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CASE REPORT
Cardiac imaging

Case report regarding the evolution of electrocardiographic and echocardiographic features in cardiac amyloidosis

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Background Cardiac amyloidosis is an important cause for heart failure with preserved ejection fraction. It is often under diagnosed due to the fact that clinicians do not always recognize the specific diagnostic findings associated with this disease, also leading to the wrong diagnosis. When left untreated further irreversible organ dysfunction occurs, with high morbidity and mortality rates.

Case summary A 71-year-old patient presented with progressive exertional dyspnoea and angina pectoris at the outpatient clinic. Medical history noted a percutaneous coronary intervention of the right coronary artery due to stable angina pectoris. The electrocardiogram showed low voltage in the limb leads and pseudo-infarct pattern in the precordial leads. Echocardiographic findings included left and right ventricular hypertrophy, decreased left ventricular systolic function, restrictive diastolic function, and 'relative' apical sparing of the left ventricle. This led to the suspicion of cardiac amyloidosis, which was confirmed with a positive bone scintigraphy using ^{99m}Technecium-DPD and the absence of monoclonal proteins. Treatment with Tafamidis was initiated.

Discussion Electrocardiographic findings suggestive of cardiac amyloidosis are low voltage in the limb leads and/or a pseudo-infarct pattern in the precordial leads. Important echocardiographic findings are left and right ventricular hypertrophy, restrictive diastolic function, 'relative' apical sparing of the left ventricle and impaired left atrial strain. The next step in confirming the diagnosis is ^{99m}Technecium PYP/DPD/HMDP bone scintigraphy and testing for monoclonal proteins. The diagnosis ATTR amyloidosis is confirmed by the combination of positive bone scintigraphy (Perugini Grade 2 or 3) and the absence of monoclonal proteins, without the necessity of performing an endomyocardial biopsy.

Keywords Cardiac amyloidosis • Electrocardiography • Echocardiography • Speckle-tracking • Case report

Learning points

- Angina pectoris can be a presenting symptom in patients with underlying cardiac amyloidosis.
- Electrocardiographic findings suggestive of cardiac amyloidosis are low voltage in limb leads and pseudo-infarct pattern in precordial leads
- Important echocardiographic findings suggestive of cardiac amyloidosis are bi-ventricular hypertrophy, restrictive diastolic function, and 'relative' apical sparing of the left ventricle using global longitudinal strain.
- Endomyocardial biopsy is not necessary to confirm the diagnosis of ATTR amyloidosis if a patient with heart failure has echocardiographic findings suggestive of cardiac amyloidosis in combination with a positive bone scintigraphy (^{99m}Technecium-PYP/DPD/HMDP) and in the absence of monoclonal proteins.

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Introduction

Cardiac amyloidosis is an important cause for heart failure with preserved ejection fraction. It is often under diagnosed due to the fact that clinicians do not always recognize the specific diagnostic findings associated with this disease, which can lead to the wrong diagnosis. When left untreated further irreversible organ dysfunction occurs, leading to high morbidity and mortality rates. Median survival ranges from less than 6 months in amyloid light-chain (AL) amyloidosis and up to three to 5 years in transthyretin (ATTR) amyloidosis.[1] The use of multiple non-invasive imaging techniques (including electrocardiography, echocardiography, cardiac magnetic resonance imaging, nuclear imaging, and serology) can be utilized to diagnose ATTR amyloidosis as the underlying cause of heart failure without the necessity of an endomyocardial biopsy.[1] Improved and widespread knowledge on these specific non-invasive diagnostic findings will lead to earlier detection and diagnosis, leading to faster initiation of treatment to slow irreversible disease progression.

