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【 REVIEW ARTICLE 】

How to Identify Transthyretin Cardiac Amyloidosis at an Early Stage

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Abstract:
Cardiac involvement of systemic amyloidosis is preferentially observed in patients with amyloid light chain amyloidosis or transthyretin amyloidosis (ATTR). Owing to the development of diagnostic modalities and changes in recognition by physicians, transthyretin cardiac amyloidosis (ATTR-CA) is now understood to be a more common cause of heart failure than previously thought. Recent progress in disease-modifying therapeutic interventions, such as transthyretin stabilizers, has resulted in ATTR-CA changing from an incurable disease to a curable disease. These interventions are particularly effective in patients with mild symptoms of heart failure, thus indicating that early detection and a precise diagnosis are important for improving the prognosis. In this review article, we summarize the recent reports of early screening of ATTR-CA and describe some important points regarding the making of a precise diagnosis, especially focusing on histological evaluations.

Key words: transthyretin amyloidosis, cardiac involvement, histology

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Introduction

Systemic amyloidosis is defined as organ dysfunction caused by the deposition of amyloid fibrils derived from various precursor proteins. To date, over 30 precursor proteins have been identified, and amyloid fibrils derived from these proteins can induce various types of organ damage. Cardiac involvement of systemic amyloidosis leads to a detrimental prognosis, and it is preferentially observed in patients with amyloid light chain (AL) amyloidosis or transthyretin amyloidosis (ATTR).

Cardiac amyloidosis (CA) is a rare cause of heart failure. However, recent studies have indicated that CA, especially wild-type transthyretin CA (ATTRwt-CA), appears to be a more common cause of heart failure than previously thought. Gonzalez-Lopez et al. showed that 13.3% of patients with heart failure with a preserved ejection fraction with left ventricular hypertrophy showed an uptake of ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy, which suggested cardiac involvement of ATTRwt (1). The prevalence of ATTR-CA as evaluated by technetium-^{99m}-pyrophosphate (^{99m}Tc-PYP) cardiac scintigraphy was found in 16% of patients with severe aortic stenosis who underwent trans-catheter aortic valve implantationbu (2).

Recent progress in therapeutic intervention has enabled ATTR-CA to change from an incurable disease to now become a curable disease. Tafamidis, which is a transthyretin stabilizer, improves the prognosis in patients with both ATTRwt-CA and hereditary transthyretin cardiomyopathy. The beneficial effects of tafamidis are apparent in patients with an early stage of heart failure as reflected by New York Heart Association functional classes I-II. These results indicate that both early detection and a precise diagnosis are important for improving the prognosis in patients with ATTR-CA.

An important issue is identifying ATTR-CA at an early stage. In this review article, we summarize the recent understanding of early screening of ATTR-CA and describe important points associated with making a precise diagnosis, especially focusing on the histological evaluation.

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Table. Electrocardiographic Findings and the Positive Rate.

	AL	ATTRwt
AF	6 - 40%	27 - 67%
AVB	15 - 26%	11 - 33%
pseudo infarct pattern	15 - 62%	18 - 71%
low voltage	27 - 60%	13 - 40%

AL: amyloid light, ATTR: amyloidosis or transthyretin amyloidosis

Identifying Transthyretin Cardiac Amyloidosis at An Early Stage

1. Medical history and physical examination

A detailed record of the medical history and a physical examination are important for the early diagnosis of ATTR-CA. In patients with ATTR, the deposition of amyloid protein occurs in various ligaments and tendons tissues, such as the transverse carpal ligament and yellow ligament, at a high rate (3, 4). The complication of bilateral carpal tunnel syndrome (CTS) is particularly characteristic, because 40-50% of patients with ATTRwt-CA have a history of CTS (5-7). In a prospective, cross-sectional, multidisciplinary study of patients who underwent carpal tunnel release surgery without heart failure symptoms, Congo red staining of tenosynovial tissue specimens detected amyloid deposits in 10.2% of patients, and 7.1% were diagnosed with ATTRmt (8). Only 14.3% of these patients with ATTR had leg edema and their mean jugular venous pressure was 6.9 cm H_2O. These findings suggest that asymptomatic ATTR can be present in patients with CTS (8). In a recent report, CTS preceded the diagnosis of CA by 5-9 years. (9) This finding indicates that ATTR-CA can be diagnosed earlier by performing cardiac screening in patients with CTS. Additionally, the complication of CTS is associated with a higher incidence of heart failure, atrial fibrillation, atrioventricular heart block, and pacemaker implantation (10).

