Early Detection of Cardiac Amyloidosis in Transthyretin Mutation Carriers
Case Series and Review of the Literature

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Summary
Diagnostic strategies for symptomatic transthyretin (ATTR) cardiac amyloidosis showing typical morphological features such as increased ventricular wall thickness and myocardial injury such as an elevation in serum troponin T level have been established, but those for subclinical cardiac amyloidosis are limited. In the era when effective therapies to suppress/delay progression of ATTR cardiac amyloidosis are available, early detection of cardiac involvement plays a crucial role in appropriate decision-making for treatment in TTR mutation carriers who have a family history of heart failure and death due to ATTR amyloidosis. Findings of three cases with known pathogenic transthyretin (TTR) mutations (p.Ser70Arg, p.Phe53Val, and p.Val50Met) and family histories of death for amyloidosis were presented. Two cases were asymptomatic, and a case carrying p.Phe53 Val had gastrointestinal symptoms and autonomic neuropathy. Levels of plasma N-terminal fragment of pro-B-type natriuretic peptide and troponin T were within normal ranges in all cases, but results of cardiac magnetic resonance (CMR) and bone scintigraphy clearly revealed the presence of cardiac involvement in all cases, even in a case without echocardiographic abnormalities including left ventricular hypertrophy and relative apical sparing of longitudinal strain shown by two-dimensional speckle-tracking echocardiography. Electrocardiography revealed modest abnormalities including reduced R wave amplitude in V2 and a trend toward left axis deviation in all cases. In conclusion, CMR, bone scintigraphy, and electrocardiography are useful for early detection of ATTR cardiac amyloidosis in TTR mutation carriers. The role of comprehensive cardiac assessment in the early detection of cardiac amyloidosis in TTR mutation carriers is discussed.

Key words: Troponin, Transthyretin amyloidosis, ATTR amyloidosis, Bone scintigraphy, Cardiac magnetic resonance, Electrocardiography

Hereditary transthyretin (ATTRv) amyloidosis is an adult-onset, autosomal dominant disease caused by extracellular deposition of transthyretin (TTR) amyloid fibrils due to TTR protein destabilization by point mutations of the TTR gene.1,4 A slowly progressive sensorimotor and/or autonomic neuropathy is a hallmark of ATTRv amyloidosis, but multiple organs including the central nervous system, eyes, thyroid, kidneys, gastrointestinal tract, and heart are involved. In addition to progression of neuropathy, heart failure and arrhythmias including ventricular tachycardia and conduction system disturbances are major causes of mortality in this disorder.5-7 ATTRv amyloidosis patients with p.Val50 Met (Val30Met) in non-epidemic areas and ATTRv amyloidosis patients with several mutations other than p.Val50 Met have onset at a later age and predominantly present cardiac amyloidosis, though the mechanisms of this variability remain unclear.7,8

Previously, transthyretin (ATTR) amyloidosis was recognized as an untreatable disorder, but several therapeutic strategies are now available. Replacement of the variant TTR gene with the wild-type TTR gene by liver transplantation is a first-line treatment for early-onset ATTR p.Val50Met, i.e., familial amyloid polyneuropathy
(TTR-FAP), since TTR is mostly produced by the liver, but its effect on late-onset ATTR p.Val50Met and cardiac ATTRv amyloidosis is limited.\(^4\) On the other hand, treatment with tafamidis, a TTR tetramer stabilizer, has been shown to extend survival in patients with ATTR amyloid cardiomyopathy.\(^{11,12}\) In addition, it was shown that gene silencing of TTR by nanoparticle delivery of small interfering RNA specifically suppressed hepatic synthesis of TTR and improved clinical manifestations of ATTR amyloidosis including amyloid cardiomyopathy.\(^{13,14}\) In parallel to recent advances in therapy for ATTR amyloidosis, diagnostic algorithms for detecting cardiac amyloidosis including wild-type transthyretin (ATTRwt) amyloidosis have been proposed. There are several clues, i.e., red flags, leading to further assessment for the diagnosis of cardiac amyloidosis: left ventricular hypertrophy with reduced electrocardiographic voltage to left ventricular mass ratio, relative apical sparing pattern of longitudinal strain (LS), heart failure with preserved ejection fraction, elevated serum troponin levels suggesting cardiomyocyte injury, and comorbidities suggesting ATTR such as neuropathy and carpal tunnel syndrome.\(^6,16,17\) Furthermore, myocardial uptake of \(^{99m}\text{Tc-DPD}\) without the presence of a monoclonal protein is thought to have high sensitivity and specificity for ATTR cardiac amyloidosis.\(^{5,18,19}\) In addition, these diagnostic algorithms have been developed for the diagnosis of established cardiac amyloidosis, and their utility for early detection of cardiac involvement in TTR mutation carriers devoid of red flags remains to be elucidated. This is an important issue in the era when effective therapies to suppress/delay progression of ATTR amyloidosis are available.

