LEFT VENTRICULAR NONCOMPACTION IN NIGERIAN CHILDREN: CASE SERIES AND REVIEW OF LITERATURE

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Abstract

Left ventricular noncompaction (LVNC) is an uncommon cardiomyopathy characterized by multiple prominent trabeculations in the ventricular wall, deep intratrabecular recesses which communicate directly with the left ventricular cavity, and thin compacted layer of myocardium, caused by in utero arrest of normal myocardial compaction. The clinical presentation and course may be benign or may manifest more aggressively with impaired left ventricular function, arrhythmias, and embolism, resulting in poor outcomes. Diagnosis requires a high index of suspicion and is established primarily by echocardiograph; treatment is symptomatic, determined by the mode of presentation and the presence or absence of complications. This case series describes clinical and echocardiographic features in twelve (12) children with LVNC at a tertiary hospital in Gwagwalada, Nigeria.

Keywords: left ventricular cardiomyopathy, children, ventricular dysfunction, echocardiography

INTRODUCTION

Left ventricular noncompaction (LVNC) is an uncommon cardiomyopathy which is increasingly being reported in all age groups.[1] It is characterized by multiple prominent trabeculations in the ventricular wall, deep intratrabecular recesses which communicate directly with the left ventricular cavity, and thin compacted layer of myocardium,[2] resulting from an intrauterine arrest of normal myocardial compaction during embryogenesis.[3] LVNC can present as an isolated form, or in association with other cardiomyopathies, congenital heart diseases, and complex syndromes which affect the heart.[4-9]

LVNC may remain asymptomatic for years, or may present with symptoms of congestive cardiac failure (CCF) and left ventricular (LV) systolic and/or diastolic dysfunction, arrhythmias, thromboembolic events, and sudden death, at any age.[9,10] Cardiac imaging is required to make a diagnosis of LVNC,[11] using echocardiography[12] and/or cardiac magnetic resonance (CMR).[13]

This case series describes clinical and echocardiographic features in twelve (12) children

with LVNC who presented to the Paediatric Cardiology Unit of the Department of Paediatrics, University of Abuja Teaching Hospital (UATH), Gwagwalada, Nigeria, between April 2014 and December 2019.

CASE SUMMARIES

Twelve paediatric age patients were diagnosed with LVNC between April 2014 and December 2019. Clinical information on the patients' demographics, clinical presentation, other relevant investigations, and follow up status was extracted from their medical records. Echocardiographic data was retrieved from the database of the University of Abuja Teaching Hospital non-invasive cardiac laboratory and reviewed. Transthoracic Echocardiography (TTE) was performed for all 12 patients using a GE Vivid e portable ultrasound machine. None had cardiac magnetic resonance imaging, due to its non-availability at our centre.

A diagnosis of LVNC was established in the presence of these criteria: (1) the presence of multiple echocardiographic trabeculations, (2) multiple deep intertrabecular recesses communicating with the ventricular cavity, as demonstrated by color Doppler imaging and the recesses demonstrated in the apical or midventricular areas of both the inferior and lateral walls, and (3) a 2-layered structure of the endocardium with a noncompacted-to-compacted ratio greater than 1.4 in children (N:C > 1.4).[10,14]

The patients ranged in age from 5 months to 17 years, 8 were adolescents. Seven were males and 5 females, male to female ratio 1.4:1.

Table I summarises the clinical presentation and follow up status of the patients. Two patients were asymptomatic and referred for screening. Another was referred following insertion of a Glenn shunt for congenitally corrected transposition of the great arteries (CCTGA), while awaiting definitive surgery. Eight patients presented with symptoms of congestive cardiac failure. Only 6 patients (50%) were regular with follow up visits, while 2 died within 1 and 2 years post-diagnosis, respectively.

Table II shows findings from echocardiography and other investigations. All 12 patients had N:C > 2.0, range 2.1 to 4.7, although N:C > 1.4 was applied for diagnosis.[13] LV dysfunction of varying severity was present in 8 patients. Of these, 5 had both systolic and diastolic dysfunction, 1 had systolic dysfunction, while 2 had diastolic dysfunction. All 8 had dilated cardiac chambers and valvular regurgitation.

