YIELD OF FAMILY SCREENING IN DILATED CARDIOMYOPATHY WITHIN LOW-INCOME SETTING; TANZANIAN EXPERIENCE

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ABSTRACT

Background: Dilated cardiomyopathy (DCM) is often familial and screening of relatives is recommended. However, studies on the yield of screening are scarce in developing countries.

Aim: To identify and characterize first degree relatives of patients with DCM in Tanzania.

Methods: We recruited first degree relatives of 57 DCM patients. DCM in relatives was diagnosed using European Society of Cardiology guidelines.

Results: We screened 120 first degree relatives, 17 (14.1%) were found to have previously unknown DCM and all were asymptomatic (100%) with median age of 37.0 years (26.0, 50.0), and were predominantly females (71%). The mean (SD) indexed left ventricular end diastolic volume was significantly higher in relatives with DCM 71(11.5) compared to relatives without DCM 50ml (11.5), p value= 0.00.

Conclusion: First degree relatives of patients with DCM are at a risk of developing asymptomatic DCM and at a young age .

Keywords: dilated cardiomyopathy; first degree relatives screening.

INTRODUCTION

Dilated cardiomyopathy (DCM) is a disease of the myocardium characterized by left or biventricular dilatation and systolic dysfunction in the absence of coronary artery disease, hypertension, valvular disease or congenital heart disease(1). DCM is a major cause of heart failure worldwide, and it is the second most common cause of heart failure in Sub Saharan Africa (SSA)(2). In Tanzania, DCM is the most common type among cardiomyopathies and the second most common cause of heart failure(3).

DCM can be classified as either familial or non-familial(4). Familial DCM occurs when at least two closely related relatives have been diagnosed with the disease or when one family member meets the diagnostic criteria for DCM and has first degree relative with autopsy proven DCM or sudden death below 50 years of age(5). Non-familial DCM can be acquired (secondary to a specific cause for example infectious, autoimmunity, toxins and others) or it can be idiopathic. It has been observed that between 20% and 35% of DCM patients have the familial form of the disease(6).

Clinically, DCM may present as an overt disease with symptoms and signs of heart failure such as shortness of breath, lower limbs swelling, abdominal distension or it can present as chest pain, arrhythmias or cardiogenic shock(7). However, by definition, DCM may be manifested only as reduced left ventricular (LV) systolic function without heart failure symptoms. In fact, overt DCM is believed to be the end result of a long standing, latent subclinical DCM(8).

First degree relatives of patients with DCM have shown an increased probability to develop DCM, therefore clinical and genetic screening of first degree relatives of patients with DCM is indicated according to guidelines (9, 10). Clinical screening entails history taking, transthoracic echocardiography and electrocardiogram (ECG). The aim of the screening is to identify the disease or its incomplete preclinical expression among asymptomatic relatives of a patient with DCM(5).

Previous studies have found the prevalence of DCM among first degree relatives to range from 5% – 11% (11-15). It has been a consensus that familial DCM will be found in at least 20-35% of

DCM patients following clinical screening of their first-degree family members using clinical features, ECG and echocardiography(14, 16). Consequently, screening of first degree relatives of patients with DCM is now a clinical routine in most developed countries (5, 17). Experience from SSA shows that, among patients with DCM, up to 26.6% have familial DCM(18). However, most of the previous studies from SSA have been done in South Africa and screening of first degree relatives of patients with DCM has never been studied in Tanzania, and it is not yet a clinical routine. The present study therefore aimed to use clinical, electrocardiography and echocardiography to screen first degree relatives of patients with DCM in order to characterize familial DCM in our local setting.

