CLINICAL STUDY

The association of cardiac ventricular hypertrophy with congenital hyperinsulinism

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Abstract

Objective: Ventricular hypertrophy (VH) has been observed in children with congenital hyperinsulinism (CHI), a condition of hypoglycaemia characterised by dysregulated insulin secretion, but the prevalence is not known.

Patients and methods: Cardiac assessment was performed in children ($n=49$) with CHI at diagnosis and follow-up. Two dimensional and Doppler echocardiography studies were used to assess cardiac structures, while M-mode study was used to measure left ventricular (LV) dimensions, subsequently converted to Z scores. Where possible, LV hypertrophy was confirmed by LV mass index (g/m^2) >95 th centile.

Results: Cardiac structural lesions were found in 14 (28%) children. At initial echocardiography, VH was present in 31 (65%) children with median (range) LV posterior wall dimension in diastole Z scores of $+1.6$ (-2.4 to $+5.8$) and interventricular septal wall dimension in end diastole Z scores of $+1.9$ (-1.7 to $+17.2$). At follow-up echocardiography, performed after an interval of 178 (45–390) days, VH persisted in 16 (33%) children. In regression analysis, the presence of VH (odds ratio (95% confidence intervals) 1.1 (1.0–1.2), $P=0.04$) at initial echocardiography was correlated with maximum glucose requirement at diagnosis, indicating that severity of CHI at presentation may play a role in the pathogenesis of VH.

Conclusions: A significant proportion of children with CHI have cardiac structural lesions. A majority also have VH, which may be associated with the severity of CHI at diagnosis. VH may persist in some children, which requires careful long-term cardiac review.

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Introduction

Congenital hyperinsulinism (CHI) is a rare disorder characterised by hypoglycaemia but is one of the most common causes of persistent hypoglycaemia in infancy and childhood (1). In CHI, secretion of insulin is dysregulated in relation to the level of blood glucose. A significant proportion of children with CHI is due to genetic defects, most commonly in genes coding for the ATP-sensitive K⁺ channels (K_{ATP} channel genes, *ABCC8* and *KCNJ11*) present in the β cells of the pancreas (2).

The clinical management of CHI involves correction of hypoglycaemia by supplemental carbohydrate, medical therapies such as diazoxide and octreotide and pancreatic surgery, the latter depending on the severity, presence of focal lesions and response to medical treatment. Such treatment decisions are

usefully aided by rapid K_{ATP} channel gene mutation analysis (3). In the initial management of CHI, children often receive large volumes of dextrose solutions to maintain euglycaemia. This may lead to inadvertent fluid overload and pulmonary oedema, unless fluid volumes are restricted by increasing the concentration of dextrose (4). Despite efforts to restrict fluid intake, fluid volume overload leading to features of heart failure is commonly encountered in the clinical management of children with CHI, suggesting the possibility of cardiac dysfunction in CHI.

In addition to volume overload, it is possible that children with CHI may have cardiac muscle hypertrophy, which could contribute to myocardial dysfunction. There are anecdotal reports of reversible hypertrophic cardiomyopathy in association with CHI (5, 6), although underlying mechanisms leading to cardiac muscle changes are unknown. It is also well recognised

that infants born to diabetic mothers have cardiomegaly, even after controlling for birth weight (7, 8). The presence of left ventricular hypertrophy (LVH) can be potentially life threatening and has been associated with the risk of sudden death, often due to arrhythmias (9, 10). Therefore, patients with CHI may be at risk of significant cardiac morbidity, particularly in long-term follow-up.

Despite the possibility of cardiac muscle involvement in CHI leading to myocardial dysfunction, echocardiography to assess cardiac muscle thickness and function is not a routine part of clinical monitoring in several clinical reviews (4, 11, 12, 13, 14). In our centre, echocardiography is performed routinely as part of clinical management of children with CHI, although the timing of echocardiography is not standardised. We have now reviewed our echocardiography analyses in CHI patients with reference to the presence of structural cardiac lesions and ventricular hypertrophy (VH).