Spinal canal stenosis and a ruptured distal biceps tendon (RBT) are common findings in patients with ATTR. A previous study showed that 14% of patients with ATTRwt had a history of clinically significant spinal canal stenosis, and a combination of CTS and spinal stenosis was present in 12% of the patients with ATTRwt (11). In another study, an RBT was found in 33.3% of patients with ATTRwt, and the presence of RBT had a positive predictive value of 66% for diagnosing ATTRwt in patients with heart failure with a preserved ejection fraction (12). Taken together, these findings suggest that CTS, spinal canal stenosis, and RBT are common extracardiac manifestations in ATTRwt, and their presence may indicate CA due to ATTRwt (Fig. 1) (13).

2. Biochemical analysis

To date, there is no biomarker either for the diagnosis or for evaluating the therapeutic effects of ATTR. Despite being a precursor protein of ATTR, serum transthyretin is not used for diagnosing ATTR because it reflects the nutritional status (14).

Some reports have shown the usefulness of high-sensitivity cardiac troponin T (hs-TnT) (15), which is usually used as a biomarker of myocardial damage, as a diagnostic biomarker of CA. Additionally, B-type natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT-proBNP) (16), which is a pivotal biomarker of heart failure, is a diagnostic biomarker of CA. Takashio et al. showed that the hs-TnT levels are persistently elevated in patients with CA compared with other types of cardiomyopathy (15). In their study, if the cut-off value of the hs-TnT level was 0.031 ng/mL, then the sensitivity for diagnosing CA was 74% and the specificity was 79% in patients with left ventricular hypertrophy (area under the curve of 0.787). Therefore, CA should be suspected in older patients with left ventricular hypertrophy in whom the hs-TnT levels continuously exceed 0.03 ng/mL. When assessing hs-TnT, ruling out confounding factors, such as myocardial ischemia, renal dysfunction, pulmonary embolism, and sepsis, is important because these conditions affect the hs-TnT levels. The level of hs-TnT is also elevated in cases of acute heart failure, and therefore, measuring the hs-TnT levels again after an improvement from the acute phase is recommended (17).

BNP and NT-proBNP are biomarkers that are commonly used for screening, the diagnosis, and the prognosis of heart failure. A suspicion of ATTRwt-CA should thus be targeted in patients with heart failure, elevated troponin levels, or BNP levels that are out of proportion to the clinical context (18). A study reported that the prognosis of ATTRwt-CA worsened due to the combination of hs-TnT (>0.05 ng/mL) and elevated NT-proBNP levels (>3,000 pg/mL) (14). In this study, the median survival time was 66 months for stage 1 (no increase in either marker), 42 months for stage 2 (increase in either biomarker), and 20 months for stage 3 (increase in both biomarkers).

Retinol binding protein 4 (RBP4) is a useful biomarker for identifying ATTR-CA in patients with heart failure. TTR usually exists as a tetramer complexed to RBP4, which is a protein integral to transport of vitamin A (19). When RBP4 is bound to TTR, the RBP4-retinol complex stabilizes the TTR tetramer, inhibiting the formation of amyloid fibrils. Circulating RBP4-TTR complexes are lower in patients with ATTR-CA and RBP4 is significantly and independently associated with ATTR amyloidosis cardiomyopathy (20).

3. Electrocardiography

Various characteristic electrocardiographic changes due to amyloid fibril deposition in the interstitial myocardium and conduction system have been recognized in patients with CA (Table). Low voltages in an electrocardiogram, despite the presence of cardiac hypertrophy, has been reported as a feature of CA (21). However, the frequency of low voltage

