ORIGINAL ARTICLE

Echocardiographic and electrocardiographic presentations of patients with endomyocardial biopsy-proven cardiac amyloidosis

Aslannif Roslan, MRCP, Suraya Hani Kamsani, MRCP, Nay Thu Win MRCP, Kin Leong Tan MRCP, Najmi Hakim, CTS, Ai Ming Tan, CTS, Wan Nabeelah Megat Samsudin, MD, Ahmad Tantawi Jauhari Aktifanus, MD, Malini Kerisnan, MD, Dalleen Leong, MD, Thamarai Supramaniam, MD, Lay Koon Tan, FACC, Amin Ariff, FACC

Non Invasive Cardiac Laboratory, Department of Cardiology, Institut Jantung Negara,Kuala Lumpur, Malaysia

ABSTRACT

Objective: Cardiac amyloidosis is under diagnosed and its prevalence is unknown. This is a retrospective, non-randomised, single centre study of patients with endomyocardial biopsy-proven cardiac amyloidosis focusing on their echocardiographic and electrocardiogram (ECG) presentations. This is the first case series in Malaysia on this subject.

Methods: We identified all of our endomyocardial biopsy-proven cardiac amyloidosis patients from January 2010 to January 2018 and reviewed their medical records. All patients echocardiographic and ECG findings reviewed and analysed comparing to basic mean population value.

Results: In total there are 13 biopsy-proven cardiac amyloidosis patients. All of the biopsies shows light chain (AL) amyloid. Majority of the patients (8, 61.5%) is male, and most of our patients (8, 61.5%) is Chinese. All seven patients on whom we performed deformation imaging have apical sparing pattern on longitudinal strain echocardiogram. Mean ejection fraction is 49.3%, (SD=7.9). All patients have concentric left ventricular hypertrophy and right ventricular hypertrophy. Diastolic dysfunction was present in all of our patients with nine out of 13 patients (69.2%) having restrictive filling patterns (E/A ≥2.0 E/e' ≥15). On electrocardiogram, 12 (92%) patients have prolonged PR interval (median 200ms, IQR 76.50ms) and 9 (69.2%) patients have pseudoinfarct pattern.

Conclusion: Echocardiography plays an important role in diagnosing cardiac amyloidosis. The findings of concentric left ventricular hypertrophy with preserved ejection fraction without increased in loading condition should alert the clinician towards its possibility. This is further supported by right ventricular hypertrophy and particularly longitudinal strain imaging showing apical sparing pattern.

KEY WORDS:
Cardiac Amyloidosis, Left Ventricular Hypertrophy, Right Ventricular involvement, Myocardial Strain, Apical Sparing, Transesophageal echocardiogram

INTRODUCTION

Cardiac amyloidosis is a disease in which a protein-based infiltrate deposits in heart tissues as beta-pleated sheets.[1] It is part of the differential diagnosis of left ventricular hypertrophy.[2] The other differentials are hypertensive cardiomyopathy and aortic stenosis, which are associated with increase in loading condition, and hypertrophic cardiomyopathy and Anderson-Fabry disease, which are intrinsic diseases of the heart.[2] The two most common types of cardiac amyloidosis, are the light chains amyloidosis (AL Amyloidosis) and the transthyretin (TTR), TTRwild and TTRmutant.[3] It is important to realize that the different types of cardiac amyloidosis are treated differently, and have different prognosis.[4] The most important initial investigation that point towards the diagnosis is transthoracic echocardiogram that shows left ventricular hypertrophy, bi-atrial dilatation, small pericardial effusion, and thickening of cardiac valves, papillary muscles, and interatrial septum, with highly refractile myocardium.[5] Previous reports of electrocardiographic (ECG) findings of patients with cardiac amyloidosis include corrected QT interval (QTc) prolongation, low-voltage, pseudo-infarct patterns, arrhythmias and conduction abnormalities.[6, 7]

In recent time, myocardial longitudinal strain showing apical sparing was shown to be highly specific for cardiac amyloidosis regardless of its etiology.[6] This is the first case series in Malaysia of 13 patients with endomyocardial biopsy-proven cardiac amyloidosis (AL Amyloidosis) concentrating on echocardiographic, ECG, clinical presentation, and cardiac biomarkers on initial presentation to our centre.

MATERIALS AND METHODS

We identified all of our endomyocardial biopsy-proven cardiac amyloidosis patients from January 2010 to January 2018 and reviewed their medical records. We gathered pertinent initial clinical presentations, blood pressure and heart rate on presentation, and their initial ECGs, looking at parameters such as the PR and QTc intervals, and presence of any pseudoinfarct pattern, arrhythmia, low voltage or left ventricular hypertrophy. We collected their initial biomarkers such as N-terminus Beta natriuretic peptide (NT-pro BNP) and high sensitivity troponin T (hs-Trop T).