Three patients had isolated LVNC, while other cardiomyopathies were diagnosed in 3, with dilated cardiomyopathy (DCM) and HIV-associated cardiomyopathy diagnosed in 2 and 1, respectively. Congenital heart defects were present in 3: aortic

stenosis (AS) secondary to bicuspid aortic valve in 1, AS secondary to dysplastic aortic valve in another, and congenitally corrected transposition of the great arteries in the 3rd. And 2 had features consistent with acute rheumatic fever (ARF).

The patients who were symptomatic and in congestive cardiac failure received antifailure medication which included beta blockers, ACE inhibitors, diuretics, and digoxin, as well as low dose aspirin, as indicated. In addition, those with acute rheumatic fever were treated with anti-inflammatory medication (aspirin and prednisolone as indicated) and antibiotics, and commenced on secondary prophylaxis with intramuscular benzathine penicillin G

Table I: Demographic data, clinical features, Ross score, and follow up status of children with LVNC

Serial number	**Age at diagnosis**	**Gender**	**Presenting symptoms**	**Ross class (Modified Ross score[15])**	**Follow up/ outcome**
1	13 years	Male	Recurrent palpitations, cough, oedema	IV	Lost to follow up after 1year
2	12 years	Female	Fever, abdominal pain, cough, vomiting, bilateral knee swelling	III	Irregular, deceased in 2nd year of follow up
3	14 years	Male	Cough, fast breathing, chest pain, fever, history of sore throat	IV	Regular over 3 years
4	5 months	Male	Referred for screening for multiple congenital anomalies (macroglossia, omphalocoele major)	I	Returned to referring centre, lost to follow up
5	8 years	Male	Weight loss, fever, cough, fast breathing	IV	Regular over 3 years
6	18 months	Female	Follow up post-Glenn shunt insertion in CCTGA	I	Lost to follow up after 6 months
7	4 years	Male	Fast breathing, easy fatigability, precordial bulge	II	Regular over 3 years.
8	11 years	Male	Cough, fast breathing, oedema	IV	Regular over 2 years
9	14 years	Female	Cough, fast breathing, oedema	IV	Regular over 1 year
10	12 years	Female	Weight loss, fever, cough, fast breathing, oedema	IV	Irregular, deceased within 1 year
11	7 years	Female	Cough, fast breathing, oedema	III	Irregular over 1 year
12	17 years	Male	Incidental finding of cardiac murmur	I	Regular over 6 months

CCTGA indicates congenitally corrected transposition of the great arteries; LVNC, left ventricular noncompaction cardiomyopathy

Table II: Noncompacted to compacted ratio, systolic and diastolic function, other abnormal echocardiographic abnormalities, and significant findings from other investigations of children with LVNC