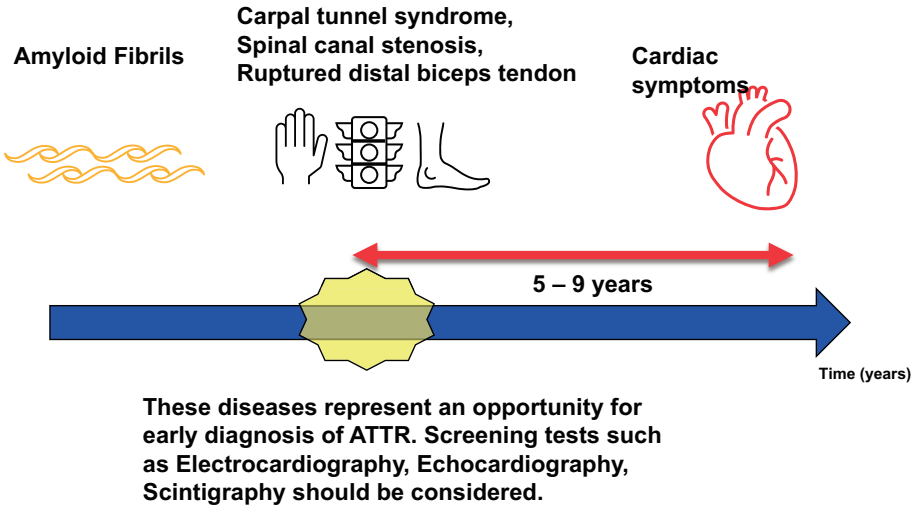

Figure 1. **A detailed medical history and physical examination are important for an early diagnosis of ATTR-CA. Carpal tunnel syndrome, spinal canal stenosis, and a ruptured distal biceps tendon precede cardiac events by 5-9 years. This indicates that ATTR-CA can be diagnosed earlier by performing cardiac screening in patients with these diseases.**

ranges from 13-40% in ATTR-CA (22, 23). Therefore, using only low voltage in electrocardiography (ECG) as a screening parameter for ATTR-CA is not recommended.

Despite non-specific findings, cardiac conduction disorder and atrial fibrillation are relatively common findings in ATTR-CA. Amyloid deposition in the conduction system causes cardiac conduction disorder. This appears as intraventricular conduction disorder, bundle branch block, and atrioventricular block. Intraventricular conduction disorder appears in the electrocardiographic findings as an expansion of QRS width. A wide QRS (QRS ≥ 120 ms) is strongly associated with ^{99m}Tc-PYP positivity, suggesting an association between ATTR and cardiac conduction disorder (24). Atrioventricular block is found in 15-26% of patients with AL amyloidosis and in 11-33% of patients with ATTRwt. Additionally, atrial fibrillation occurs in 6-40% of patients with AL amyloidosis and in 27-67% of patients with ATTRwt (5, 7, 25-27). The mechanism of atrial fibrillation may be a direct effect of amyloid deposition in the atrium, or the secondary factor of left atrial overload due to left ventricular diastolic dysfunction or an increase in left ventricular filling pressure. Although the timing of onset of atrial fibrillation in ATTRwt is not clear, ATTRwt should be ruled out in older patients with unexplained cardiac hypertrophy and atrial fibrillation.

Pseudo-infarct patterns are also relatively common with any type of CA. Pseudo-infarct patterns are found with an abnormal Q wave and poor R progression in precordial leads, despite no coronary artery disease. The positive rate of a pseudo-infarct pattern increases in proportion to the degree of progress of late gadolinium enhancement (LGE) in cardiac magnetic resonance imaging (CMR). The progression of amyloid deposition is associated with the appearance of a pseudo-infarct pattern (28).

4. Echocardiography

Echocardiography is a non-invasive method of assessing the cardiac morphology and function in patients with CA. The morphometric findings of CA often include biventricular hypertrophy with increased echogenicity of the myocardium, bilateral atrial enlargement, valve/papillary muscle thickening, atrial septal thickening, and pericardial effusion (29). A high-intensity echo within a thickened myocardium is called granular sparkling, which is one of the most well-known echocardiographic characteristics of CA. However, this sign is observed not only in CA, but also in other types of cardiomyopathy, and the sensitivity in amyloidosis is only 30% and the specificity is 71-81% (30). Moreover, recent echocardiographic imaging has been equipped with harmonic imaging as a standard feature, and therefore, it may cause normal hypertrophy to appear as granular sparkling.

A reduced atrial function due to amyloid protein deposition in the atrium is another characteristic of CA. In hereditary transthyretin cardiomyopathy with left ventricular hypertrophy, left atrial dysfunction has been reported, regardless of the atrial size (31). A decrease in the atrial strain rate during atrial systole and the left ventricular deformity index, regardless of the atrial size during atrial contraction, are strong predictors of atrial arrhythmia (e.g., atrial fibrillation). Atrial dysfunction is strongly associated with ventricular deformity (32-34).

Recently, speckle tracking echocardiography has been shown to be a useful modality for identifying CA (35-37). The condition of a relatively preserved longitudinal strain of the apex is called an apical sparing pattern, which is characteristic of CA, unlike other diseases with left ventricular hypertrophy (35-37).