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Corresponding Author: Aslannif Bin Roslan
Email: dr.aslannif@ijn.com.my

For the echocardiographic indices, we documented the degree of wall thickness at end diastole in parasternal long axis view (interventricular septum and posterior wall), the biplane Simpson ejection fraction (EF), and the size of both the atrias (in apical 4-chamber view) and the left ventricle (parasternal long axis view). We also looked at the ratios of early diastolic over atrial contraction blood velocity (E/A) and early diastolic blood velocity over medial mitral annulus tissue velocity (E/e') (from pulse wave mitral inflow at the leaflet tips and pulse wave tissue Doppler at the septal annulus respectively) for assessment of diastolic function. We assessed systolic pulmonary artery pressure (from maximum tricuspid regurgitation gradient and estimation of right atrial pressure from the size and collapsibility of inferior vena cava), right ventricular hypertrophy (subcostal 4-chamber zoom view of right ventricle lateral wall), pericardial effusion and its size, valvular regurgitation, eyeball assessment of interatrial septum and where available, the longitudinal strain pattern. For our longitudinal strain, we used General Electric Vivid E9 machine. Three consecutive cardiac cycles of the three apical views were acquired and stored digitally as raw data, for subsequent post-processing analysis. For each of the apical views (two-chamber (2CH), three-chamber (3CH), and four-chamber (4CH), three sampling points were placed manually at the septal and lateral mitral annulus and at the apical endocardium. A region of interest (ROI) was then generated by the software to cover the entire thickness along the left ventricle myocardium. Longitudinal two-dimensional speckle-tracking strain values were obtained from one representative cycle, avoiding premature beats. The peak global longitudinal strain values were estimated after the aortic valve closure had been identified visually, frame-by-frame, in the apical long-axis (APLAX) view. Normal mean global peak longitudinal strain for Vivid GE E9 is –24.3% (SD=3.4).

Finally, we looked at the time taken from initial investigation to diagnosis and patients' outcome. The ethical approval of the study is from Institut Jantung Negara Ethic Committee. Our reference number is IJNREC/366/2018.

RESULTS

All 13 of our biopsy-proven cardiac amyloidosis were AL amyloid. Eight (61.5%) patients were male and 5 (38.5%) were female. The mean age at presentation was 62.9 (SD=12.1) years. Mean systolic blood pressure was 104 mmHg and mean diastolic blood pressure was 65.6 mmHg. Majority of patients present with symptoms of dyspnoea (n=11, 84.6%) and lower limb oedema (n=8, 61.5%). The average time between clinical presentation and diagnosis of cardiac amyloidosis is 4.6 months. Five (38.5%) patients died at the average of three months after diagnosis.

All patients (100%) have ejection fraction above 40% (mean 49.3, SD=7.9%), concentric left ventricular hypertrophy and right ventricular involvement (mean 0.87, SD=0.28cm). Of those patients whom longitudinal strain is available (n=7), all showed typical apical sparing pattern. Diastolic dysfunction was present in all of our patients. Nine out of 13 patients (69.2%) have restrictive filling patterns (E/A ≥2.0 E/e' ≥15) while four out of 13 patients (30.8%) have pseudonormal filling patterns (E/A ≥ 0.8-2.0). The RA (right atrium) size and LA (left atrium) size is dilated in all patients.

Twelve out of 13 (92.3%) patients have elevated mean left atrial pressure as estimated by E/e' ≥15 (mean 23.2 SD=9.5). All our patients have thickened interventricular septum (median 1.70, IQR 0.40cm) and posterior wall (mean 1.72, SD=0.51cm). The systolic pulmonary artery pressure is only mildly elevated (mean 35.1, SD=12.9mmHg). Seven out of 13 patients (53.8%) have reduced right ventricular function (TAPSE <1.7). Eight out of 13 patients (61.5%) have increased interatrial septal thickness. Ten out of 13 patients (76.9%) have pericardial effusion and nine out of 13 patients (69.2%) have pleural effusions.

The average heart rate on presentation was 75.9 beats per minute (SD= 25.1). Apart from one patient with complete heart block, all the others (n=12) have significantly prolonged PR interval (median 200ms, IQR 76.50ms). Three out of 13 patients (23%) have low voltage QRS, 1(7.7%) have ECG changes fulfilling the LVH criteria, and the rest (n=9, 69.2%) have normal QRS voltage. From the point of view of arrhythmias, two patients (15.4%) have paroxysmal atrial fibrillation, one (7.7%) have complete heart block, one (7.7%) have intermittent complete heart block, one (7.7%) have sinus pause, one (7.7%) have ventricular fibrillation episode and one (7.7%) have non- sustained ventricular tachycardia on 24 hours Holter monitoring. The median corrected QT interval on ECG is 457ms (IQR= 33.5ms).