METHODOLOGY

Study design

Hospital based descriptive cross-sectional study at the echocardiography laboratory at JKCI from September, 2021 to February, 2022. JKCI is a national tertiary level hospital which receives patients referred from regional and zonal referral hospitals in Tanzania. First degree relatives (aged 18 and above) of 57 patients diagnosed with DCM without a known cause, attending at JKCI who are either newly or previously diagnosed were involved. The index patients are available from a list of an on-going DCM study cohort which enrolled patients aged 18 years and above with clinical diagnosis of heart failure and sonographic diagnosis of DCM with ejection fraction ≤45% without known cause. First degree relatives were defined as parents, children or siblings of the index patient. The sampling frame included all first degree relatives who are related to DCM patients. All available relatives related to a particular index patient were asked informed consent to participate in the study.

Demographic and clinical data

A clinical research form collected demographic characteristics including age, sex, occupation as well as area of residency. It also recorded cardiovascular risk factors including history of hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption.

In every participant, a thorough history and physical examination was done. Blood pressure was taken using an automated digital sphygmomanometer with the patient in sitting position. The

average of two readings taken at least 5 minutes apart was recorded as the patient's blood pressure. Patient's body weight (in kg) was taken using a well-calibrated weighing scale, with patient wearing no shoes or heavy clothing. Height (in cm) was taken using a stadiometer and recorded to the nearest centimeter. Height and weight were used to calculate body mass index (BMI) using the formula: height (kg)/weight (m^2). Overweight and obesity were defined as BMI ≥25 kg/m^2 and ≥30kg/m^2 respectively.

Electrocardiogram

A 12-lead resting electrocardiogram was obtained from all participants A GEMAC2000 machine was used. Reading and interpretation of the ECG was done manually by the investigator and proofread by a cardiologist. The following parameters were recorded: Rate, Rhythm, Axis, Atrial enlargement, Ventricular enlargement, Bundle brand blocks, ST segment changes, T wave changes, QTc interval, PR interval and Premature Ventricular Complex (PVC).

Echocardiogram

The echocardiogram was performed using the American Society of Echocardiography Guidelines(19). A Siemens Acuson machine was used. Images from 2-Dimensional, M-Mode and Doppler (color and tissue) recordings were taken. All measurements were done during the echocardiographic examination and data were retrieved from computer generated values inbuilt in the echocardiogram machine. The obtained data were then transferred to pre-coded recording papers for each participant. Images were also stored in the echocardiogram machine hard disc for later re-reading. All echocardiographic examinations were verified by experienced cardiologists. LV ejection fraction was determined using the Biplane Simpson's method and was taken as a measure of LV systolic function. DCM in a relative was diagnosed with the combination of major and minor criteria as per ESC guidelines(5). Some minor criteria were not used due to limited availability and/or high cost, these are Late enhancement (LGE) of non-ischemic origin on cardiac magnetic resonance imaging; Evidence of non-ischemic myocardial abnormalities (inflammation, necrosis and/or fibrosis) on endomyocardial biopsy as well as serum organ-specific and disease-specific Anti-heart antibody. DCM was diagnosed if a relative met 2 minor criteria or 1 major criterion without any minor criteria. Visual assessment of left ventricular function was also applied to observe regional myocardial function(20).

Variables

Left ventricular ejection fraction (LVEF) and Indexed Left Ventricular End Diastolic Volume LVEDV-I were used to determine the proportion of DCM among first degree relatives.

Independent variables included socio-demographics such as age, gender, level of education, occupation and residence. Dependent variables included dilated cardiomyopathy, arrhythmia and ECG and echocardiographic findings.

Data entry and analysis

Data were analyzed using R statistical package and presented as median with interquartile range for continuous variables and percentages for categorical variables, as appropriate. Comparison between relatives with DCM and relatives without DCM was done using Fisher's exact test for parametric variables and Wilcoxon rank sum test for non-parametric variables. A p-value of <0.05 was considered statistically significant.

Ethical considerations

Ethical clearance was obtained from MUHAS Ethical Review Board, and permission to conduct the study was obtained from JKCI management. A signed informed consent was obtained from all study participants before enrolment. Clinical findings and results were communicated as early as possible to the respective participants. Participants found to have DCM were referred to attend clinic at JKCI if they lived in Dar Es Salaam or to their respective regional referral hospitals if they lived upcountry. Participants who were not found to have DCM were advised to repeat screening every three to five years and refrain from excessive alcohol drinking. They also received health education to decrease overall risk to life-style related illnesses.