Objectives

To review echocardiography results to identify the prevalence and persistence of VH in children with CHI.

Patients and methods

We reviewed echocardiography results at diagnosis and follow-up in a cohort of children with CHI in a single centre. Case notes were reviewed in a retrospective audit for all children with CHI undergoing echocardiography over the previous 5 years ($n=49$). Children with complex congenital heart disease requiring cardiac surgery were included in this review but ventricular parameters to assess VH were not analysed in this group. The assessment of VH was limited to those without complex congenital heart defects requiring cardiac surgery ($n=48$).

The diagnosis of CHI was made on biochemical assessment, in association with an increased glucose requirement and absence of ketogenesis (11). Severity of CHI was assessed by maximum glucose requirement expressed as mg/kg per day. Genotyping for mutations in K_{ATP} channel (*ABCC8* and *KCNJ11*), *HNF4A*, *GLUD1* and *GCK* genes was assessed following diagnosis of CHI. Oral diazoxide was used as first-line treatment, with octreotide used in those who were non-responsive to diazoxide. PET-CT scan using 18 fluoroDopa was performed to diagnose focal CHI. All children were followed in paediatric endocrinology clinics at variable intervals depending on glycaemic stability at clinical assessment.

Children with CHI underwent cardiac assessment by one of two paediatric cardiologists (G C and N M) at the earliest opportunity after diagnosis of CHI and where possible before commencing diazoxide. The presence of a patent ductus arteriosus (PDA) was not considered as

pathologic unless accompanied by other structural lesions or flow abnormalities or persistence at follow-up echocardiography. The presence of a patent foramen ovale was not considered as a structural lesion. Atrial septal defect (ASD) was considered pathologic if the child required further follow-up assessment.

VH was determined as left ventricular (LV), right ventricular (RV) or biventricular (BV), depending on the ventricle affected. The diagnosis of LVH was made by a paediatric cardiologist if LV dimensions exceeded the upper end of the normal range expected for the child's age and weight and were recorded in the case notes. Quantitative parameters for LVH, i.e. LV posterior wall dimension in end diastole (LVPWd) and interventricular septal wall dimension in end diastole (IVSd) measurements, were obtained where possible ($n=33$). These parameters have been widely used in M-mode echocardiography in children and are repeatable and reproducible (15). LV parameters were recorded in centimetres and converted to Z scores using reference standards from a cohort of healthy children from Europe (16). In addition to LV parameters, where possible, LV mass index (LVMI, $\text{g}/\text{m}^{2.7}$) was measured (17) and values >95 th centiles (18) were considered to be confirmatory of LVH ($n=33$). In regression analysis testing, VH was considered as an ordinal variable when testing for association with variables related to the type and severity of CHI.

The presence of RV hypertrophy (RVH) was based on subjective assessment without the use of quantitative parameters. Electrocardiogram (ECG) voltage criteria were used to corroborate the presence of RVH in those in whom a diagnosis of RVH was made. ECG was not used for the diagnosis of LVH. Fractional shortening (FS) and ejection fraction (EF) were measured to quantify systolic function of the left ventricle. Diastolic dysfunction was assessed informally and recorded only if significantly abnormal.

Results

A total of 49 children (37 males) with CHI underwent cardiac assessment and echocardiography after diagnosis. The median (range) age at presentation of hypoglycaemia was 1 (1–300) days. Eight children presented late (range 60–300 days). The first echocardiography was performed 26 (1–89) days after diagnosis of CHI, with 95% of children undergoing scanning between 18 and 33 days. A second follow-up echocardiography was performed at varying intervals of 178 (45–390) days after initial echocardiography.

Forty-three children underwent genotyping with 22 (51%) children having K_{ATP} channel gene mutations. Of those with mutations, 15 were heterozygous and seven were either homozygous or compound heterozygous. One child had a mutation in *HADH*, while no mutations were identified in *ABCC8*, *KCNJ11*, *HNF4A*,

Figure 1 Treatment outcomes and overall M-mode echocardiography findings in children with diffuse and focal CHI in this cohort (n=48).

