CASE REPORT

Two Siblings Diagnosed to Have Transthyretin-related Familial Amyloid Cardiomyopathy Around the Same Time at Different Hospitals

Masatoshi Miyamura¹, Fumio Terasaki¹, Kazuya Ishibashi², Chihiro Shimazaki³, Fumiharu Kimura⁴, Hiroko Kuwabara⁵, Motomu Tsuji⁷, Yuro Shibayama⁵, Yoshiki Sekijima⁶, Kana Tojo⁷ and Nobukazu Ishizaka¹

Abstract

Mutation in the transthyretin (TTR) gene may clinically manifest as cardiomyopathy. Here, we describe 69-year-old and 72-year-old brothers who were diagnosed as having TTR-related familial amyloid cardiomyopathy by endomyocardial biopsy at different hospitals at around the same time. They were not from an endemic area of familial amyloid polyneuropathy. Genetic analysis showed a base change in the TTR gene leading to a p.Val30Met mutation in both patients. Screening of family members, as well as detailed family history taking, is important for the diagnosis of cardiomyopathy of unknown etiology.

Key words: familial amyloid polyneuropathy, transthyretin, cardiomyopathy, siblings, non-endemic


Introduction

Cardiac involvement represents the most serious complication of systemic amyloidosis, and the clinical features and prognosis of systemic cardiac amyloidosis differ according to the type of systemic amyloidosis (1). Transthyretin (TTR) is a homotetrameric serum and cerebrospinal fluid protein that transports both thyroxine and the retinol-retinol binding protein complex (2), and mutations in the TTR gene cause TTR-related hereditary amyloidosis, including familial amyloid polyneuropathy (FAP) and familial amyloid cardiomyopathy (FAC). The clinical spectrum of TTR-related hereditary amyloidosis can vary widely from exclusive neurologic involvement to a strictly cardiac presentation (3, 4). The prognosis of TTR-related hereditary amyloidosis is, in general, better than that of acquired monoclonal immunoglobulin light-chain amyloidosis (AL amyloidosis), which is the most frequent form of systemic amyloidosis (1). In this case report, we demonstrate two male siblings who had heart failure symptoms and were diagnosed to have TTR-related amyloidotic cardiomyopathy at approximately the same time in different medical institutes.

Case Report

A 69-year-old Japanese man (case 1) presenting with mild heart failure symptoms visited the cardiology section of the hospital (OMC) and underwent preoperative screening for lumbar disc herniation on November 2010. He had been diagnosed as having cardiomyopathy at 53 years of age by cardiac ultrasonography (details unknown). His father died of leukemia, although the precise information was not available. He had one brother and four sisters, and at the time, none of them, except for his brother (case 2), had cardiac abnormalities. Chest X-ray showed mild cardiomegaly with...
cardiothoracic ratio of 61% (Fig. 1A). On the other hand, electrocardiography (ECG) revealed a low voltage in limb leads, first-degree atrioventricular block, Q waves in leads V1-V3 (anterior pseudo-infarction pattern), and ST depression in leads V5 and V6 (Fig. 1B). A cardiac ultrasonography showed that the enlargement of left ventricle (LV) with a diastolic dimension of 60 mm and a decreased ejection fraction of 32.9%, and impaired diastolic function with E/e’ of 19 and a deceleration time of 134 msec. The LV wall was slightly hypertrophied with interventricular septum and posterior wall thicknesses of 11 mm and 12 mm, respectively (Fig. 1C). Technetium-99m (99mTc) hydroxymethylene diphosphonate (HMDP) scintigram showed positive uptake to the heart (Fig. 1D). Coronary artery angiography showed no significant luminal narrowing in the coronary arteries. An endomyocardial biopsy was then performed. Histologic and immunohistochemical analysis showed marked amyloid deposition in the interstitium, which was specifically stained with anti-TTR antibody (Fig. 2A-D). Neurologic examination, including the nerve conduction study, demonstrated the presence of sensorimotor polyneuropathy in both the upper and lower limbs. Based on these clinical and pathological findings, he was diagnosed as having TTR-related amyloid cardiomyopathy. After receiving written informed consent, we carried out genetic analysis (5). For DNA analysis, total genomic DNA was extracted from leukocytes, and polymerase chain reaction followed by restriction enzymatic digestion with Bal I and then by electrophoresis was performed as described elsewhere (5). The analysis showed that a genomic mutation in TTR corresponding to a substitution of Methionine for Valine at position 30 (p.Val30Met) was present. The p.Val30Met is the most common mutation in FAP and more than 80% of Japanese patients have this mutation.