Therefore, the aim of this case series was to demonstrate the impact of comprehensive cardiac assessment on detection of cardiac involvement in TTR mutation carriers who have affected parents and/or relatives and to make a clue to develop appropriate follow-up assessments of the heart for TTR mutation carriers.

**Case Report**

**Case 1:** A 52-year-old woman was referred to our institution for predictive genetic testing and cardiac assessment. Her mother was diagnosed as having dilated cardiomyopathy in her 40s and died from heart failure at the age of 59 years. Her second oldest brother experienced alternating diarrhea and constipation at the age of 46 years, leading to a diagnosis of ATTR amyloidosis with p.Ser70Arg (c.210T>G, Ser50Arg) mutation, and he died from malnutrition and infection at the age of 49 years. Results of predictive genetic testing revealed that she and her oldest brother were p.Ser70Arg mutation carriers. The oldest brother had been suffering from shortness of breath on exertion, and laboratory studies revealed a high level of serum NT-proBNP (869 pg/mL). Diagnosis of cardiac amyloidosis was suggested by comprehensive assessment of the heart, and accumulation of amyloid fibrils was confirmed by a minor salivary gland biopsy, leading to the diagnosis of ATTRv cardiac amyloidosis. She also received abdominal fat aspiration, which yielded a positive result. Considering her family history, cardiac examinations were performed, though she was asymptomatic. Electrocardiography showed a trend toward low voltage in the limb leads and left axis deviation (−14°) and a reduction in R wave amplitude of V2 (Figure 1A). There were no abnormalities in laboratory studies including levels of NT-proBNP (106 pg/mL) and troponin T (< 0.003 ng/mL), echocardiographic findings including 2-D speckle-tracking echocardiography, and neurological examinations (Table 1 and Figure 1B). Results of a CMR study revealed endocardial LGE and an increase in native T1 value (1151 msec, Figures 1C-E). Furthermore, apparent myocardial uptake of \(^{99m}\text{Tc-DPD}\) was found, suggesting a diagnosis of ATTRv cardiac amyloidosis (Figure 1F, G). Treatment with patisiran, an RNAi therapeutic, was commenced.

**Case 2:** A 28-year-old man with gastrointestinal amyloidosis was referred to our institution. His father was also diagnosed as having amyloidosis on the basis of results of colon biopsy, though genetic analyses were not performed, and he died in his 40s. Four months earlier, he had gastrointestinal symptoms including nausea and diarrhea, which had progressively worsened. On admission of the patient to our institution, there were no abnormal neurological findings including sensory/motor disturbance and tendon reflex, but a Schellong test was positive. Immuno-histochemical analyses of colon biopsy samples were positive only for staining with anti-TTR antibodies, and the results of genetic testing revealed p.Phe53Val (c.157T>C, Phe33Val) mutation of TTR. Elevation of NT-proBNP and troponin T levels was not found, but electrocardiography revealed left posterior fascicular block and poor R wave progression in precordial leads (Figure 2A). In echocardiographic analyses, there were no overt findings suggesting amyloid cardiomyopathy including wall thickening, though the papillary muscle appeared to be thick, and a trend for a relative apical sparing pattern of LS was found (Figure 2B). Results of a CMR study revealed LGE in the endocardium and papillary muscle and an increase in native T1 value (1197 msec, Figure 2C-E). In addition, myocardial uptake of \(^{99m}\text{Tc-DPD}\) was clearly found (Figure 2F, G). Diagnosis of ATTRv cardiac amyloidosis was made on the basis of results of endomyocardial biopsy. Treatment with patisiran was commenced. One year later, gastrointestinal symptoms tended to be relieved, and progression of cardiac amyloidosis was not observed.