Timeline

July 2014	Referral to cardiologist by general practitioner (GP) due to angina pectoris (CCS class II) and exertional dyspnoea. MIBI-SPECT; no ischaemia.
July 2015	Stable angina pectoris. Echocardiogram: normal left ventricular function and mild aortic stenosis. Positive ergometry. Coronary angiogram one vessel disease right coronary artery (RCA), fractional flow reserve-guided (0.78) percutaneous coronary intervention RCA performed.
October 2016	Persistent stable angina pectoris. Echocardiogram: severe concentric left ventricular hypertrophy with normal systolic function and mild aortic stenosis. Coronary angiogram; stent patent, no other significant stenosis.
June 2017	Persistent stable angina pectoris despite medical treatment. Echocardiogram: severe concentric left ventricular hypertrophy with normal ejection fraction, restrictive diastolic function, and mild aortic stenosis. Suspected microvascular disease and treatment with calcium-antagonist initiated.
January 2018	Patient asked to be referred back to his GP.
December 2019	New referral to cardiologist due to exertional dyspnoea, decreased exercise tolerance and angina pectoris. Echocardiogram: severe concentric left ventricular hypertrophy, ejection fraction 40% and restrictive diastolic function, suspect for cardiac amyloidosis. DPD scan is performed and positive (Perugini Grade 3). Absence of monoclonal proteins. The diagnosis ATTR amyloidosis is made and treatment with Tafamidis is initiated.

Case presentation

A 71-year-old man was referred to our outpatient clinic for echocardiography with symptoms of decreased exercise tolerance, exertional dyspnoea and angina pectoris. Relevant medical history reports fractional flow reserve-guided (0.78) percutaneous coronary intervention (PCI) of the right coronary artery (RCA) in 2015 due to stable angina pectoris. Angina pectoris persisted during follow-up and coronary angiography was repeated in 2016. The stent was patent with no new significant coronary artery disease. The last echocardiography performed in 2017 described mild aortic stenosis, left ventricular hypertrophy and a restrictive diastolic function. The diagnosis microvascular coronary artery disease was suspected. Treatment with calcium-antagonists was initiated with moderate improvement in symptoms. At the time of referral the patient used metoprolol 50 mg once daily, amlodipine 5 mg once daily, nitroglycerine plaster 5 mg/24 h once daily, and acetylsalicylic acid 80 mg once daily.

The patient reported a significant decline in his ability to exercise. The patient used to cycle more than 15 000 km a year but is currently only able to cycle short distances using electrical support.

Physical examination revealed a man of average stature (body mass index 24 kg/m^2) with a blood pressure of 133/75 mmHg and a pulse of 57 b.p.m. A systolic murmur (Grade II/VI) was heard at the right second intercostal space. Further physical examination revealed no further abnormalities.

The electrocardiogram showed sinus rhythm 57 b.p.m., normal electrical axis, first degree atrioventricular block, QRS duration of 94 ms, low voltage in the limb leads and pseudo-infarct pattern in the precordial leads. Compared to the previous electrocardiograms low voltage in the limb leads were progressive (*Figure 1*). Although the first electrocardiogram from 2016 does not meet the criteria for low voltage in the limb leads, it is disproportionally low compared with the amount of left ventricular hypertrophy on the echocardiogram.

Left and right ventricular hypertrophy with a decreased systolic left ventricular function (41%) was seen on echocardiogram (*Figure 2* and Supplementary material online, *Videos S1* and *S2*). Further echocardiographic findings were mild aortic stenosis, bi-atrial dilation, interatrial septum thickening, and restrictive diastolic function (*Figure 3*). The global longitudinal strain (GLS) of the left ventricle was decreased (-8.8%) with 'relative' apical sparing (*Figure 2*). Moreover, left atrial GLS was impaired (*Figure 4*). These echocardiographic findings raised a high suspicion of cardiac amyloidosis.

Current echocardiographic findings were compared to previous findings. This revealed progressive thickening of both ventricles and the interatrial septum (*Figure 2*). Over time the diastolic dysfunction became restrictive with an increase in *E/A* ratio, decrease of e′ and reversal of pulmonary vein flow (*Figure 3*). Pattern of 'relative' apical sparing of the left ventricle became more pronounced (*Figure 2*).