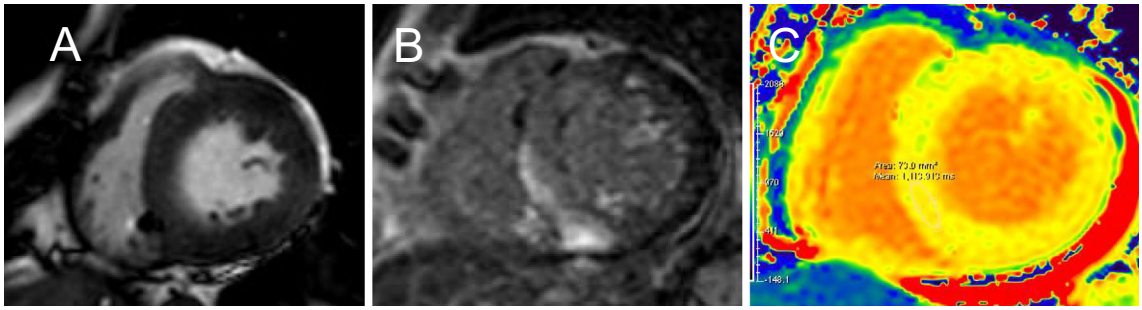

Figure 2. Representative CMR imaging in patients with ATTRwt-CA. Cardiac magnetic resonance imaging in patients with ATTRwt-CA. (A) Cine CMR shows concentric hypertrophy of the left ventricle. (B) LGE images show a heterogeneous pattern in the left and right ventricles, and a dark blood pool. (C) The native T1 relaxation time shows a considerable elevation.

5. Scintigraphy

Radioisotope scanning plays an important role in diagnosis of CA. In particular, a tracer that can detect calcium, such as ^{99m}Tc-PYP, ^{99m}Tc-hydroxymethylene diphosphonate, and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid, appears to be a strong screening tool for ATTR-CA. While ATTR shows the uptake of these tracers in the myocardium, AL does not show any uptake, even in the presence of heart lesions. These characteristics enable physicians to distinguish AL from ATTR (38). The degree of the accumulation of ^{99m}Tc-PYP can be evaluated by the visual evaluation method and the quantitative evaluation method. The visual evaluation method has grades 0-3, and grades 2 and 3 are positive. The quantitative evaluation method measures the heart-to-contralateral ratio, and it is positive when >1.5 after 1 hour and >1.3 after 3 hours (39). If these scintigraphic findings are positive and blood/urine M protein is negative, then the positive predictive value of ATTR CA is 100% (40). There is a trend to make a definite diagnosis without performing a tissue biopsy in many countries. However, in Japan, a tissue biopsy with amyloid deposits is necessary for a definitive diagnosis of amyloidosis. A relationship between the degree of the myocardial uptake of ^{99m}Tc-PYP and the prognosis of ATTR-CA has also been demonstrated (41). A heart-to-contralateral ratio >1.6 has been reported to be an independent poor prognostic factor of ATTR-CA (41).

6. Cardiac magnetic resonance imaging

CMR is an important and essential modality for assessing cardiomyopathy. Cine magnetic resonance imaging can evaluate morphology, such as left ventricular hypertrophy and contraction, pericardial effusion, and pleural effusion, but these findings are non-specific. CMR with LGE is currently considered to be one of the most reliable methods for assessing CA, and the diagnostic ability of LGE has a sensitivity and specificity of 85-90% (42). Typical LGE findings of CA are the appearance of the following: (1) global LGE with predominant left subendocardial or transmural LGE, (2) LGE of the right ventricular wall, left atrial wall, and atrial septum, and (3) a low blood signal called a dark blood pool (28). LGE is considered to reflect ischemia, which progresses due to amyloid deposited in interstitial tissue, subendocardial fibrosis, and microvessels (22, 23, 28). LGE has been proposed to shift from subendocardial to transmural LGE with the progression of disease, and LGE shows various patterns depending on the stage (28, 43). Therefore, LGE has a significant correlation with the clinical, morphological, functional, and biochemical markers, and it positively contributes to the prognostic evaluation of CA (44).