DISCUSSION

Cardiac amyloidosis is an underdiagnosed condition and its prevalence is unknown. The two commonest types of cardiac amyloidosis are light chains (AL) and transthyretin (TTR) cardiac amyloid and less commonly, isolated atrial amyloidosis (IAA) and secondary (AA) amyloidosis.[8] Secondary amyloidosis is caused by serum amyloid A and called AA amyloidosis. It is seen in association with rheumatic disorders such as juvenile or adult rheumatoid arthritis and ankylosing spondylitis, as well as with inflammatory bowel disease. Hepatic and renal amyloid deposition dominates the clinical features, and clinical heart disease related to cardiac amyloidosis is rare.[9]

AL Amyloidosis affected both genders with slight predominance of men over women and it is usually diagnosed at the age of 55-60 years.[10] This is also reflected in our study, which shows slight male predominance (8 vs 5) with average age of diagnosis of 62.8 years. One notable result of our series is the absent of TTR cardiac amyloidosis diagnosis which suggest unfamiliarity with its diagnosis and the lack of access to pyrophosphate imaging.

Echocardiography is one of the most important imaging modalities to diagnose cardiac amyloidosis. The diagnosis must always be sought in patients with wall thickness more than 1.3cm without increase in loading conditions (hypertension and aortic stenosis).[10] In most hypertensive patients, left ventricular wall thickness is normal or only mildly increased (<1.3cm).[11] As athletes with wall thickness more than 1.3cm are exceedingly rare and more than 1.5cm

Table I: Demographic data

Parameters	Mean and SD
Age	62.9 (SD=12.1)
Gender	
Male	8 (61.5%)
Female	5 (38.5 %)
Ethnicity	
Malay	4 (31%)
Chinese	8 (61.5%)
Indian	No
Others	1 (7.5%)
Type of biopsy	All endomyocardial biopsy
Type of amyloidosis	All light chain Amyloidosis (AL Amyloidosis)
Comorbidities	
Hypertension	4 (30%)
Diabetes Mellitus	No
Coronary Artery Disease	2 (15%)
Chronic Kidney Disease	No
Liver Disease	2 (15%)
Others	1 (Multiple Myeloma, 7.5%) 1 (Hypocortisolism), 7.5%)
No comorbids	3 (25%)

Table II: Initial echocardiographic parameters

Parameters	Mean, SD	Median IQR	Normal Value (Male)	Normal Value (Female)
Left ventricular ejection fraction	49.3, 7.9		62 (SD = 5)	64 (SD =5)
Right ventricle lateral wall, cm	0.87, 0.28		0.3 – 0.5	0.3 – 0.5
Interventricular septum, cm		1.70,0.40	0.6 -1.0	0.6 – 0.9
Posterior wall, cm	1.72, 0.51		0.6 -1.0	0.6 – 0.9
Systolic pulmonary artery pressure, mmHg	35.1, 12.9		18-25	18-25
E/e'	23.2, 9.5		< 8.0 (normal) 8-15 (indeterminate) > 15.0 (elevated)	< 8.0 (normal) 8-15 (indeterminate) > 15.0 (elevated)
E/A	2.4, 2.1		0.8 – 2.0 (normal/pseudonormal) < 0.8 (impaired relaxation) > 2.0 (restrictive)	0.8 – 2.0 (normal/pseudonormal) < 0.8 (impaired relaxation) > 2.0 (restrictive)
LA, cm^2	24.6, 8.2		< 20.0	< 20.0
RA, cm^2	19.2, 4.3		< 18.0	< 18.0
LVIDd, cm	4.1, 1.2		50.2(SD=4.1)	45 (SD=3.6)
LVIDs, cm	3.2, 0.6		32.4 (SD=3.7)	28.2 (SD=3.3)
TAPSE, cm	1.6, 0.4		> 1.7	> 1.7
LA volume, cm^3	82.4, 22.0		< 34cm3/m2	< 34cm3/m2
LV Mass, g	261.5, 117.5		88-224	67 -162
Global longitudinal strain Apical 3 chamber	-7.3, 4.8		–24.3 (SD=3.4)	–24.3 (SD=3.4)
Global longitudinal strain Apical 4 chamber	-8.9, 3.8		–24.3 (SD=3.4)	–24.3 (SD=3.4)
Global longitudinal strain Apical 2 chamber	-9.8, 3.3		–24.3 (SD=3.4)	–24.3 (SD=3.4)
Global longitudinal strain average	-8.7, 3.2		–24.3 (SD=3.4)	–24.3 (SD=3.4)
Relative wall thickness		0.88, 0.37	< 0.42	< 0.42
Right ventricle lateral tricuspid systolic tissue velocity (RVS') wave cm/s	9.6, 2.2		> 9.5	> 9.5
Fractional Area Change (FAC)%	25.4, 5.3		> 35%	> 35%
Early diastolic septal tissue velocity (E' Septal) cm/s	4.2, 1.5		10.1 (SD=3.1)	10.3 (SD=2.9)
Early diastolic lateral tissue velocity (E' Lateral), cm/s	4.8, 2.5		13.5 (SD=4.0)	13.5 (SD=4.1)

Reference from Roberto M. Lang, P. Badano, Victor Mor-Avi, Jonathan Afilalo, Anderson Armstrong, Laura Ernande et.al .Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults. An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal – Cardiovascular Imaging (2015) 16, 233–271 doi:10.1093/ehjci/jev014.