**Case 3:** A 49-year-old man was referred to our institution for predictive genetic testing. His father was diagnosed as having late-onset ATTR with p.Val50Met (c.148 G>A, Val 30Met) of TTR and died in his 70s. He was asymptomatic and showed no muscle weakness and orthostatic hypotension, but reduction in senses of touch, pain, and temperature was found in neurological examinations. Histological analyses of colon biopsy specimens and genetic testing of TTR led to a diagnosis of ATTR amyloidosis with p.Val50Met mutation. Elevation of NT-proBNP and troponin T levels was not found (Table), but slight abnormalities were found in electrocardiography (Figure 3A): reduction in R wave...
wave amplitude of V2 and a trend toward left axis deviation (−22°). Echocardiography and CMR revealed moderate wall thickening of the basal portion of the interventricular septum (12 mm) and interatrial septum, where reduction in LS detected (Figure 3B, C). In addition, there were typical findings of CMR and bone scintigraphy for amyloid cardiomyopathy, i.e., endocardial LGE, increased native T1 value, and overt myocardial uptake of 99mTc-DPD (Figure 3D-G). After confirmation of the absence of serum and urinary monoclonal protein, treatment with patisiran was initiated.

**Discussion**

All of the cases presented here had known pathogenic TTR mutations and family histories of death for amyloidosis. Although cardiac symptoms and elevation in troponin T and NT-proBNP levels were not found, results
of CMR and DPD scintigraphy clearly revealed the presence of cardiac amyloidosis in all cases, even in a case without echocardiographic abnormalities including left ventricular hypertrophy and relative apical sparing of LS.

The role of CMR and DPD scintigraphy for early detection of cardiac amyloidosis in TTR mutation carriers: Results of studies in patients with established cardiac amyloidosis have shown that myocardial scintigraphy with bone-avid tracers has high sensitivity and specificity for diagnosis of ATTR cardiac amyloidosis if monoclonal proteins do not exist in serum and urine. However, evidence regarding the utility of myocardial scintigraphy with bone-avid tracers for early detection of cardiac amyloidosis in TTR mutation carriers is limited. In a study by Haq, et al. in which myocardial scintigraphy with Tc-Pyrophosphate (99mTc-PYP), a bone-avid tracer, was performed in 12 asymptomatic TTR mutation carriers without echocardiographic and biochemical abnormalities, diagnostic myocardial uptake of Tc-PYP, i.e., grading scale of 2 or 3 by Perugini, et al., was found in seven cases, indicating the presence of subclinical ATTR cardiac amyloidosis. Those results taken together with our results showing apparent myocardial uptake of Tc-DPD in all cases with TTR mutations indicate that assessment of the heart by myocardial scintigraphy with bone-avid tracers is a promising approach for detection of subclinical cardiac amyloidosis in TTR mutation carriers. However, there are several limitations. First, Azevedo Coutinho, et al. examined the utility of DPD scintigraphy for detection of cardiac amyloidosis in 179 patients with ATTR p.Val50Met mutation including 92 patients with early-onset disease, 33 patients with late-onset disease, and 54 asymptomatic p.Val50Met carriers. Among 33 ATTR patients with late-onset disease p.Met30Val, known as a predominantly cardiac form ATTR, 18 patients had no septal wall thickening defined as septal wall thickness of less than 13 mm at the time of examination, and 5 of those patients had myocardial DPD uptake, suggesting the utility of DPD scintigraphy for early detection of cardiac amyloidosis as shown in the findings of case 3. On the other hand, 17 patients (18%) with early-onset disease had septal wall thickening, and only 4 of those patients had positive DPD uptake. In addition, endomyocardial biopsy was performed in two patients with septal wall thickening and no DPD uptake, leading to a diagnosis of cardiac ATTR amyloidosis.

