Received: 29 November 2017 | Accepted: 23 January 2018

DOI: 10.1111/chd.12592

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Prevalence of left ventricular hypertrabeculation/noncompaction among children with sickle cell disease

M. Louise Morrison MD[1] | Corrina McMahon MD[2] | Riona Tully MBBCh[1] | Noelle Enright MBBCh[1] | Ricardo Pignatelli MD[3] | Jeffrey A. Towbin MD[4] | Colin J. McMahon MBBCh[1]

[1]Department of Pediatric Cardiology, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland

[2]Department of Hematology, Our Lady's Hospital for Sick Children, Crumlin Dublin, Ireland

[3]Texas Children's Hospital, Houston, Texas, USA

[4]St. Jude Children's Research Hospital, and LeBonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, Tennessee, USA

Correspondence
Prof. Colin McMahon, Department of Paediatric Cardiology, Our Lady's Children's Hospital, Cooley Road, Crumlin, Dublin, Ireland.
Email: cmcmahon992004@yahoo.com

Abstract

Objectives: Incidence of sickle cell disease (SCD) in Ireland has dramatically increased. Disease survival has also steadily improved however cardiovascular manifestations remain important causes of morbidity. These include reports of left ventricular hypertrabeculation (LVHT)/noncompaction. We sought to investigate the prevalence of LVHT among a large cohort of children with SCD.

Methods: We retrospectively reviewed the records of all patients with a diagnosis of SCD who had undergone surveillance echocardiography at Our Lady's Children's Hospital Crumlin (OLCHC) from 1998 to 2015. Demographics, hemoglobin phenotype and treatment information was recorded. LV systolic function, evidence of LVHT, and possible pulmonary arterial hypertension was assessed.

Results: Two hundred thirty-six patients had echocardiograms available for interpretation. One hundred twenty-one (51.3%) were female; mean age was 11.3 years (± 4.1 years). Twenty-six patients (11%) had features of LVHT on echocardiography. Eleven patients (4.7%) had borderline features of LVHT. Mean LVEDD across the whole cohort was 4.2 ± 0.69 cm, LVEDD *z*-score of 1.44 ± 1.9, and mean LVSF was 37.3% ±15.7%. There were no significant differences in terms of age, LVEDD, LVEDD *z*-score, or LVSF between patients with and those without LVHT.

Conclusions: The prevalence of LVHT/noncompaction in children with SCD is lower than the adult population and LV systolic function is well preserved throughout our patient group. The mechanism behind the development of LVHT in this population remains speculative. Further work is required in this field. Sickle cell patients require longitudinal evaluation to ascertain changes in left ventricular function and the presence of LVHT/noncompaction.

KEYWORDS
LVHT/noncompaction, pediatric, sickle cell disease

1 | INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive condition affecting millions of African/Afro-Caribbean individuals worldwide. In Ireland the incidence has dramatically increased over the past 15 years due to the influx of migrants. There are now over 400 children with SCD and around 100 adults compared with just 2 children affected in 2000.[1]

Survival among those with SCD has steadily increased however in adult life patients accumulate end organ damage and failure. Cardiovascular manifestations are a common feature and an important cause of morbidity. They include pulmonary hypertension and progressive left ventricular dilatation and dysfunction.[2] A high proportion of African/Afro-Caribbean patients with heart failure fulfill criteria for left ventricular hypertrabeculation (LVHT)/noncompaction.[3] LVHT, a possible precursor to LV noncompaction cardiomyopathy (LVNC), has also been recorded among black athletes.[4] Previous reports of adults with SCD have noted LVHT occurring in up to 28% of patients.[5] We sought to investigate the prevalence of LVHT among a large cohort of children (<18 years) with SCD.