RESULTS

Baseline characteristics of study participants

A total of 216 first degree relatives from 57 DCM index cases were invited for screening between September 2021 and February 2022. Among those, only 120 (56%) participants came for screening. Ninety six participants did not come due to several reasons as showed in figure 1

The median (IQR) age of participants was 39.0 (29, 49) years. Slightly over half were females (53.3%), the majority lived in Dar Es Salaam (84.2%) and 48.3% were related to the index case as

his or her child. Six participants (5%) were active smokers, 26 (21.6%) used alcohol, 14 (11.6%) were hypertensive and 5 (4.2%) were diabetic. Of the invited family members, more men refrained from participating (71; 73.9%) due to various reasons as described in flow diagram. Other findings are as shown in Table 1.

Seventeen relatives were diagnosed with DCM. All relatives diagnosed with DCM had no symptoms during screening 17(100%). Only 2 relatives (1.7%) of the study population presented with dyspnea and had history of hypertension. No other symptoms were found. In some patients without DCM we recorded subtle changes in electrocardiography which included left atrium enlargement (13; 11.1%), incomplete right bundle branch block 6(5%) seen in Table 2.

Relatives with and without DCM did not differ in terms of age, sex, blood pressure levels and other characteristics as shown in Table 1 and 2.

Relatives with DCM had significantly higher left ventricular diastolic diameter at 49.5(46.9, 51.9) with p <0.001. The mean indexed left ventricular end diastolic volume was significantly higher in relatives with DCM 71(11.5) compared to relatives without DCM 50(11.5), p value= 0.00. The median (IQR) ejection fraction was significantly lower in relatives with DCM 62(61, 65) compared to relatives without DCM 65(61.65), p value=0.021. Moreover, relatives with DCM had significantly higher median (IQR) left atrium diameter 36.9(36.3, 38.8) compared relatives without DCM 35.2(32.4, 27.5), p value=0.024 (Table 3).

Table 4 shows characteristics of relatives with DCM; there were 2 sets of relatives with DCM that belonged to the same index DCM case, cases 4 and 5 were related to a 26 year old female and both were siblings, while cases number 7 and 8 were related to a 63 year old male and both were his children.

DISCUSSION

This is the first study done in Tanzania on relatives of patients with DCM; we screened 120 first degree relatives from 57 patients with DCM attending the only tertiary specialized cardiac hospital in the country; by means of history, physical examination, electrocardiography and echocardiography.

In our study 17 participants were found to have DCM, giving a proportion of 14.1% among the screened relatives. Our findings are slightly higher compared to other studies in which the prevalence of DCM among first degree relatives of patients with DCM has been found to range between 5-11% (11-14, 21). This could be influenced by a variable proportion of participation; bearing in mind the number of family members eligible and invited for screening was 216, minimum proportion of affected relatives in our series is 7.8%. This calls for another study to review the challenges of screening relatives in cardiomyopathies including DCM to fully understand the low participation rate.

Our findings suggest that familial DCM tends to occur at a young age and it is in keeping with a genetic etiology of the disease(22). A study done in Italy in which first degree relatives of DCM patients were consecutively enrolled to be screened for familial DCM found that the mean age of onset of familial DCM was 32 years(23). Young age, as opposed to any other clinical feature has been shown to be predictive of familial DCM(24).

Although it is widely recognized that male sex is an important risk factor for developing systolic heart failure, studies that examine the role of sex on DCM specifically are scant(25, 26). Similar to this finding in our study, others have also found more females than males in familial DCM in screening; a study done at Mayo clinic found the number of females affected by familial DCM to be 75% of all affected relatives(12). Another familial DCM screening study which was done in Italy found the number of females among those found to be affected by DCM during screening to be 85.7%(27). However, we cannot rule out the possibility that in our series, males could have been severely affected and died young or were very sick and refused to participate.