To confirm the suspicion of cardiac amyloidosis a bone scintigraphy (using technecium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid (^{99m}Tc-DPD)) was performed which was positive (Perugini Grade 3) (*Figure 5*). Blood testing confirmed the absence of monoclonal proteins, leading to the diagnosis of ATTR amyloidosis. To differentiate between wildtype and hereditary ATTR amyloidosis blood samples were taken and analysed. No genes associated with

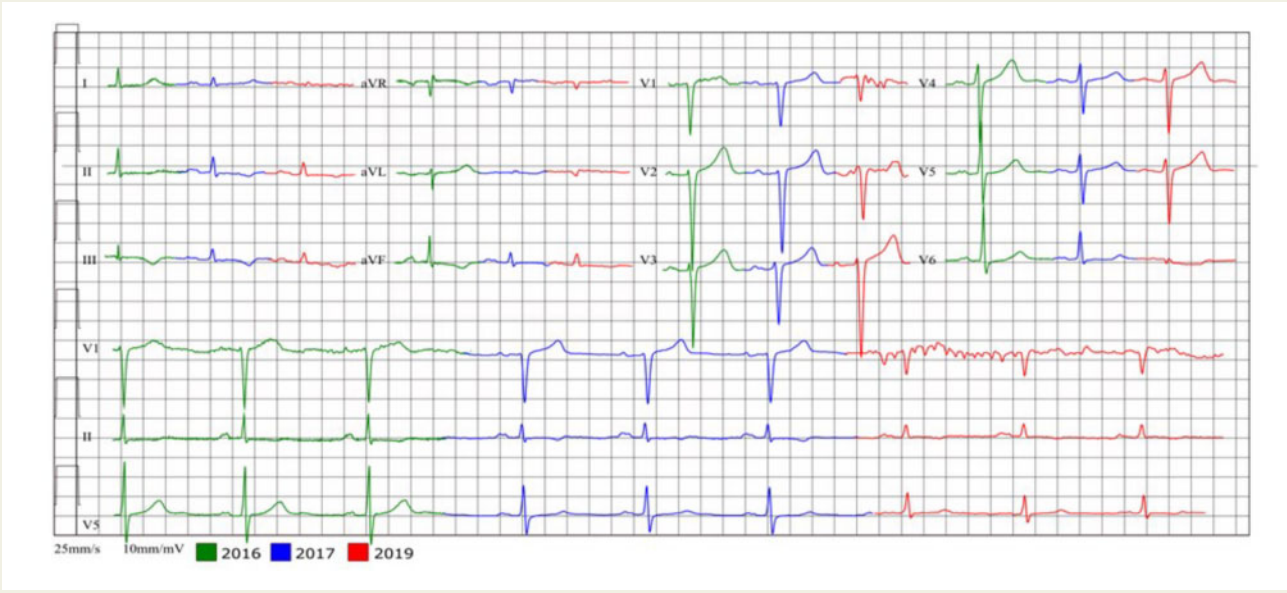

Figure 1 Electrocardiograms in chronological order (*A*: merged electrocardiogram, *B*: 2016, *C*: 2017, *D*: 2019).