Therefore, DPD scintigraphy is not a sensitive examination for detection of cardiac amyloidosis in p.Val 50Met carriers with early-onset disease. Importantly, this is the case with ATTRv patients carrying p.Phe84Leu (Phe64 Leu): among 19 ATTR p.Phe84Leu patients with cardiac amyloidosis, only 2 patients showed high-grade, i.e., diagnostic, myocardial uptake of DPD or hydroxyl-methylene-diphosphonate (HMDP). Thus, the association of genotypes with sensitivity of DPD scintigraphy for detection of cardiac amyloidosis needs to be analyzed in detail. Second, although the radiation exposure dose from bone scintigraphy with SPECT/CT is small, the effect of its repetitive/annual examination through a long-term follow-up period on the patient’s health has not been established. Finally, bone scintigraphy analyzes whether there is TTR amyloid deposition in the heart, namely, a “yes or no” approach. The role of bone scintigraphy in differential diagnosis of myocardial injury including ischemic injury and other cardiomypathies is limited. It should be emphasized that TTR mutation carriers may suffer from myocardial diseases including ischemic heart disease other than cardiac amyloidosis during a long-term follow-up period. On the other hand, a CMR study including LGE and T1 mapping is a gold standard imaging for etiological diagnosis of myocardial injury and has no risk of exposure to ionizing radiation. Characteristics of an LGE pattern and prominent elevation in the native T1 value are common findings regardless of the type of cardiac amyloidosis, which does not theoretically depend on the type of TTR mutation. Although caution is required for magnetic objects including implanted pacemakers and allergy for contrast reagents, a CMR study may be more appropriate than bone scintigraphy for assessment of the heart in TTR mutation carriers.

The role of echocardiography for early detection of cardiac amyloidosis in TTR mutation carriers: In addition to thickening of the ventricular/atrial wall, papillary muscle, and valves, a relative apical sparing pattern of LS shown by 2-D speckle-tracking echocardiography, which is defined as a reduction of the basal and middle segment LS relative to apical LS, is a distinct feature of amyloid cardiomyopathy and plays a role in the prediction of prognosis in patients with cardiac amyloidosis. The mechanism of an apical sparing pattern in amyloid cardiomyopathy is unclear, but the pattern is similar to the distribution pattern of amyloid accumulation as shown by analyses of myocardial uptake of bone-avid tracers and an autopsy case. In addition, the results of a study by Lee, et al. showed that the extent of relative apical sparing was positively correlated with mean left ventricular wall thickness, indicating that the extent of a relative
apical sparing pattern is severity-dependent. In TTR mutation carriers including a case with normal ventricular wall thickness, an apparent apical sparing pattern was not observed, though CMR and DPD scintigraphy clearly indicated amyloid accumulation. Therefore, although the presence of an apical sparing pattern is useful for differentiating cardiac amyloidosis from left ventricular hypertrophy as the guideline recommends, it is unlikely to be a sensitive marker for early detection of cardiac involvement in asymptomatic TTR mutation carriers.

**Early electrocardiographic signs for detection of cardiac amyloidosis in TTR mutation carriers:** Different from DPD scintigraphy and CMR, electrocardiography is inexpensive and can be performed repeatedly for obtaining a clue for detection of myocardial amyloid accumulation. There are several electrocardiographic hallmarks suggesting cardiac amyloidosis: reduced electrocardiographic voltage to left ventricular mass ratio, poor R wave progression and a pseudoinfarct pattern without coronary artery disease, and conduction disturbances such as atrioventricular blocks, bundle branch blocks, and intraventricular conduction disturbances, the presence of which has
been shown to be associated with severity of cardiac amyloidosis. Thus, the role of electrocardiography in early detection of amyloid accumulation in TTR mutation carriers remains to be elucidated. In the electrocardiography of case 2, poor R wave progression together with left posterior fascicular block was observed. Reduced R wave amplitude in V2 and a trend toward left axis deviation found in case 1 and case 3 may be antecedent findings of poor R wave progression and left posterior fascicular block. Prominent accumulation of amyloid at the basal and mid portions of the interventricular septum, i.e., apical sparing, may contribute to reduced R wave amplitude in V2 as shown in Figure 1 (case 1) and Figure 3 (case 3). Nevertheless, the significance of these minor electrocardiographic findings for early detection of cardiac amyloid accumulation in asymptomatic TTR mutation carriers should be confirmed in a future study including periodic assessment of electrocardiography.