2 | METHODS

We retrospectively reviewed the records of all patients with a diagnosis of SCD who had undergone surveillance echocardiography at Our Lady's Children's Hospital Crumlin (OLCHC), which is the national pediatric center for cardiology and hematology in the Republic of Ireland, over an 18-year period (1998–2015). We recorded demographic information, hemoglobin phenotype and treatment information. Echocardiograms were reviewed by a consultant pediatric cardiologist to assess LV systolic function using left ventricular end-diastolic dimension (LVEDD), LVEDD *z*-score and left ventricular shortening fraction (LVSF). And also reviewed for evidence of possible pulmonary arterial hypertension using presence of right ventricular hypertrophy (RVH), D-shaped LV, and measurable tricuspid regurgitation (TR) jet. LVHT/non-compaction was defined as localized protrusion of the ventricular wall $\geq$3 mm in end-diastole and associated inter-trabecular recesses.[4] Echocardiograms had not previously been assessed for LVHT. Incidence of arrhythmia in the population was not assessed in this study. Data obtained was analyzed using IBM SPSS statistics version 21.0 for Mac (IBM Corp 2012, Armonk, New York). Descriptive variables were given as frequencies with relative percentages. Frequency data was compared using x^2 testing, continuous data was analyzed using *t* test. A *P* value of $<$.05 was considered significant.

3 | RESULTS

There were 243 children with a diagnosis of SCD who had attended for surveillance echocardiography. Two hundred thirty-six patients had usable echocardiograms with good quality images. One hundred twenty-one (51.3%) were female; mean age was 11.3 years ($\pm$4.1 years).

The majority of patients were homozygous for hemoglobin SS, 81.9%, with 9.5% being compound heterozygotes for hemoglobin SC. Distribution of hemoglobin phenotype is given in Figure 1. Seventy-two patients (30.5%) had been receiving therapy with hydroxyurea and 18 patients (7.6%) had undergone splenectomy. Forty-nine patients (20.8%) had been receiving long-term transfusion.

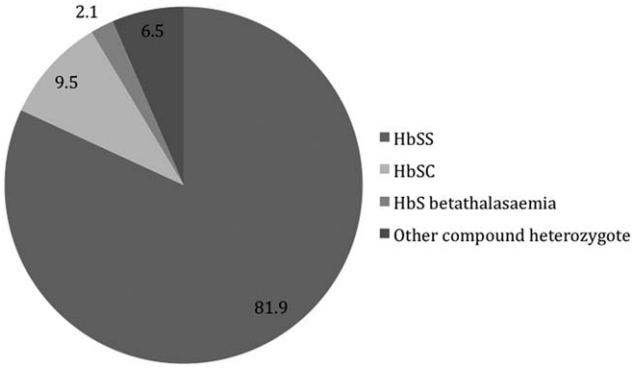

FIGURE 1 Distribution of hemoglobin phenotype (expressed as percentage)

Twenty-six patients (11%) had features of LVHT on echocardiography. Figure 2 demonstrates typical echocardiographic appearance of LVHT in this patient group. A further 11 patients (4.7%) could be considered to have some borderline but not entirely diagnostic features of LVHT. Mean LVEDD across the whole cohort was 4.2 $\pm$ 0.69 cm with LVEDD *z*-score of 1.44 $\pm$ 1.9, 36.6% of patients had a LVEDD *z*-score $>$2 indicating some evidence of LV dilatation above the mean. Mean LVSF was 37.3% $\pm$ 15.7%. There were no significant differences in terms of age, LVEDD, LVEDD *z*-score, or LVSF between patients with and those without LVHT, Table 1. There were no significant differences in terms of SCD management between patients with and those without LVHT, Table 2. There was no evidence of possible pulmonary arterial hypertension any patient's echocardiogram as assessed by presence of RVH, D-shaped LV, or raised TR jet.

4 | DISCUSSION

To our knowledge this is the only report to date examining the issue of LVHT in a large cohort of children with SCD in Ireland. We