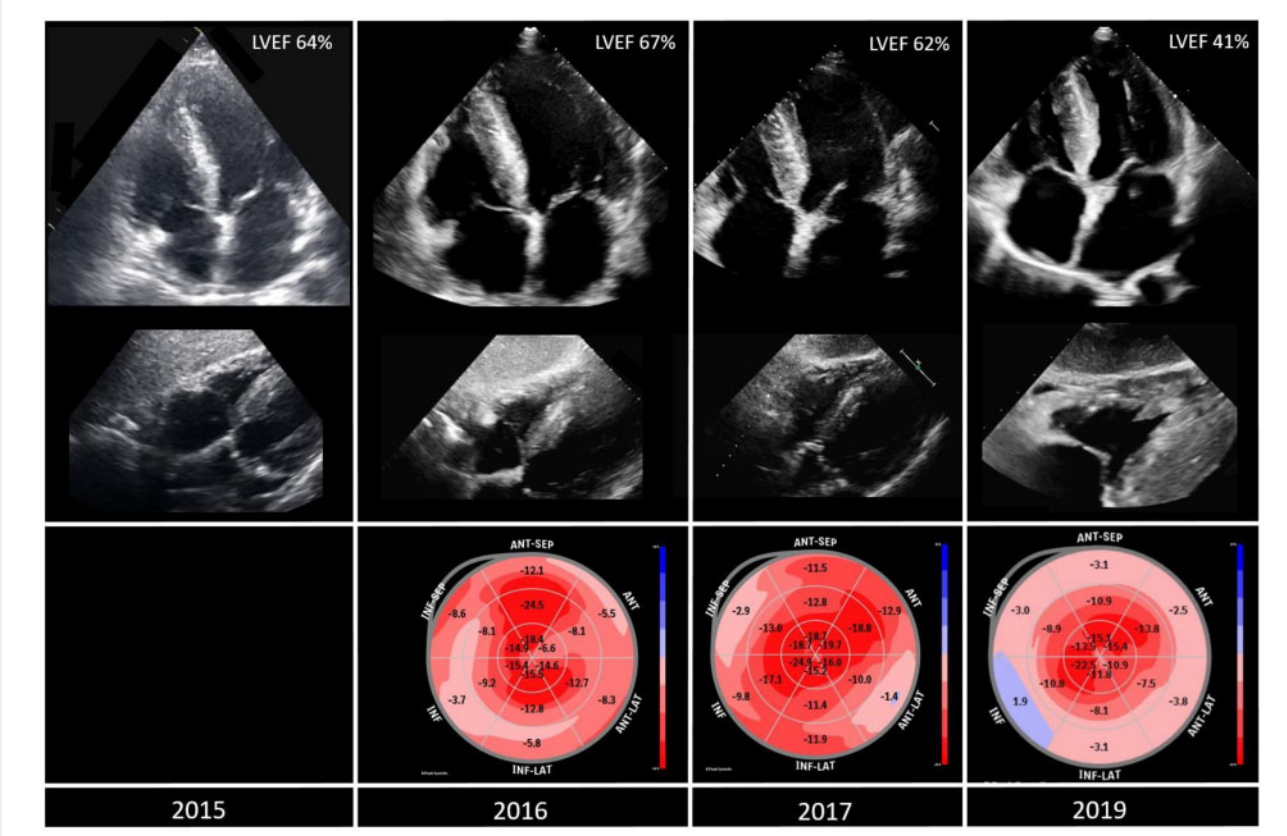

Figure 2 (1) Apical four-chamber view depicting the left ventricular hypertrophy and calculated left ventricular ejection fraction (LVEF) using the biplane Simpson method. (2) Subcostal view depicting the right ventricular hypertrophy. (3) Global longitudinal strain (GLS) of the left ventricle with apical sparing.

