Cardiac Amyloidosis Associated With Amyloidogenic Transthyretin V122I Variant in an Elderly Japanese Woman

Tsuneaki Yoshinaga, MD; Masahide Yazaki, MD; Masakazu Ohno, MD; Satoshi Kodama, MD; Jun Koyama, MD; Yoshiki Sekijima, MD

Hereditary ATTR amyloidosis is an inherited systemic amyloidosis caused by transthyretin (TTR) mutations. Among >100 amyloidogenic TTR variants, ATTR V30M (p.V50M) is the most common one, causing severe peripheral neuropathy and autonomic neuropathy as well as cardiomyopathy, and a large number of patients with this variant have been reported worldwide, especially in Portugal, Sweden, and Japan. While ATTR V122I (p.V142I) is also one of the most prevalent TTR variants, this is known to cause severe amyloid cardiomyopathy with carpal tunnel syndrome (CTS) at advanced age (>60 years). Of particular interest is the significant ethnic differences in the prevalence of this TTR variant, with the majority of ATTR V122I patients being African-American, and the prevalence of the mutation in this race being approximately 4%. While a few cases of TTR mutation have also been described in Caucasian subjects, this mutation has not been reported in Asian patients even in the quarter of a century since the first African-American case was described. Here we present clinical imaging of severe cardiac amyloidosis in an elderly Japanese woman: the first case of V122I TTR variant to be...
The patient was a 71-year-old Japanese woman with a history of cerebral infarction probably due to embolism in the left middle cerebral artery at age 69. Neurological deficits, including right hemiplegia and loss of consciousness, were reversed on tissue-plasminogen activator infusion. While atrial fibrillation was not detected, anti-coagulation therapy was begun. Over 2 years, the patient gradually noticed palpitation, and the development of cardiomegaly was seen. The patient was referred to a cardiology clinic with suspected amyloid cardiomyopathy due to thick left ventricular wall on echocardiogram and low voltage on electrocardiogram (Figure 1A). Gastrointestinal biopsy showed TTR-related amyloid deposits (Figure 2A–C). Amyloid cardiomyopathy was therefore suspected and the patient was admitted to hospital for further examination. The patient had clinical signs and symptoms of heart failure (New York Heart Association grade III), presenting with orthopnea and dyspnea on exertion followed by swelling of the extremities. These were typical signs of peripheral neuropathy except for numbness in the palms, with mild atrophy of the thenar muscles of both hands. Chest roentgenogram showed marked cardiomegaly (Figure 1B), and echocardiogram indicated severe left ventricular hypertrophy with an intraventricular septum at 22.3 mm and posterior wall at 21.1 mm (normal, <12 mm; Figure 1C). Myocardial uptake was noted on 99mTc-tc99m technetium-pyrophosphate scintigraphy (Figure 1D). Serum B-type natriuretic peptide was highly elevated (582.3 pg/mL; normal, <20 pg/mL). On nerve conduction study, the bilateral median nerve terminal latency was elongated, indicating CTS. After obtaining informed consent, DNA analysis of TTR was performed, and heterozygous V122I mutation was identified (Figure 2D). No other mutations were present in TTR. The patient had no family history of cardiomyopathy, and a diagnosis of sporadic hereditary ATTR amyloidosis was made. On haplotype analysis using the six polymorphisms in TTR, the haplotype was found to be consistent with type I.3,4 The patient was started on oral tafamidis, a TTR-tetramer stabilizer,5 in addition to treatment for congestive heart failure.

The V122I TTR variant is the most common cause of cardiac amyloidosis in African-American patients.1 The reported clinical picture in patients with V122I is almost identical: late-onset cardiomyopathy without severe neuropathy except CTS; and this clinical phenotype is similar to that of senile systemic amyloidosis (SSA), associated with amyloid fibrils derived from only wild-type TTR. This mutation in African-American patients was thought to have originated in Western Africa,6 and the haplotype in the majority of African-American patients is consistent with type III,7 different to that in the present case. Together with the present results, these data indicate that this mutation can occur worldwide, in any ethnicity. While the precise frequency of this mutation in the Asian population remains unknown, some patients, especially in sporadic cases, may have been misdiagnosed with SSA or primary AL amyloidosis due to the clinical similarity. Given that the treatment strategy of oral TTR-tetramer stabilizers has recently been established for hereditary ATTR amyloidosis, not for SSA,8,9 correct diagnosis is of great importance. Careful differential diagnosis including genetic testing of TTR is mandatory, especially in elderly patients with hypertrophic cardiomyopathy regardless of family history or ethnicity, even in Asian people.

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Disclosures
The authors declare no conflict of interest.

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