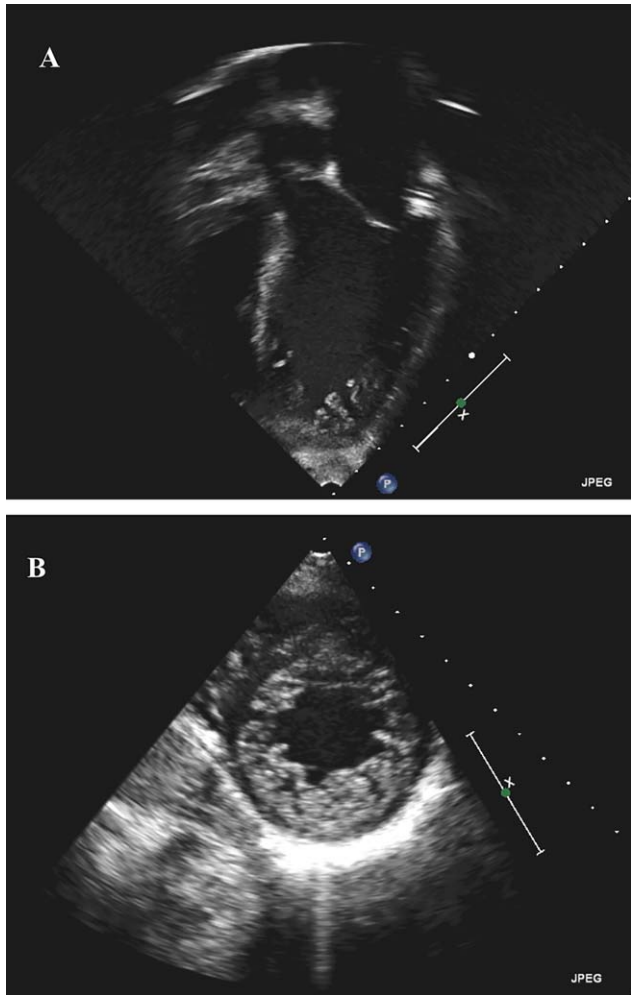

FIGURE 2 Echocardiographic images from sickle cell patient with features of LVHT. (A) Apical view demonstrating hypertrabeculation and recesses. (B) Short-axis view demonstrating a hypertrophied LV with trabeculations and deep recesses

TABLE 1 Comparison of age and LV dimensions between groups

	Sickle cell patients with LVHTn = 26	Sickle cell patients without LVHTn = 210	*P* value (95% CI)
Age (years)	11.7 (±5.3)	11.1 (±3.9)	0.55 (−2.2, 1.2)
LVEDD (cm)	4.3 (±0.69)	4.2 (±0.7)	0.25 (−0.5, 0.1)
LVEDD *z*-score	2.1 (±2.1)	1.4 (±1.8)	0.1 (−1.6, 0.2)
LVSF	35.6 (±5.5)	36.2 (±4.9)	0.6 (−1.6, 2.9)

LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVSF, left ventricular shortening fraction.

demonstrate that 11% of children with SCD have typical features of LVHT on echocardiography with a further 4.7% exhibiting some but not all diagnostic features. This indicates a lower prevalence than adult studies, which have reported almost 30% of patients with SCD having features of increased LVHT on echocardiography with 8% of these actually fulfilling diagnostic criteria for LV noncompaction.[5] The prevalence of isolated LVNC in the general population remains uncertain. Diagnosis is becoming more frequent, probably due to an increased awareness and improved imaging technology. Prevalence has been reported as between 0.05 and 0.26% of all comers for adult echocardiographic examinations across large institutions.[6,7]

Despite finding evidence of LVHT, LV systolic function remains well preserved throughout our patient group. Although almost 40% of patients had evidence of ventricular dilatation with LVEDD *z*-scores >2, there was no difference between patients with and without LVHT in terms of LV size and function. None of the children with SCD in this series had evidence of pulmonary hypertension on echocardiography.

Many other studies have described the increase in left ventricular size in both adults and children with SCD.[8–11] Chronic anemia, like that found in SCD, is associated with a high cardiac output, which is facilitated by an increase in stroke volume and resultant ventricular dilatation.[9] Despite the increase in dimension, ventricular function is often reported as normal using conventional echocardiographic measures