Serial number	N/C ratio	Systolic function	Diastolic function	Other abnormal echo findings {Additional diagnosis}	Significant findings from other investigations
1	3.5:1	Impaired (EF=23%)	Impaired (E/A=6.0)	Dilated LA and LV, MR, TR, PR {DCM}	CXR-cardiomegaly with biventricular configuration and obliteration of cardiophrenic and costophrenic angles
2	2.8:1	Normal (EF=66%)	Impaired (E/A=3.14)	Dilated LA and LV, prolapsed AML, MR, AR, PR {ARF}	ECG-LAE, LVH; CXR-cardiomegaly; elevated ESR; leucocytosis, lymphocytosis, anaemia; elevated ASO titre; *Streptococcus* spp isolated from pharynx
3	3.7:1	Impaired (EF=46%)	Normal (E/A=1.7)	Dilated LA and LV, thickened MV, poor coaptation and prolapse of AML, ruptured chordae tendinae, MR, TR, AR, PR {ARF}	ECG-Prolonged PR interval, RV conduction delay; CXR-cardiomegaly with biventricular configuration: elevated ASO titre
4	4.1:1	Normal (EF=65%)	Normal (E/A=1.5)	Nil	Nil
5	4.7:1	Impaired (EF=39%)	Impaired (E/A=2.96)	Dilated RA, LA, RV and LV, bicuspid aortic valve, aortic stenosis, MR, TR, PR, RV dysfunction (TAPSE=13.4mm), pericardial effusion {Congenital AS}	Nil
6	2.1:1	Normal (EF=57%)	Normal (E/A=1.2)	Ventriculoarterial and arterioventricular discordance, ventricular inversion, dilated RA and RV, large VSD, secundum ASD, stenosed MPA, MR, TR, spongy RV myocardium, good functioning Glenn conduit {CCTGA with Glenn shunt}	Nil
7	2.3:1	Normal (EF=60%)	Impaired (E/A=2.2)	Dilated LA, LV hypertrophy, dysplastic aortic valve with valvular, subvalvular and supravalvular stenosis, dilated ascending aorta and transverse arch, dilated coronaries, AR {Congenital AS}	Nil
8	2.8:1	Impaired (EF=30%)	Impaired (E/A=5.2)	Dilated LA and LV, hypokinetic septal and lateral wall motion, MR {DCM}	Nil
9	2.5:1	Impaired (EF=14%)	Impaired (E/A=2.4)	Dilated LA and LV, MR, TR {DCM}	Nil
10	2.7:1	Impaired (EF=42%)	Impaired (E/A=2.1)	Dilated LA and LV, MR, TR {HIV cardiomyopathy}	Positive for HIV antibodies
11	2.8:1	Normal (EF=68%)	Normal (E/A=1.8)	Dilated LA and LV, MR	Nil
12	2.1:1	Normal (EF=67%)	Normal (E/A=1.7)	Nil	Nil

AML indicates anterior mitral leaflet; AR, aortic regurgitation; ARF, acute rheumatic fever; AS, aortic stenosis; ASD, atrial septal defect; ASO titre, antistreptolysin O titre; CCTGA, congenitally corrected transposition of the great arteries; CXR, chest radiograph; DCM, dilated cardiomyopathy; E/A, ratio of peak velocity blood flow in early diastole to peak velocity flow in late diastole; ECG, electrocardiogram; EF, ejection fraction; ESR, erythrocyte sedimentation rate; LA, left atrium; LAE, left atrial enlargement; LV, left ventricle; LVNC, left ventricular noncompaction cardiomyopathy; LVH, left ventricular hypertrophy; MPA, main pulmonary artery; MR, mitral regurgitation; MV, mitral valve; N/C, noncompacted to compacted ratio; PR, pulmonary regurgitation; PR interval, time from onset of atrial depolarization to onset of ventricular depolarization; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VSD, ventricular septal defect.