Recently, T1 mapping in CMR has been developed as a useful modality for the early diagnosis of CA and assessment of the severity of amyloid deposits. T1 mapping is a method that quantitatively measures the myocardial T1 relaxation time, which is acquired without the use of contrast, and it evaluates myocardial damage quantitatively. Because the sensitivity of detecting myocardial damage is higher in T1 mapping than in LGE, this method is expected to be useful for the early detection of CA. Post-contrast extracellular volume (ECV) mapping also estimates the size of the extracellular space and it has good sensitivity for identifying amyloidosis. The native T1 relaxation time and ECV of CA are significantly higher than those in similar morphological diseases, such as hypertrophic cardiomyopathy and aortic stenosis (45). The sensitivity of native T1 alone is 80-92% and the specificity is 56-91%, and the sensitivity of ECV is 93% and the specificity is 82%. Therefore, evaluations with other parameters are expected to improve the diagnostic ability for CA (43, 46, 47). Representative CMR images in patients with ATTRwt-CA are shown in Fig. 2.

Important Points for Making a Definite Diagnosis of Cardiac Amyloidosis

The definitive diagnosis of systemic amyloidosis is based on histological evidence of amyloid deposition by Congo red or direct fast scarlet staining. If amyloid deposition cannot be detected by these methods, then an electron microscopic examination should be considered (48). If amyloid deposits are detected, then additional immunohistochemical staining for precursor proteins can be used to identify the

type of amyloidosis. In the case of CA, identification using primary antibodies of κ chain, λ chain, and transthyretin is important.

With regard to the site of biopsy, amyloid deposition can be detected at a high probability by performing it in an organ showing symptoms or imaging findings that suggest amyloid deposition. However, relatively minimally invasive sites, such as abdominal fat or the gastrointestinal tract, are often selected as the primary biopsy site in older patients. This is because a diagnosis of CA is acceptable if the clinical and imaging evidence highly suggests CA and there is histological confirmation of amyloid deposition in non-cardiac tissue. An abdominal fat aspiration biopsy is widely performed because it is safe and convenient. This type of biopsy is minimally invasive and has the advantage that it can be performed repeatedly at multiple sites. However, the amyloid detection rate with an abdominal fat aspiration biopsy is reported to be 14-15% in ATTRwt, which is lower than that in other types of systemic amyloidosis (49, 50). The reason for this finding is because amyloid deposits are mainly found in the deep layer of subcutaneous fat tissue and they show a patchy distribution in ATTRwt (51). Additionally, because the amount of samples from an abdominal fat aspiration biopsy is small, immunohistological typing is difficult if there is little amyloid deposition. Therefore, surgical abdominal wall skin biopsy, including the deep subcutaneous fat pad, is often selected with the aim of improving the diagnostic rate. A surgical skin biopsy can be safely performed at the bedside, and its sensitivity has been reported to be as high as 73%, which is useful for the histopathological diagnosis of ATTRwt (51). In the gastrointestinal tract, amyloid fibril deposits are mainly on the muscularis mucosa and the vascular wall of the submucosa. However, in the case of ATTRwt, amyloid deposits are predominantly detected in the walls of the small arteries, and the distribution of amyloid deposits is not uniform; therefore, the diagnostic rate is not high (52).

As described above, the frequency of sampling errors is not small in tissue biopsy samples that are obtained from abdominal fat or the gastrointestinal tract. Therefore, an endomyocardial biopsy is sometimes necessary in cases in when it is important to consider both invasiveness and risk. Although the myocardium is a highly invasive organ for biopsy, the frequency of serious complications in endomyocardial biopsy is reported to be less than 1% (53, 54). In the heart, amyloid protein is typically deposited from the endocardium, and diffusely deposited in the left and right ventricles. There is no difference in the ratio of sampling error between the right and left ventricles, and the detection rate of amyloid deposits is considered to be almost 100% (49, 55). In the early stage of ATTRwt, the detection rate of amyloid is not high in biopsies except for in the myocardium. Additionally, the accuracy of diagnosis may improve by performing an endomyocardial biopsy with reference to ^{99m}Tc-PYP scintigraphy (39).

Conclusion

We reviewed the recent knowledge of ATTR-CA, especially focusing on early screening and making a definite diagnosis. Clinical suspicion is most important for identifying patients with ATTR-CA at an early stage. ATTR-CA is becoming a curable disease, but the types of therapeutic intervention are limited. Therefore, further research to clarify the mechanism of onset and the development of ATTR-CA from multiple points of view is required.

Author's disclosure of potential Conflicts of Interest (COI).
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