TABLE 2 Comparison of sex and treatments received between groups

	Sickle cell patients with LVHTn = 26	Sickle cell patients without LVHTn = 210	Chi-square (*P* value)
Male	18	97	4.92 (0.02)
Female	8	113	
Had hydroxyurea	10	62	1.12 (0.29)
No hydroxyurea	15	147	
Had splenectomy	1	17	0.53 (0.46)
No splenectomy	24	193	
Had transfusion	3	56	1.33 (0.25)
No transfusion	22	164	

such as ejection fraction and fractional shortening, as with our cohort.[8] A number of authors now focus on the use of tissue Doppler measures in patients with SCD, which, in many cases, are abnormal suggesting significant systolic and diastolic dysfunction.[2,8,11] As one might expect such changes in dimension result in increased LV mass and are more common in older patients.[2] Niss et al. reported on 134 patients with SCD and also conducted a meta-analysis of 68 studies, finding significant left atrial enlargement, evidence of diastolic dysfunction, enlarged LV end-diastolic volume, and normal shortening fraction consistent with restrictive physiology.[12]

The mechanism behind the development of increased LVHT in this population remains speculative. The increase in LV mass described above often takes the form of eccentric hypertrophy.[2] It is conceivable that some individuals may be predisposed for this to express as hypertrabeculation with development of crypts/recesses. The fact that the prevalence of LVHT is lower in children with SCD than in adults, may support the theory that it is an exaggerated physiological response as the patient is exposed to a high preload and increased stroke volume over a lifetime of illness. This infers a maladaptive physiological response rather than a primary myopathic process, coincidental or otherwise. No patient in this pediatric cohort met criteria for LVNC with significantly depressed systolic function, although this has been reported in a small number of adult patients.[5] One must also consider the role that black ethnicity may play in determining the ventricular response to chronic anemia as there is also a higher prevalence of LV trabeculation among African/Afro-Carribean elite athletes.[4]

The clinical significance of the appearance of such trabeculations in this population remains an important and as yet unanswered question. In our patient group LV systolic function remained well preserved. The emergence of LVHT in the setting of good systolic function may alert to individuals who require more frequent imaging surveillance or earlier introduction of medical therapy to halt progression to LV dilatation and dysfunction.

Previously, Alter and Maisch reported on the combined occurrence of LVNC, skeletal myopathy, and hereditary spherocytosis.[13] It has been observed that there is a relationship between congenital diseases with muscular and erythrocyte pathology, such as choreoacanthocytosis, McLeod syndrome, or hereditary spherocytosis with ankyrin alterations and the homology between spectrin and dystrophin.[14] In some patients with SCD and LVNC, it has been speculated that there may be either a common chromosomal or a mutant gene involved. This needs further cytogenetic investigation.

Song recently described a patient with atrial septal defect with right-sided noncompaction, proposing that the atrial septal defect resulted in right heart volume overload, followed by neuroendocrine adaptations with increased sympathetic activity.[15] It is proposed that circulating catecholamines result in increased contractility and heart rate. Shorter diastolic time due to tachycardia, increased intramyocardial tension from right ventricular dilatation, and increased myocardial oxygen demand, may result in subendocardial ischemia, leading to the acquired form of LVHT/noncompaction. This same mechanism underlying SCD, specifically, as a consequence of severe anemia leading to LVHT/noncompaction as in hereditary spherocytosis.

Niss et al. recently examined for the presence of myocardial fibrosis in 25 individuals with SCD and correlated this with diastolic dysfunction.[16] They found 71% of patents had diastolic abnormalities, 29% met criteria for diastolic dysfunction, among whom there was a greater degree of diffuse myocardial fibrosis, lower hemoglobin, increased left atrial volume, and higher NT-proBNP. This further highlights the need for longitudinal follow-up of this patient cohort, particularly among those patients with LVHT noncompaction given the risk of arrhythmia reported by Brescia et al. in the left ventricular noncompaction cardiomyopathy group.[17] Incidence of arrhythmia was not examined in this study.