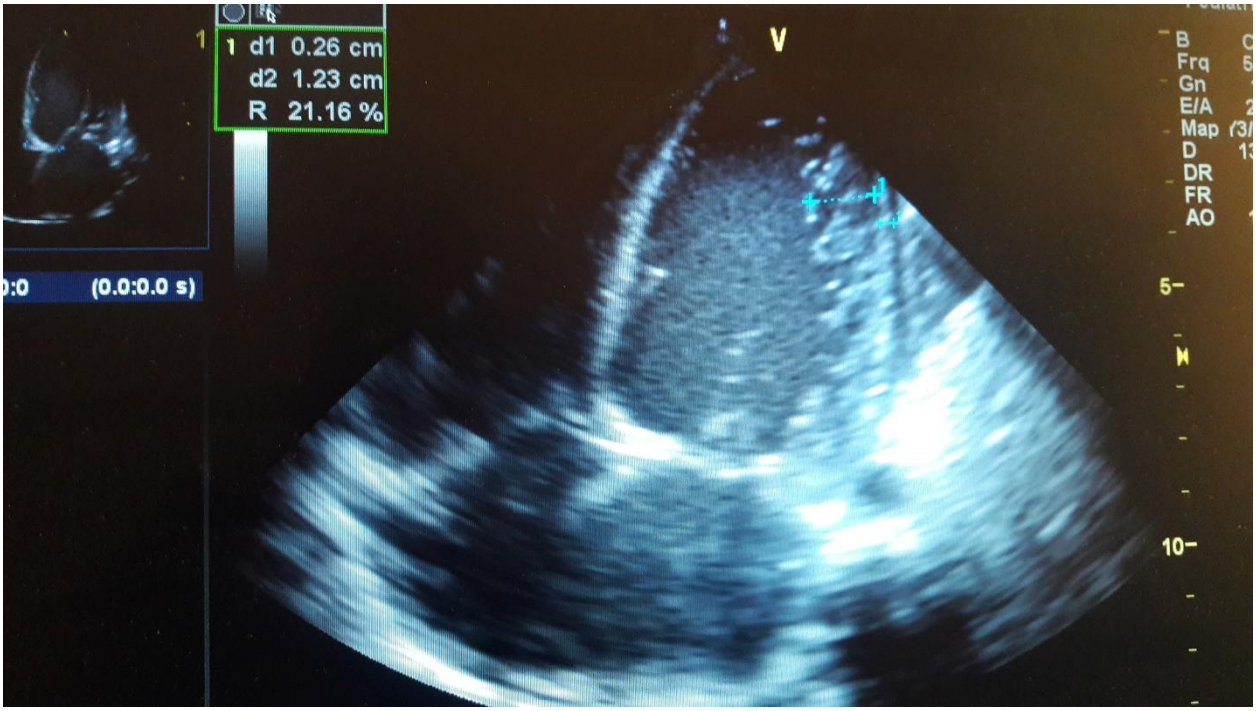

Figure 1: Apical 4-chamber transthoracic echocardiographic image of patient with LVNC demonstrating prominent ventricular trabeculations and deep intertrabecular recesses predominately in the apical and lateral walls. Original clinical image from UATH non-invasive cardiac laboratory.

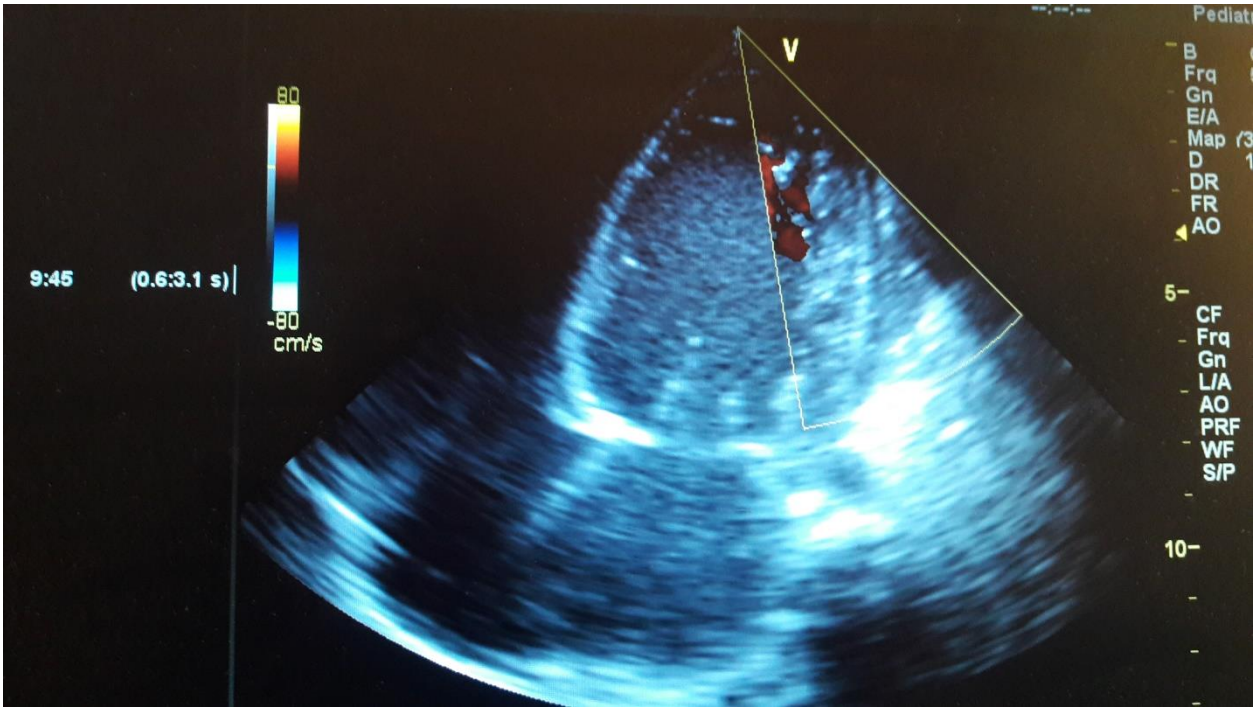

Figure 2: Apical 4-chamber echocardiographic view of same patient with color Doppler demonstrating communication of intertrabecular recesses with the ventricular cavity. Original clinical image from UATH non-invasive cardiac laboratory.