All affected relatives were asymptomatic during screening; this finding is similar to an Irish study which consecutively screened 200 first degree relatives from 56 families and found that 100% of relatives in whom DCM was diagnosed were asymptomatic(11). Our finding is also similar to an American study which found 80% of relatives who were found to be affected by DCM during screening were asymptomatic(12). Our findings reiterate the need for ongoing periodic cardiac screening of asymptomatic relatives to allow for early detection of pre-clinical disease(28).

ECGs abnormalities seen in our study are in keeping with studies done elsewhere. In an Italian familial DCM screening study, characteristic ECG findings among those found to be affected by DCM included chamber enlargement, low amplitude QRS complexes, right axis deviation, PVC and hemi block(27). In another study, the ECG findings obtained during screening of relatives of patients with DCM included atrial fibrillation, PVC, hemi-blocks, atrio-ventricular blocks and chamber enlargement(21).Presence of subtle electrocardiographic and echocardiographic changes in asymptomatic first degree relatives as seen in our study could be indicative of a pre-clinical disease(16).

Non-response of some of the invited family members could create a selection bias and therefore the number may not reflect the true magnitude of familial disease. There is also a possibility that majority of the relatives who declined to participate was already affected and had ill health. Conversely, those who came were likely to be diseased and therefore came forward to get screened. High non-response rates in familial DCM screening studies have been observed by others as well. A familial DCM screening study by McKenna et al found the non-response rate among contacted first degree relatives to be 26%. Additionally, 25% of DCM patients didn't wish their first degree relatives to be contacted(11). In that study, the reasons for not attending for screening included residing abroad, or subjects did not reply to invitation or were still to be contacted to attend screening. In another study, the non-response rate was found to be 30% and the reasons of not participating in screening in this particular study included living too far from the medical center, being uninterested, too high cost of travel and others didn't give a reason(12). As with other screening studies, familial DCM screening studies face an inherent challenge of non-response (12-14, 21). This study sets a baseline for further studies with bigger sample size and possible establishment of family screening program in patients diagnosed with DCM.

Though it is not the focus of this study, we observed notable incidences of cardiovascular risk factors such as obesity, alcohol consumption and elevated blood pressure during screening. This is in agreement with previous community screening done in Dar Es Salaam involving 6691 participants in which over two-thirds of participants were alcohol consumers and 6.9% had a positive smoking history, 4.7% had a history of diabetes mellitus and 18.1% had elevated blood

pressure. Overweight and obesity were observed in 34.8 and 32.4% of participants, respectively(29). This finding alerts us on a changing society and calls for collaborative and concrete measures to control these risk factors for cardiovascular diseases.

STUDY LIMITATIONS

This study may overestimate or underestimate the true prevalence of dilated cardiomyopathy among first degree relatives of patients with dilated cardiomyopathy because of the significant number of first degree relatives who didn't turn up for screening. Only a prospective study screening all available first degree relatives on a regular basis would determine the exact prevalence of dilated cardiomyopathy among first degree relatives of patients with dilated cardiomyopathy. Nevertheless, while the actual prevalence is most likely to be close to our findings we demonstrate that the minimum prevalence of DCM at the time of screening is 7.8 % of 216 relatives including the ones who didn't participate. Other limitation is the lack of access to other diagnostic modalities that have been described in criteria for family disease such as cardiac MRI, endomyocardial biopsy as well as antibodies studies. However, this is inherent to a real-world study and reflects the local situation in many developing countries.

CONCLUSION

First degree relatives of patients with dilated cardiomyopathy are at risk of developing asymptomatic disease at a young age. The identification of newly affected individuals with dilated cardiomyopathy may benefit from early management even if they are asymptomatic. Also, the affected individuals need close monitoring for any complications. There is a need to create community awareness to encourage more relatives of DCM patients to be screened as well as education of health professionals. The findings obtained from this study should raise awareness among clinicians and family member of patients with DCM beyond economically developed countries settings.

