.3 (4.6)| 8.1 (3.0) | 53.8 (49.5)| 29.5 (28.2)    | 5.3 (7.0) | 55.6 (47.1)|
| Ulnar nerve    | 3.1 (3.8)| 5.4 (5.8) | 55.6 (49.9)| 28.2 (29.7)    | 9.9 (6.9) | 53.1 (46.8)|
| Tibial nerve   | 5.0 (5.7)| 8.4 (4.3) | 41.5 (41.4)| 52.5 (51.7)    |           |           |
| Peroneal nerve | 4.9 (6.8)| 3.5 (4.0) | 43.0 (42.7)| 53.8 (53.4)    |           |           |
| Sural nerve    |          |           |           | 5.5 (7.4)      | 57.9 (40.7)|          |

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Figure. A: Echocardiography. The arrow indicates ventricular wall thickening and a granular sparkling pattern. B: $^{99m}$Tc-pyrophosphate myocardial scintigraphy. The arrow indicates a site of $^{99m}$Tc-pyrophosphate accumulation, which suggests amyloid deposition in the myocardium. C: Cardiac magnetic resonance image with non-contrast T1 mapping. A markedly elevated myocardial native T1 value was obtained. D: Anti-PGP9.5 antibody staining of a skin specimen: the intra-epidermal nerve fiber (arrows) density was reduced. Scale bar=50μm. E: A MALDI-TOF MS analysis detected the variant peak of ATTR Y114S in addition to a wild-type TTR peak. F: A genetic analysis of exon 4 in the TTR gene. One base pair substitution (c.401A>C, p. TTR Y114S) was found.

In conclusion, we reported the clinical features of a patient with hereditary ATTR Y114S amyloidosis. The clinical characteristics included progressive cardiomyopathy with a poor vital prognosis, a late onset of disease, sporadic occurrence, bilateral carpal tunnel syndrome, hypothyroidism, and mild small fiber neuropathy.

The authors state that they have no Conflict of Interest (COI).

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

The authors declare no conflicts of interest in association with the present study.

Standard protocol approval.

This study was approved by the Institutional Review Board of the Graduate School of Medical Sciences, Kumamoto University (No. 1387).

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