GLUD1 or *GCK* genes in 19 (45%) children. A flow diagram outlining CHI treatment outcomes and overall M-mode echocardiography findings is given in Fig. 1.

Cardiac structural lesions

ASD, PDA, pulmonary stenosis (PS), ventricular septal defect (VSD), aortic stenosis (AS), mitral valve prolapse, double outlet right ventricle (DORV) and malposed great arteries were found in 14 (28%) children. ASD was the commonest abnormality and was present in isolation in four children and in association with PS and VSD in another two children. Mild AS was present in one child with normal aortic arch and normal valvular structure, with no evidence of significant LV outflow tract obstruction (initial aortic tract outflow velocity 2 m/s). Systolic function was satisfactory with EF 76%. In follow-up after 4 weeks, there was no evidence of AS (velocity 1.5 m/s) and no surgical intervention was required. This child had LVH, but the cause was unlikely to be secondary to the relatively mild AS. In two children with PS, the severity was noted as mild and moderate with peak velocity < 3 and 3 m/s respectively. There was no ECG evidence of RVH. In follow-up assessment, surgical intervention was not required for either of the two children. One child with DORV and malposed great arteries had complex cardiac surgery and was therefore excluded from analysis of VH. None of the other children in this cohort required cardiac surgery. In those with cardiac structural lesions (n=13), eight children had LVH, one child had biventricular hypertrophy (BVH) and four children did not have any evidence of VH.

VH at initial and follow-up echocardiography

VH was present at initial echocardiography in 31 (65%) children in this cohort, with LVH in 26 (55%), RVH in two (4%) and BVH in three (6%) children. VH was observed in 70% of those undergoing initial

echocardiography within 33 days, compared with 63% of those undergoing initial echocardiography later ($P=0.6$ for difference). At follow-up echocardiography, persistence of VH was noted in 16 (33%) children.

At initial echocardiography, LVMI (83.9 (47.1–150.9)) g/m^{2.7} values confirmed the presence of LVH in 21 out of 33 children, where such measurements were obtainable. In one child who was born with intrauterine growth retardation with a birth weight of 1.74 kg, LVMI was <95th centile, but other parameters suggested LVH at the age of 2 weeks. In another child of normal weight, LVMI was >95th centile, but other parameters did not suggest LVH. This child had follow-up scans, which were reported as normal.

The median (range) LVPWd at initial echocardiography was 0.4 (0.2–0.9) cm with derived Z scores of +1.6 (–2.4 to +5.8) (Fig. 2). In comparison, LVPWd at follow-up echocardiography for 11 patients in whom LV parameters were available was 0.5 (0.3–0.7) cm with Z scores of +1.3 (–0.4 to +3.6). There was no significant reduction in LVPWd Z scores between initial and follow-up echocardiography ($P=0.9$), suggesting the persistence of LVH at a later date. The median (range) IVSd at initial echocardiography was widely variable at +0.5 (+0.2 to +5.0) cm with Z scores of +1.9 (–1.7 to +17.2). At follow-up echocardiography, IVSd was 0.5 (0.4–1.0) cm with Z scores of +2.1 (+0.3 to +7.7) (Fig. 2), but the difference from initial echocardiography was not significant ($P=0.6$). The presence of cardiac structural lesions was not correlated with the presence of VH ($P=0.6$) at initial echocardiography. Similarly, there was no difference in LVPWd Z scores between those with and without cardiac structural lesions ($P=0.9$).

Figure 2 Box plots (median, 95% confidence intervals and outliers) of Z scores for LVPWd and IVSd parameters at initial and follow-up echocardiography in children with CHI. The asterisks and the open circle indicate outliers.