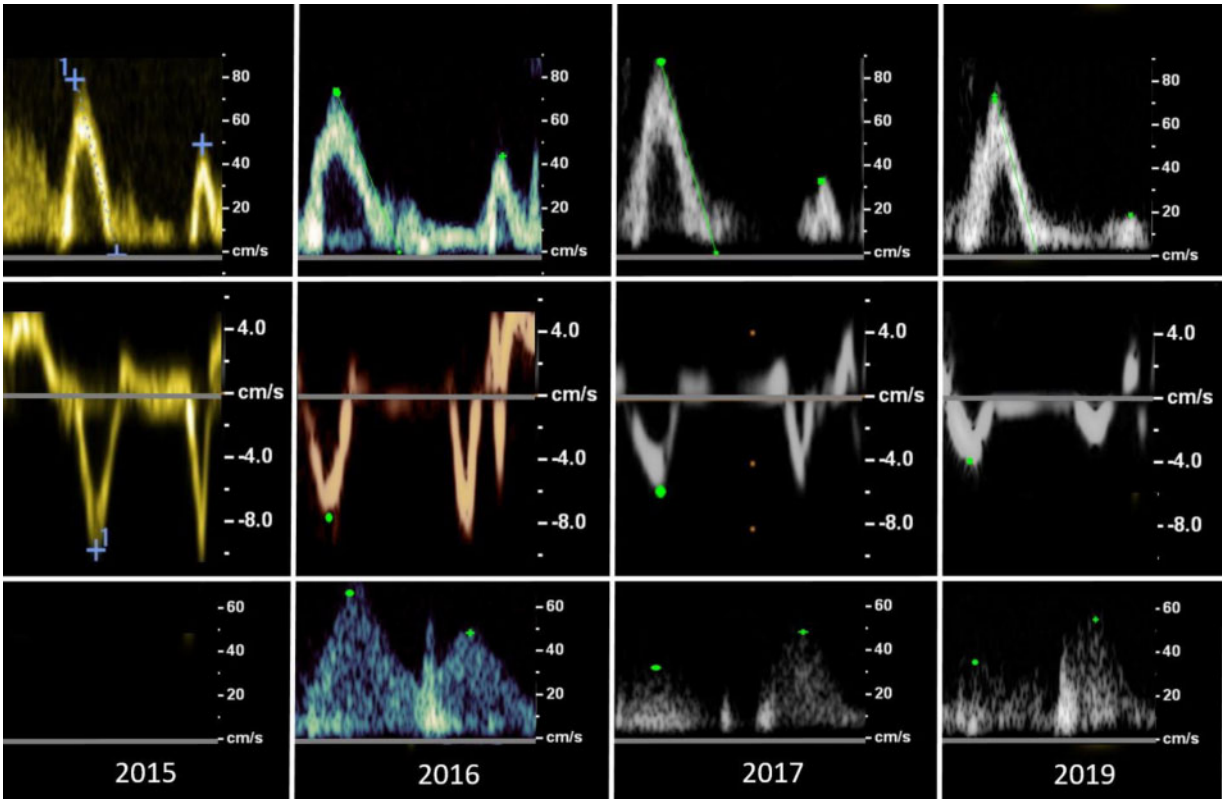

Figure 3 Diastolic function parameters; *E/A* ratio, e′ septal, and pulmonary vein flow.

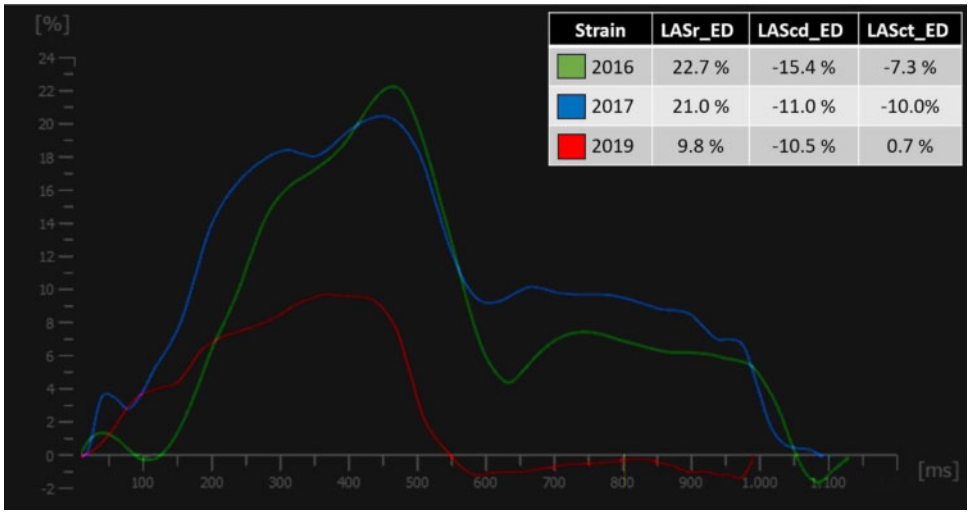

Figure 4 Left atrial global longitudinal strain in chronological order. Zero strain reference at end-diastole. LASr_ED, left atrial strain during reservoir phase; LAScd_ED, left atrial strain during conduit phase; LASct_ED, left atrial strain during contraction phase.

hereditary ATTR amyloidosis were found, confirming the diagnosis of wildtype ATTR amyloidosis. Treatment with Tafamidis 80 mg once daily (built up over 4 weeks from 20 mg once daily) was initiated and will be continued indefinitely. As follow-up an echocardiogram will be repeated 1 year after treatment with Tafamidis.