The commencement and timing of follow-up in TTR mutation carriers: With the growing importance of pre-
dictive genetic testing and early detection of amyloid accumulation in the era when effective therapies to delay progression of ATTR amyloidosis are available, several recommendations regarding follow-up assessment and management for TTR mutation carriers have been proposed.31-33) The commencement and timing of follow-up in TTR mutation carriers depend on the predicted age of disease onset (PADO).34) PADO is determined by the typical type of mutation.35) PADO is determined by the typical age of onset for the specific mutation and the age of onset in index patients with ATTRv amyloidosis.36) After baseline assessments, annual monitoring for early detection of TTR-related neural and organ damage should be started 10 years before the PADO, which is followed by their close follow-up as carriers approach the PADO.37) However, an evidence-based follow-up strategy for early detection of cardiac involvement in TTR mutation carriers including intervals of examinations is not available. In addition, although the findings from our cases indicated the utility of CMR, DPD scintigraphy, and electrocardiography rather than serum biomarkers and echocardiography for early detection for cardiac amyloidosis in TTR mutation carriers, it remains unclear which modalities and markers are the best for early detection of cardiac amyloidosis. Importantly, safety and costs for performing multiple imaging studies including scintigraphy and CMR should be considered, especially in young TTR mutation carriers. Thus, further analyses in a large number of TTR mutation carriers with various mutations are needed to demonstrate how to monitor TTR mutation carriers who have no evidences of cardiac amyloidosis.

**Treatment for cardiac amyloidosis in TTR mutation carriers:** There are two available medical therapy for TTR mutation carriers: stabilization of TTR by tafamidis and gene silencing of TTR by patisiran. Based on the results of a placebo-controlled randomized trial including patients with ATTRwt and ATTRv cardiac amyloidosis showing favorable effects of tafamidis on clinical outcomes,11,12) presence of heart failure and echocardiographic evidence of left ventricular hypertrophy, i.e., an end-diastolic interventricular septal wall thickness of ≥12 mm, are required for initiation of treatment with tafamidis in ATTRv amyloidosis patients.38) Therefore, TTR mutation carriers with asymptomatic cardiac amyloidosis such as our three cases do not fulfill requirements for the treatment with tafamidis. On the other hand, patisiran was approved for treatment of ATTRv amyloidosis by the Ministry of Health, Labour and Welfare, Japan, based on the results of the APOLLO phase 3 study.39) Thus, ATTRv amyloidosis patients with radiographic and pathological evidences of cardiac involvement, but not with its echocardiographic evidences and heart failure symptoms, are eligible for the treatment with patisiran. However, the long-term effect of patisiran on survival and cardiovascular events in TTR mutation carriers with asymptomatic cardiac amyloidosis is necessary for rigorously addressing this issue.

**Limitation:** There are obvious limitations in the present report. First, there is selection bias since this study is a case series study in a single center. Second, findings in ATTRv amyloidosis patients with only three mutations were presented. Third, this paper focused on TTR mutation carriers who have affected parents and/or relatives. However, cardiac amyloidosis is frequently found in non-endemic ATTRv patients without typical polyneuropathy and autonomic dysfunction as you suggested. Mild electrocardiographic abnormalities are thought to be a plausible clue detected in annual physical check-up, which may lead to a chance to receive CMR and scintigraphy in non-endemic ATTRv patients, though their specificity is limited. A separate project is apparently needed to resolve this issue. Fourth, the effect of patisiran on cardiac amyloidosis was not examined. Theoretically speaking, patisiran suppresses further accumulation of amyloid, but does not remove amyloid deposition. Indeed, electrocardiographic changes remained in two cases (case 1 and case 2) who received the treatment with patisiran more than 1 year at this time. On the other hand, it was shown that the treatment with patisiran during median 18.7 months may reverse the progression of the cardiac manifestations in ATTRv amyloidosis patients.40) Further follow-up period is needed to confirm it in our cases. Finally, the utility of Pittsburgh compound B positron emission tomography, a specific technique for amyloid detection, for early diagnosis of cardiac amyloidosis in TTR mutation carriers was not analyzed.39)

**Conclusions**

CMR, bone scintigraphy, and electrocardiography are useful for early detection of ATTRv cardiac amyloidosis in TTR mutation carriers without cardiac symptoms and elevations in NT-proBNP and troponin T levels, though the sensitivity of bone scintigraphy is likely to depend on the type of mutation.

**Disclosure**

**Conflicts of interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval:** Ethical approval was not required to write this report.

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