DISCUSSION

There has been an upsurge in the documentation and characterization of LVNC in adults and children over the last 2 decades.[1,10,16] Earlier reports showed a preponderance in paediatric age groups,[5] with subsequent reports describing LVNC in adults.[9,11] LVNC occurs in 0.81 per 100,000 infants per year with 0.12 cases per 100,000 children per year, and has a prevalence of 0.014% to 1.3% in patients referred for echocardiography.[7,9,10,16]

The World Health Organisation as well as the European Society of Cardiology list LVNC as an unclassified cardiomyopathy.[17] However, the American Heart Association classifies it as a genetic cardiomyopathy, which may be familial or sporadic.[6] Various genes have been described in the familial form of the disease, including mutations in G4.5 gene on Xq28 (14) cardiac specific CSX gene disrupting the TAZ protein leading to dysregulated remodeling of cardiolipin and Barth syndrome, characterized by hypertrabeculation and noncompaction in utero and failure to thrive, as well as specific mutations in genes in the Notch1 pathway leading to dysregulated signaling and hyper trabeculation and noncompaction.[4,18]

LVNC may exist in the isolated form which is not associated with other cardiac anomalies; or may be non-isolated associated with other cardiomyopathies, complex syndromes, and congenital heart defects such as coronary artery anomalies, conotruncal anomalies (absence of the pulmonary valve, pulmonary atresia, tricuspid atresia), Ebstein anomaly, transposition of the great arteries, pulmonic stenosis, ventricular septal defect, atrial septal defect, and hypoplastic heart syndrome; abnormalities of the left ventricular outflow tract and valve anomalies are common probably due to abnormalities in ventricular development.[4-10,11,19] Similarly, both the isolated form of LVNC and LVNC associated with other cardiac anomalies were demonstrated in our patients. Majority of the patients reviewed had LVNC in association with other cardiac pathologies, which is a frequent occurrence in children.

Clinical presentation of LVNC is nonspecific and wide,[20,21] and is dependent on the form of LVNC, whether isolated or in association with CHD, syndromes or other diseases, the age of the patient, or whether asymptomatic patients are diagnosed during family or other screening.[16] Clinical symptoms at presentation are frequently indicative of ventricular dysfunction and include nonspecific chest pain or discomfort, symptoms of congestive cardiac failure, failure, or arrhythmias.[9,11] LV systolic dysfunction is the most common finding in both children and adults (up to two thirds of patients) and depends on the extent of noncompacted cardiac segments;[11,19] cardiac failure is present in more than 50% of patients.[16] This protean presentation of LVNC was

also evident in our patients, ranging from asymptomatic to congestive cardiac failure with marked impairment of ventricular function, and is consistent with published literature. In patients with advanced disease, progressive deterioration in cardiac function occurs, which may result in the development of fatal complications such as thromboembolic events, arrhythmias, and sudden cardiac death.[19,20] The poor outcome associated with the disease may explain the 2 mortalities documented in our patients, likely worsened by poor treatment compliance occasioned by irregular follow up care.

ECG findings may be normal or nonspecific,[10,19] and include marked biventricular hypertrophy with extreme QRS voltage, isolated or diffuse T-wave inversion, ventricular and supraventricular tachycardia, Wolff-Parkinson-White syndrome (WPW), and premature atrial and ventricular contractions.[10] The presence of ECG abnormalities does not correlate with the extent of LVNC.[11] Our patients also presented with this variation in ECG findings, from normal findings to ventricular hypertrophy and conduction delay, some of which could have been caused by coexisting cardiac pathologies as well.