The prevalence of LVHT/noncompaction is significant in children with SCD but lower than the adult population. Although this study is limited by its retrospective nature, it highlights an interesting area in a growing patient group in Ireland. Despite increasing longevity for SCD patients, mortality and morbidity from cardiovascular sequelae remains significant. Further work is required in this field. Children with SCD require close surveillance with serial imaging for LV dilatation and evidence of LVHT/noncompaction.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Collated data, performed analysis and drafted the first draft of the manuscript: Dr. Morrison and Dr. Tully

Collated data on patients with sickle cell disease and edited the manuscript: Dr. Corrina McMahon

Advised on the research topic and edited the manuscript: Prof. Towbin

Edited the manuscript and provided many suggestions for improving the submission: Dr. Pignatelli

Devised the study, edited the manuscript and submitted the manuscript: Prof. McMahon

ORCID

Colin J. McMahon MBBCh http://orcid.org/0000-0003-0337-9338

REFERENCES

[1] O'Carroll S. Sickle cell: Ireland's new disease, which affects 400 children and 100 adults. The Journal Apr 10th 2014. Thejournal.ie last accessed 20th July 2017.

[2] Gladwin MT, Sachdev V. Cardiovascular abnormalites in Sickle Cell Disease. *J Am Coll Cardiol.* 2012;59(13):1123–1133.

[3] Kohli SK, Pantazis AA, Shah JS, et al. Diagnosis of left ventricular non compaction in patients with left ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? *Eur Heart J.* 2008;29:89–95.

[4] Gati S, Chandra N, Bennett RL, et al. Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes?. *Heart.* 2013;99:506.

[5] Gati S, Papadakis M, Van Niekerk N, Reed M, Yeghen T, Sharma S. Increased left ventricular trabeculation in individuals with sickle cell anaemia: physiology or pathology?. *Int J Cardiol.* 2013;168(2):1658–1660.

[6] Ritter M, Oechslin E, Sütsch G, Attenhofer C, Schneider J, Jenni R. Isolated noncompaction of the myocardium in adults. *Mayo Clin Proc.* 1997;72(1):26–31.

[7] Sandhu R, Finkelhor RS, Gunawardena DR, Bahler RC. Prevalence and characteristics of left ventricular noncompaction in a community hospital cohort of patients with systolic dysfunction. *Echocardiogrpahy.* 2008;25:8–12.

[8] Eddine AC, Alvarez O, Lipshultz SE, Kardon R, Arheart K, Swaminathan S. Ventricular structure and function in children with sickle cell disease using conventional and tissue Doppler echocardiography. *Am J Cardiol.* 2012;109(9):1358–1364.

[9] Batra AS, Acherman RJ, Wong W, et al. Cardiac abnormalities in children with sickle cell anaemia. *Am J Hematol.* 2002;70(4):306–312.

[10] Ahmed S, Siddiqui AK, Sadiq A, Shahid RK, Patel DV, Russo LA. Echocardiographic abnormalities in sickle cell disease. *Am J Hematol.* 2004;76(3):195–198.

[11] Adjagba P, Habib G, Robitaille N, et al. Impact of sickle cell anaemia on cardiac chamber size in the pediatric population. *Cardiol Young.* 2017;27(05):918–924.

[12] Niss O, Quinn CT, Lane A, et al. Cardiomyopathy with restrictive physiology in sickle cell disease. *JACC Cardiovasc Imaging.* 2016;9(3):243–252.

[13] Alter P, Maisch B. Non-compaction cardiomyopthy in an adult with hereditary spherocytosis. *Eur J Heart Fail.* 2007;9(1):98–99.

[14] Finsterer J, Stollberger C. Myopathy associated with spherocytosis and left ventricular hypertrabeculation/non-compaction. *Eur J Heart Fail.* 2007;9(1):100

[15] Song ZZ. A combination of right ventricular hypertrabeculation/non-compaction and atrial septal defect. *Int J Cardiol.* 2011;148(2):e25–e27.

[16] Niss O, Fleck R, Makue F, et al. Association between diffuse myocardial fibrosis and diastolic dysfunction in sickle cell anemia. *Blood.* 2017;130(2):205–213.

[17] Brescia CT, Rossano JW, Pignatelli R, et al. Mortality and sudden death in pediatric left ventricular non-compaction cardiomyopathy in a tertiary referral center. *Circulation.* 2013;127(22):2202–2208.

How to cite this article: Morrison ML, McMahon C, Tully R, et al. Prevalence of left ventricular hypertrabeculation/noncompaction among children with sickle cell disease. *Congenital Heart Disease.* 2018;13:440–443. https://doi.org/10.1111/chd.12592