There was no correlation of FS with LVPWd ($P=0.4$) or IVSd ($P=0.6$) Z scores at initial echocardiography. FS at initial echocardiography was 38 (23–56) % and that at follow-up echocardiography was similar at 43 (27–50) % ($P=0.4$ for difference). EF was normal in all children (74 (51–88) %, normal values $>50\%$ in this age group) and did not correlate with LVPWd ($P=0.8$) and IVSd ($P=0.7$). No child had significant diastolic dysfunction; therefore, measurement of diastolic function markers was not formally recorded. All children were stable in clinical follow-up and none required long-term cardiac medication in the form of diuretics, ACE inhibitors, digoxin or inotrope support. One child (patient 29) had supraventricular tachycardia at diagnosis, which resolved later. However, this child did not have evidence of cardiac structural lesions or VH.

VH in relation to factors influencing CHI outcomes

The presence of VH was assessed in relation to factors characterising CHI disease severity and outcomes. K_{ATP} channel gene mutations, severity of hypoglycaemia (maximum glucose requirement) at presentation and achievement of spontaneous remission of CHI were not associated with a higher probability of VH, either at initial or at follow-up echocardiography, when tested independently. For those treated with diazoxide, initial LVPWd (1.9 (−0.9 to +5.8) vs 1.2 (−2.4 to +2.9), $P=0.03$) but not IVSd ($P=0.5$) Z scores were relatively higher in those responsive to diazoxide than in those who were unresponsive to diazoxide and therefore treated by octreotide or surgery. However, at follow-up echocardiography, LVPWd ($P=0.7$) and IVSd ($P=0.3$) Z scores were similar between those treated with or without diazoxide.

VH at initial echocardiography was similar in children with focal CHI as in those with diffuse CHI (5 (71%) vs 26 (63%), $P=0.6$ for difference), in keeping with initial LVPWd ($P=0.08$) and IVSd Z scores ($P=0.5$). At follow-up echocardiography, no child with focal CHI treated with lesionectomy had VH. In contrast, 16 (39%) children with diffuse CHI had persistent VH ($P=0.04$).

We investigated the possible correlation of VH at initial echocardiography with birth weight and gender in addition to the variables tested independently as earlier in a regression equation. In backward Cox regression (−2 log likelihood 124.0, $P=0.04$), maximum glucose requirement correlated with the presence of initial VH (odds ratio (95% confidence intervals, CI) 1.1 (1.0–1.2), $P=0.04$) when age at echocardiography was used as a time variable. In backward linear regression, children achieving remission appeared to have a greater degree of LVH at initial echocardiography with LVPWd Z score coefficient (CI) of 1.7 (0.4–3.0), $P=0.009$. In contrast, maximum glucose requirement was positively correlated with IVSd Z score

(0.4 (0.1–0.7), $P=0.006$), while birth weight was also positively correlated (1.2 (0.05–2.5), $P=0.04$), as expected. However, at follow-up echocardiography, no variable was correlated with the persistence of VH (−2 log likelihood 31.4, $P=0.9$).

Discussion

In this study, we observed that a significant proportion (28%) of children with CHI had cardiac structural lesions. A majority (65%) of children with CHI had evidence of VH at initial echocardiography, by subjective assessment, LVHs and Z score analysis of commonly used M-mode echocardiography parameters. The presence of VH was independent of body weight, gender and the presence of K_{ATP} channel gene mutations. However, maximum glucose requirement, indicating severity of CHI at diagnosis, was correlated with VH. Follow-up echocardiography showed a reduction in the presence of VH, with persistence in 33% of children with CHI.

The association of VH and increased incidence of cardiac structural lesions has not been described in children with CHI. The association of LVH and fatal arrhythmias is well recognised in adults; using the same principles, it would be important to recognise the presence of VH in patients with CHI with a view to intervene with medical therapy, if necessary, to prevent cardiac dysfunction and the potential development of life-threatening arrhythmias.

Although the review uncovers an important area in the long-term management of patients with CHI, we accept that our analysis suffers from inherent weaknesses in study design. This is a retrospective analysis where initial and follow-up echocardiograms were not suitably standardised. As a consequence, there has been significant variation in the intervals to initial and follow-up echocardiography. However, Z score analysis of M-mode echocardiogram dimensions and time variable corrections in regression analyses suggest significant association of VH in CHI patients despite temporal non-standardisation.