Cardiac imaging is the mainstay of the diagnosis of LVNC,[11,12,13] and is based on the finding of thickened myocardium with a two-layered structure consisting of a thin, compacted epicardial layer and a much thicker, noncompacted endocardial layer.[11] 2D transthoracic echocardiography is the first choice for diagnosis, and demonstrates both broad trabeculae and deep intertrabecular recesses in the LV myocardium, typically located in the LV apex and the midinferior and lateral walls.[4] Conversely, the basal and midinterventricular septum scanned by an apical 4-chamber view is usually free of trabeculae .[4] It may be necessary to also utilise atypical views and contrast for better visualization of the more apical segments of the LV and detection of the prominent trabeculae.[4]

\Several criteria have been established for the diagnosis of LVNC using echocardiography. The most commonly used is that described by Jenni *et al*[11], viz (a) two-layered appearance of the myocardium with a thin, compacted outer (epicardial) band and a thicker, noncompacted inner (endocardial) layer, end-systolic ratio between noncompacted and compacted myocardium greater than 2.0 in adults and 1.4 in children, (b) presence of prominent left ventricular trabeculations, predominantly in the apical and midventricular areas of both the inferior and lateral walls, (c) multiple deep intertrabecular recesses communicating with the ventricular cavity, as visualized at color Doppler imaging, and (d) absence of additional coexisting cardiac abnormalities (in the presence of isolated LVNC).[14,16] The echocardiographic diagnosis of LVNC in our patients was consistent with this criteria. None of our patients had other imaging modalities such as CMR and computed tomography (CT)

imaging which may be utilised for enhanced localisation and morphological description of the myocardium,[16] more so as these were not available at our centre.

There are no specific management guidelines for LVNC.[4,16] In isolated LVNC, differential diagnoses such as prominent hypertrabeculation with normal compacted LV layer, apical HCM, DCM, endocardial fibroelastosis, and LV apical thrombus must be excluded. Asymptomatic patients with normal LV size and function require regular clinical monitoring. Treatment is directed at the phenotype and presence or absence of the main complications of heart failure, arrhythmias and thromboembolism.[4] Systolic and diastolic dysfunction can be managed with beta blockers, ACE inhibitors, diuretics, and digoxin, as indicated; heart transplant is indicated in patients who develop refractory heart failure.[20] Institution of oral anticoagulants should be individualized to patients' needs; either for primary prevention of embolic events based on the phenotype or in the presence of chamber enlargement, LV dysfunction, arrhythmias, prior embolic events, or proven atrial or ventricular thrombi.[4,16] These treatment modalities were instituted in our patients in whom the above-listed indications were present. The risk for sudden cardiac death and arrhythmias may require annual Holter monitoring; electrophysiologic studies and anti-arrhythmic therapies may also be indicated in patients who are symptomatic.[4] Echocardiographic screening should be performed in 1st degree relatives, as well as screening for neuromuscular disorders due to association of LVNC with non-cardiac disorders.[9,22]

The severity and progression of heart failure, presence of arrhythmias and thromboembolism determine the prognosis of patients with LVNC. Some patients may remain asymptomatic, while others may develop symptoms early, with rapid deterioration terminating in death soon after diagnosis.[20] Paediatric patients may demonstrate an "undulating phenotype" with recovery in systolic ventricular function for a variable period of time before deteriorating further, which may account for many patients presenting as adults.[10] ECG abnormalities are prominent, however, systemic embolic events are not.[10] The occurrence of embolic events, ventricular arrhythmias and sudden death appears to be significantly lower in paediatric patients.[10]

CONCLUSION

This case series documents the occurrence of this rare cardiomyopathy in Nigerian children presenting to our hospital. LVNC is a disease of increasing clinical importance, impacting significantly on cardiac function and long term survival of affected individuals. A high index of suspicion and sound diagnostic techniques are important to ensure early diagnosis, treatment, prevention of life-threatening complications, and improvement in the quality of life of patients. The renewed interest and

awareness occasioned by previous and ongoing research should be sustained to yield better understanding of the disease and the possible development of specific management modalities towards achieving improved outcomes.

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