Discussion

Retrospectively the initial presenting symptom of angina pectoris, proven epicardial coronary artery disease with a PCI of RCA and later diagnosis of microvascular disease was the main focus during

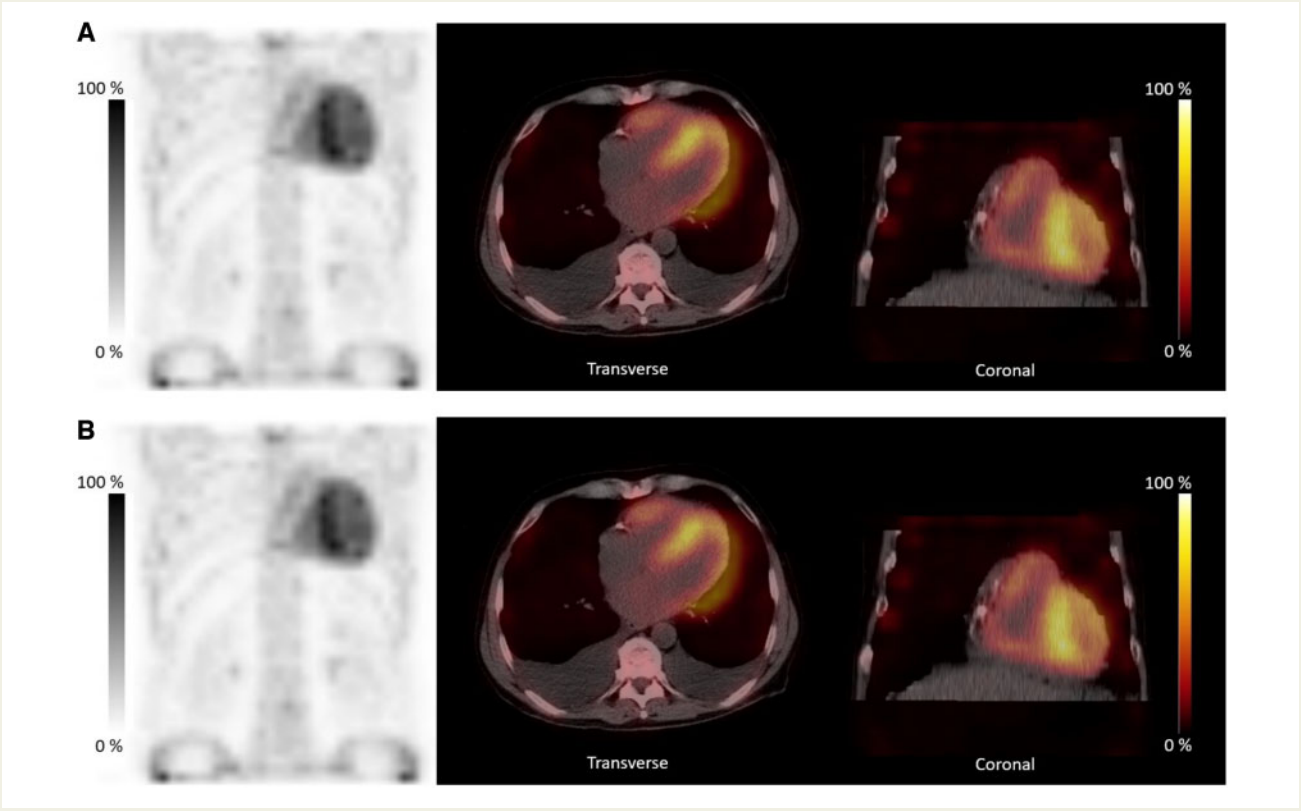

Figure 5 Bone scintigraphy (^{99m}Technecium-DPD) with HCL ratio of >1.5 and Grade 3 according to the Perugini grading system.

follow-up. Throughout the years angina pectoris persisted despite treatment. It is probable that the underlying cause of these symptoms was the ATTR amyloidosis and not the coronary artery disease itself. Cardiac amyloidosis mainly causes heart failure with preserved ejection fraction and there are no typical symptoms related to cardiac amyloidosis. An important note is that angina pectoris can occur in the setting of cardiac amyloidosis whilst coronary angiography reveals no epicardial coronary artery disease.[2] One study has shown that in patients with proven cardiac amyloidosis microvascular coronary dysfunction is present. Angina pectoris was the prevailing symptom in 26% of these patients.[2] Showing that clinicians should look further in cases of patients with angina pectoris and no epicardial coronary artery disease, using additional diagnostic tools such as electrocardiography and echocardiography.