Measurements of outflow tract obstruction have not been analysed in the study as records were obtainable only in a small proportion of children. However, in those with PS, the degree of obstruction was well characterised. In one child with AS and LVH, it was unlikely that LVH was a consequence of the structural lesion and was therefore more likely due to CHI. Another weakness of this study is the lack of echocardiography assessment for diastolic dysfunction to characterise LVH from a functional perspective. However, this being a pilot observational study, the need for detailed Doppler trans-mitral velocity studies was not anticipated. It is expected that future study protocols will incorporate more rigorous investigation modalities.

The finding of LVH in children with CHI is in keeping with anecdotal observations and case reports (5, 6) and

is similar to that seen in infants of diabetic mothers (7, 8). Some children with CHI are relatively macrosomic at birth and hence may have a greater cardiac muscle mass. In our study, we controlled for the effects of birth weight, gender and age at presentation by conversion of LV parameters to Z scores and noted the presence of VH even after adjusting for body size.

Maximum glucose requirement, corresponding to output of insulin and hence the severity of CHI, was correlated with VH at initial echocardiography, when adjusting for other variables. This indicates that the severity of CHI may influence the degree and persistence of VH. However, in our cohort, we observed that children who achieved remission of CHI had greater LV parameters, indicating LVH at initial echocardiography. While it is known that remission of CHI is not correlated with markers of severity (3), the association of remission with LVH in this cohort may suggest that initial CHI severity may play a greater part in the pathogenesis of VH. In children with focal CHI, the amelioration of VH following lesionectomy supports this notion. In contrast, the correlation of cardiac structural lesions and persistent VH may suggest different mechanisms of pathogenesis responsible for the incidence and persistence of VH.

All children in this cohort had been initially treated with diazoxide as first-line treatment for CHI. It is possible that VH was secondary to the use of diazoxide, while acting on K_{ATP} channels also present in the myocardium. However, VH was also present in some children before commencing diazoxide, which indicates that the influence of diazoxide as a causative factor for VH is unlikely. Further, in rat models, diazoxide appears to reduce VH, suggesting that VH observed in children with CHI is not causally associated with diazoxide (19).

We were not able to determine the cause of cardiac structural lesions in this retrospective study. For a more definitive assessment of factors influencing VH, a larger cohort should be examined for longitudinal trends in LV parameters with growth, CHI treatment and achievement of remission. Although in our cohort systolic function was normal and no child required long-term medication for cardiac dysfunction, diastolic function was not formally recorded. Therefore, the natural history and long-term outcome of VH will need further evaluation.

It is now known that K_{ATP} channels that are present in β cells in the pancreas are also present in rat atria and ventricles with differential responses to therapeutic agents (20). It is possible that K_{ATP} channel abnormalities may be a common factor underlying CHI and VH in children, but as yet, there is no evidence to support this notion. Further, abnormal K_{ATP} channel function is unlikely to explain VH in those without K_{ATP} channel gene mutations, in children responsive to diazoxide treatment and in those achieving spontaneous remission, i.e. in conditions with adequate pancreatic K_{ATP} channel activity.

Conclusions

In this cohort of patients with CHI, echocardiography detected the presence of cardiac structural lesions in a significant proportion (28%) of children. A majority (65%) of children with CHI had VH, mostly of the left ventricle, which was confirmed by analysis of LV echocardiography parameters. It is possible that factors influencing the severity of CHI may be involved in the pathogenesis of VH. VH may persist at follow-up echocardiography, implying the need to investigate long-term cardiac outcomes in all children with CHI.

We would recommend that echocardiography should be performed to exclude structural cardiac lesions and quantify LVH. Repeat echocardiography should be performed, even after improvement of hypoglycaemia, until VH is no longer present.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

All authors in this manuscript have contributed substantially to the manuscript, either in design, data collection or analysis, and drafting of the article and have provided final approval before submission of the manuscript.

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