At about the same time, a 72-year-old Japanese man (case 2), the elder brother of case 1, visited the cardiology section of another hospital (SKH) because of worsening dyspnea. Unlike case 1, he had not been diagnosed to have cardiomyopathy. Chest X-ray showed mild cardiac enlargement with a cardiothoracic ratio of 60% (Fig. 1E) and ECG revealed normal sinus rhythm, complete right bundle branch block, and right axis deviation (Fig. 1F). Cardiac ultrasonography showed a non-dilated LV (diastolic dimension of 49 mm) with wall thickening (interventricular septum, 13 mm) and a diffuse reduction of wall motion (ejection fraction of 38%). Coronary artery angiography showed normal coronary arteries. Histological and immunohistochemical analysis of biopsied myocardial samples showed marked TTR deposition in the interstitium (Fig. 2F-H). In this patient, a p.Val30Met mutation in TTR was also found (Fig. 3). In this case, neurologic examination did not dem-
Here, we have reported two brothers who were referred to two different hospitals owing to the development of heart failure symptoms at about the same time. No significant coronary artery stenosis was found in either patient, and prominent deposition of amyloid that stained positive for TTR was demonstrated in the cardiac interstitium of biopsy specimens from both patients. Subsequent genetic analysis revealed that both patients possess a heterozygous p.Val30Met mutation in the TTR gene; thus, a diagnosis of FAC was made for these two brothers.

p.Val30Met is the most common genetic mutation found in TTR-related hereditary amyloidosis (3), although more than 20 other point mutations in TTR gene have been reported in Japan (6). Several foci of the p.Val30Met mutation have been noted in Oporto in Portugal, the northern part of Sweden, and Kumamoto and Nagano, in Japan (7-10), leading to so-called endemic p.Val30Met-type TTR-related hereditary amyloidosis. Patients with p.Val30Met TTR may also be found outside these endemic foci, and are referred to as non-endemic p.Val30Met TTR-related hereditary amyloidosis. As compared with endemic p.Val30Met-type TTR-related hereditary amyloidosis, cardiac involvement is more frequent and more prominent (11-13), and family history is less frequent (14) in non-endemic p.Val30Met-type TTR-related hereditary amyloidosis. In addition, age at onset of non-endemic p.Val30Met-type TTR-related hereditary amyloidosis (52-80 years) is higher than that of the endemic disorder (30-40 years) (15). In addition, in those late-onset cases, male predominance was accompanied by a low incidence of family history and symptomatic siblings (16).

In case 1, 99mTc-HMDP scintigraphy showed positive up-
take to the heart (Fig. 1D), the finding being consistent with several previous papers that demonstrated the affinity of cardiac amyloid for a bone scanning agent, $^{99m}$Tc-HMDP (17, 18). Intense uptake of $^{99m}$Tc-HMDP is also demonstrated in various non-cardiac tissues with systemic amyloidosis. Recent studies also suggest the usefulness of $^{99m}$Tc-3,3-diphosphono-1,2-propanodicarboxylic acid ($^{99m}$Tc-DPD) scintigraphy across a wide spectrum of morphologic/functional cardiac involvement, allowing an early diagnosis of the disease (19, 20), although the present cases did not undergo $^{99m}$Tc-DPD scintigraphy. Further studies on the sensitivity and specificity of $^{99m}$Tc-HMDP scintigraphy for the diagnosis of cardiac amyloidosis will be warranted.

The hometown of the two siblings reported in this paper was not in an endemic area in Japan, and both men were around the age of 70 years, consistent with the onset of non-endemic p.Val30Met-type TTR-related hereditary amyloidosis, although one of these patients had been diagnosed as having cardiomyopathy at between 50 and 60 years of age (details unknown). It has been reported that a family in an endemic region in Japan had two siblings who had severe amyloid heart disease at disease onset, and developed polyneuropathy with autonomic features at an advanced stage (21). Although the present cases seem to originate from non-endemic areas, neurologic function should be followed carefully.

TTR-related FAC is, in general, considered to have a better prognosis compared with AL amyloidosis (22). On the other hand, replacement of failed organs and liver transplantation is thus far the only option for patients with TTR-related FAC is, in general, considered to have a better prognosis compared with AL amyloidosis (22). On the other hand, replacement of failed organs and liver transplantation is thus far the only option for patients with TTR-related hereditary amyloidosis (11). New therapies based on stabilization of the native tetrameric structure of TTR, disruption of the established deposits using antibodies and drugs, and gene therapy (24).

In summary, we have demonstrated two male siblings who, at around 70 years of age, were diagnosed to have FAC caused by p.Val30Met mutation in the TTR gene. Considering that TTR-related FAC is frequently misdiagnosed or underdiagnosed, especially when neurologic involvement is mild or absent (25), detailed family-history taking, and, when necessary, screening of cardiac function in family members, should be considered for the full diagnosis of TTR-related FAC.

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

References

3. Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol 7: 398-408, 2010.
7. Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain 75: 408-427, 1952.


© 2012 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html