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AUTHORS CONTRIBUTION

All authors conceived and designed the study; Data collection: LSF and JJ; Data analysis: LSF,JJ and PC; LSF and JJ wrote the first draft of the paper and subsequent drafts in collaboration with PC,LVL,EK,HM,AK,GD and FA. All authors have revised final version to be published.

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DISCLOSURE

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Figure1. Flowchart showing relatives screening

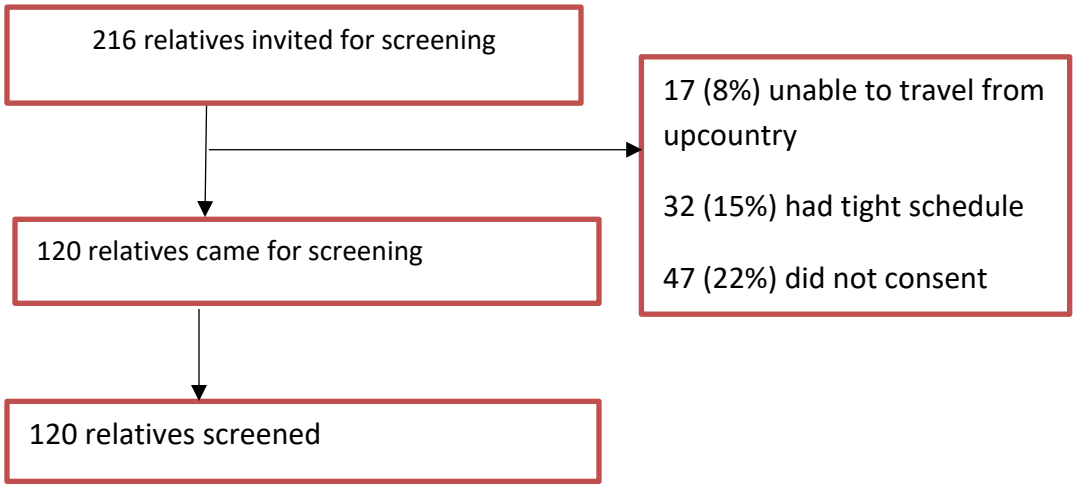

Table1. Baseline characteristics of study participants (N = 120)

Characteristics	n (%)/median (IQR)
Median Age, (years)	39.00(29.75,49.00)
Gender, n (%)	
Male	56 (46.7)
Female	64 (53.3)
Residence, n (%)	
Dar Es salaam	101 (84.2)
Upcountry	19 (15.8)
Relationship to Index case, n (%)	
Parent	11 (9.2)
Sibling	51 (42.5)
Child	58 (48.3)
Cigarette smoking, n (%)	6 (5.0)
Alcohol use, n (%)	26 (21.7)
Excessive alcohol use, n (%)	3 (2.5)
Known hypertensive, n (%)	14 (11.7)
Known Diabetes Mellitus, n (%)	5 (4.2)
Known Dyslipidemia, n (%)	1 (0.8)
Median Body Mass Index, (kg/m²)	27.95(24.9,31.6)
Obesity status, n (%)	
Normal	32 (26.7)
Overweight	46 (38.3)
Obese	42 (35.0)

IQR-interquartile range

Table2. Clinical and electrocardiographic findings in first degree relatives of patients with DCM

Variable	All relatives n=120 Median (IQR) n (%)	Relatives without DCM n=103	Relatives with DCM n=17
Age(years)	39.00 (29.75, 49.00)	40.00 (30.00, 48.50)	37.00 (26.00, 50.00)
Age<45	40 (33%)	34 (33%)	6 (35%)
Females	64(53%)	52(50%)	12(71%)
Signs and symptoms			
Asymptomatic	118 (98%)	101 (98%)	17 (100%)
Dyspnea	2 (1.7%)	2 (1.9%)	0 (0%)
Systolic Pressure	142 (128.75,152.25)	141 (128.50,155.00)	146 (129.00,150.00)
Diastolic Pressure	85 (76.75, 93.25)	86 (78.50, 94.00)	81 (69.00, 87.00)
ECG findings			
Prolonged QTc interval	7 (5.8%)	6 (5.8%)	1 (5.9%)
Incomplete LBBB	1 (0.8%)	0 (0%)	1 (5.9%)
Incomplete RBBB	6 (5.0%)	6 (5.8%)	0 (0%)
PVC	2(1.6%)	1(0.9%)	1(5.9%)
LAD	2(1.6%)	2(1.9%)	
RAD	0(0%)	0(0%)	0(0%)