Electrocardiographic findings suggestive for cardiac amyloidosis are low voltage and pseudo-infarct pattern. Low voltage is defined as a QRS-voltage amplitude of ≤0.5 mV in the limb leads. Previous studies report the presence of low voltage in patients with proven cardiac amyloidosis ranging from 46% up to 57%.[3–5] Pseudo-infarct pattern in the precordial leads is found in 40.2–47% of patients with cardiac amyloidosis, whereas left ventricular hypertrophy is described in only 16%.[4,5] Electrocardiographic findings alone cannot be used to diagnose cardiac amyloidosis, it is a supportive finding and additional diagnostic assessment is necessary.

Echocardiography is an important and frequently used non-invasive diagnostic tool that is easily accessible. There are multiple echocardiographic findings that are suggestive for cardiac amyloidosis and should be recognized by clinicians. It is important to note that the majority of echocardiographic findings are seen at a later stage of the disease.

The echocardiographic findings suggestive of cardiac amyloidosis are left and right ventricular hypertrophy, bi-atrial dilation, thickening of the interatrial septum, thickening of the valvular leaflets, and presence of pleural and/or pericardial effusion.[1] In the earlier stages of the disease the left ventricular systolic function remains normal, but during disease progression worsening of the left ventricular systolic function will occur.[1] Diastolic function changes with gradual decrease of the A-wave, an increase of the *E*/*A*-ratio and progressive increase in the deceleration time. The pulmonary vein flow reverses due to high filling pressures. Tissue Doppler signals of septal and lateral mitral valve annulus decrease over time.[1] Speckle tracking can be used to determine the GLS of the left ventricle. If 'relative' sparing of the apex is present, it is highly suggestive of cardiac amyloidosis.[1,6] Strain imaging of the left atrium has been reported to show significant impairment of the reservoir and booster pump function.[1]

It is not possible to distinguish AL from ATTR amyloidosis based on the echocardiographic findings alone. Although research has shown that there are some differences between echocardiographic patterns of ATTR and AL amyloidosis. These differences include increased dimensions of both the left and right ventricular chambers, larger atria and higher left and right ventricular wall thickness in ATTR compared to AL amyloidosis.[1,7]

Echocardiographic findings alone are not sufficient for the diagnosis cardiac amyloidosis. Two additional diagnostic tests have to be

performed to be able to confirm the diagnosis.[1,8] The first test is a bone scintigraphy using ^{99m}Technecium PYP/DPD/HMDP as tracer. It has been shown that bone scintigraphy has a high sensitivity and specificity for diagnosing ATTR cardiac amyloidosis.[9] There are important pitfalls to consider with a recent study showing low sensitivity in a subgroup of patients with Phe64Leu mutation related ATTR amyloidosis.[10] The second test is screening of blood samples for the presence of monoclonal proteins. The diagnosis ATTR amyloidosis is confirmed by a combination of positive bone scintigraphy Perugini Grade 2 or 3 and the absence of monoclonal proteins, with specificity and positive predictive value of 100%.[8] If this combination of results is found, no endomyocardial biopsy needs to be performed to confirm of the diagnosis.[8]

Confirmation of the diagnosis ATTR amyloidosis is important because targeted therapy can be initiated with the aim to slow disease progression. The current treatment options for ATTR amyloidosis are Tafamidis, Inotersen, and Patisiran.[11–13] Recent randomized controlled trials have shown that treatment with Tafamidis or Patisiran leads to lower all-cause mortality rates and less hospitalizations.[11,12] Inotersen has been shown to stabilize cardiac function, increase distance in 6-min walking test and decrease in left ventricular mass.[13]

Conclusion

This case report describes the natural disease progression of a patient with ATTR amyloidosis using a variety of electrocardiographic and echocardiographic findings. Improved and widespread knowledge of these specific non-invasive diagnostic findings will lead to earlier detection and diagnosis, leading to faster initiation of treatment to slow irreversible disease progression.

Lead author biography

Drs Fabienne E. Vervaat is cardiologist in training at Catharina Hospital (Eindhoven, the Netherlands), a regional referral hospital for cardiac amyloidosis. Her areas of interest are refractory angina pectoris and coronary artery disease in general.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

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