Table III : Biochemical parameters

Parameters	Mean, SD	Normal Value (Male)	Normal Value (Female)
Hs Troponin T (pg/ml)a	60.1, 35.8	< 14	< 14
NT- pro BNP (pg/ml)b	8066, 6950	< 450	< 450

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b. Michael Weber and Christian Hamm. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart. 2006 Jun ; 92(6) : 843-849.

Table IV: Specific echocardiographic parameters and its frequency

Echo Parameters	Total (%)
Apical sparing pattern (Longitudinal strain only done in 7 patients out of 13. (n=7)	7 (100%)
Right ventricular hypertrophy (> 5mm) (n=13)	13 (100%)
E/e' ≥ 15 (n=13)	12 (92.3)
Pericardial effusion(n=13)	10 (76.9)
Pleural Effusion(n=13)	9 (69.2)
E/A ≥ 2.0(n=13)	9 (69.2)
Increase in interatrial septal thickness(n=13)	8 (61.5)
TAPSE < 1.7 (n=13)	7 (53.8)
E/A ≥ 0.8-2.O(n=13)	4 (30.8)

Table V: ECG parameters

ECG Parameters	Frequency
Heart rate, Mean (SD), bpm	75.9 (SD=25.1)
Prolonged PR interval, Mean (SD) , ms	225.3 (SD=55.5)
Low voltage QRS (n=13)	3 (23%)
LVH on ECG (n=13)	1 (7.7%)
Normal QRS voltage (n=13)	9 (69%)
Paroxysmal atrial fibrillation (n=13)	2 (15%)
Complete heart block (n=13)	1 (8%)
Intermittent complete heart block (n=13)	1 (8%)
Sinus pause (n=13)	1 (8%)
Ventricular fibrillation episode (n=13)	1 (8%)
Non-sustained ventricular tachycardia (n=13)	1 (8%)
Pseudo infarct pattern in ECG (n=13)	9 (69%)
QTc interval, median and IQR,ms	457,33.5

are almost non-existent,[12] the three commonest differential diagnosis left are hypertrophic cardiomyopathy, cardiac amyloidosis and Andersons-Fabrys disease. At initial diagnosis, cardiac amyloidosis patients usually have normal or near normal ejection fraction,[13] as is reflected in our study in which all patient have EF ≥40%. All of our cardiac amyloidosis patients have left ventricle wall thickness more than 1.3cm with normal or small left ventricular cavity (concentric left ventricular hypertrophy).

Similar with other study that shows high specificity for apical sparing in longitudinal strain for cardiac amyloidosis,[9] all seven of our patients in which strain are available, indeed showed apical sparing. This is important as it also used to differentiate cardiac amyloidosis from other thickened wall cardiomyopathy with echocardiography. For example, in hypertensive patients, the strain is mostly reduced at the basal interventricular septum and in hypertrophic cardiomyopathy the reduction is at the thickest part of the left ventricle wall.[14]

Another important finding is the difference between restrictive cardiomyopathy and restrictive haemodynamic. Traditionally, cardiac amyloidosis is classified as restrictive cardiomyopathy,[15] however, as seen in our study, even though majority (69.2%) indeed have restrictive filling patterns, a significant number (30.8%) have pseudonormal filling patterns. It is also interesting to note that all of our patients have right ventricular hypertrophy (RVH), and it is important to do proper measurements of RVH from subcostal 4-chamber zoom view. As there are no specific definition of thickened interatrial septum and granular appearance of myocardium, these criteria are dependent on subjective interpretation and its utility is uncertain.

The classical teaching in cardiac amyloidosis is that the combination of thickened walls with low voltage QRS in electrocardiogram (ECG) are highly specific for cardiac amyloidosis.[6,16] However, in our study only three patients (23%) have this combination, suggesting this finding needs to be interpreted cautiously. The most significant ECG finding in this series is that all of our patients have significantly prolonged PR interval (mean 225.3, SD 55.5ms).

CONCLUSION

Echocardiography plays an important role in diagnosing cardiac amyloidosis. The findings of concentric left ventricular hypertrophy with preserved ejection fraction without increase in loading condition should alert the clinician towards its possibility. This is also supported by right ventricular hypertrophy and particularly longitudinal strain imaging showing apical sparing.

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