ECG-electrocardiogram; LBBB-left branch bundle block; RBBB-right branch bundle block; PVC-;LAD-left axis deviation; RAD-right axis deviation

Table3. Echocardiographic findings in first degree relatives of patients with DCM (n=120)

Variable	Relatives without DCM n=103 Median(IQR) Mean(SD)	Relatives with DCM n=17 Median(IQR) Mean(SD)	P value
LVIDd (mm)	43.4 (41.0, 47.5)	49.2 (46.9, 51.6)	**<0.001**
LVEDV-I	50.7(11.5)	71.5(11.5)	**0.000**
LVPWd (mm)	10.50 (9.45, 12.50)	9.17 (8.80, 10.60)	**0.005**
IVSd(mm)	11.40 (10.00, 12.30)	10.60 (9.40, 11.90)	0.3
IVSs(mm)	15.80 (14.10, 17.50)	14.60 (12.50, 16.90)	0.2
LAs diam (mm)	35.2 (32.4, 37.5)	36.9 (36.3, 38.8)	**0.024**
FS	36.0 (32.9, 40.3)	35.3 (31.9, 40.1)	0.8
LAsAOd	1.26 (1.15, 1.32)	1.43 (1.25, 1.48)	0.014
LV EF Simpson	65 (62, 70)	62 (61, 65)	**0.021**
LVEDV Simpson(ml)	102 (82, 115)	102 (87, 129)	0.5
LVMI	94 (81, 116)	109 (92, 128)	0.2
Diastology			0.094
Normal	86 (83%)	12 (71%)	
Grade I dysfunction	13 (13%)	2 (12%)	
Grade II dysfunction	3 (2.9%)	3 (18%)	
Grade III dysfunction	1 (1.0%)	0 (0%)	

LVIDd – Left ventricular internal diameter in diastole ;LVEDV-I- Indexed Left Ventricular End Diastolic Volume ; LVPWd – Left ventricular posterior wall thickness in diastole; LVEDV – Left ventricular end diastolic volume; IVSs – Interventricular septum thickness in systole; LVMI – Left ventricular mass index; FS-fractional shortening; LV EF- left ventricular ejection fraction: LAs-left atrial size;

Table4. Demographic and clinical details of first degree relatives found to have DCM

Case No.	Age (years)	Sex	Symptoms	ECG	EF (%)	ECHO LVEDVI (ml/m²)
1	55	M	None	**LBBB**	**45**	63
2	37	F	None	Normal	62	**67**
3	57	F	None	**PVC**	64	**81**
4€	21	F	None	Normal	72	**63**
5€	20	F	None	Normal	69	**62**
6	38	F	None	Normal	66	**70**
7*	22	F	None	Normal	**48**	**62**
8*	26	M	None	Normal	62	**93**
9	39	F	None	Normal	72	**68**
10	27	M	None	Normal	**46**	**99**
11	56	F	None	Normal	61	**68**
12	46	F	None	Normal	62	**64**
13	52	M	None	Normal	68	**75**
14	23	M	None	Normal	62	**87**
15	26	F	None	Normal	62	**64**
16	50	F	None	Normal	60	**67**
17	32	F	None	**Left atrial enlargement; Left ventricular enlargement**	55	**63**

*; € - came from the same family

EF-ejection fraction; LVEDV-I- Indexed Left Ventricular End Diastolic Volume ; LBBB- left branch bundle block ; PVC-premature ventricular contractions.