A low incidence of preoperative neurosonographic abnormalities in neonates with heart defects

Jansen, F.A.R.; Haak, M.C.; Wesemael, M.S. van; Harkel, A.D.J.D.J. ten; Lith, J.M.M. van; Blom, N.A.; Steggerda, S.J.

Early Human Development 148 (2020) 105097

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

A low incidence of preoperative neurosonographic abnormalities in neonates with heart defects

Fenna A.R. Jansen[a,*], Monique C. Haak[a], Miriam S. van Wesemael[a,b], A.D.J. Derk-Jan ten Harkel[c], Jan M.M. van Lith[a], Nico A. Blom[c], Sylke J. Steggerda[b]

[a] Leiden University Medical Center, Department of Obstetrics – Division of Prenatal Diagnosis and Fetal Medicine, Leiden, the Netherlands
[b] Leiden University Medical Center, Willem Alexander Children's Hospital, Department of Neonatology, Leiden, the Netherlands
[c] Leiden University Medical Center, Willem Alexander Children's Hospital, Department of Pediatric Cardiology, Leiden, the Netherlands

ARTICLE INFO

Keywords:
Congenital heart defects
Cerebral development
Neonatal
Cranial ultrasound

ABSTRACT

Background and aim: To investigate whether neonates with prenatally detected congenital heart defects (CHD) demonstrate cerebral abnormalities on early preoperative cranial ultrasound (CUS), compared to healthy neonates, and to measure brain structures to assess brain growth and development in both groups.
Study design, subjects and outcome measures: Prospective cohort study with controls. Between September 2013 and May 2016 consecutive cases of prenatally detected severe isolated CHD were included. Neonatal CUS was performed shortly after birth, before surgery and in a healthy control group. Blinded images were reviewed for brain abnormalities and various measurements of intracranial structures were compared.
Results: CUS was performed in 59 healthy controls and 50 CHD cases. Physiological CUS variants were present in 54% of controls and in 52% of CHD cases. Abnormalities requiring additional monitoring (both significant and minor) were identified in four controls (7%) and five CHD neonates (10%). Significant abnormalities were only identified in four CHD neonates (8%) and never in controls. A separate analysis of an additional 8 CHD neonates after endovascular intervention demonstrated arterial stroke in two cases that underwent balloon atrioseptostomy (BAS). Cerebral measurements were smaller in CHD neonates, except for the cerebrospinal fluid measurements, which were similar to the controls.
Conclusions: The prevalence of significant preoperative CUS abnormalities in CHD cases was lower than previously reported, which may be partially caused by a guarding effect of a prenatal diagnosis. Arterial stroke occurred only in cases after BAS. As expected, neonates with CHD display slightly smaller head size and cerebral growth.

1. Introduction

Congenital heart defects (CHD) occur in 7–8 per 1000 newborns and are responsible for significant morbidity and mortality [1]. Survival has increased over the last decades, but these infants remain at increased risk for neurodevelopmental delay (NDD) [2–6]. Until recently, this was assumed to result from perioperative cerebral injury, caused by hypoxia or thrombo-embolic events [7,8]. Cerebral imaging abnormalities are, however, also reported *before* surgery in 36% of CHD neonates, and include ischemic lesions, hemorrhage and delayed maturation [9–20]. It has been suggested that children with CHD display abnormal prenatal development of the brain, leading to an increased vulnerability for cerebral injury [21]. A widely available and cheap method to detect cerebral injury is to perform bed-side cranial ultrasound (CUS). Seven CUS studies are available reporting cerebral abnormalities in CHD neonates. Several of these are, however, hampered by selection bias, caused by the inclusion of selected types of CHD and some included syndromal cases [17–19], and most studies assessed cases in which CHD was diagnosed *after* birth [14,16,17,20]. In severe CHD without a prenatal diagnosis, neonates may experience a period of hemodynamic collapse and hypoxia, which could cause damage to the brain. This could influence previous reported CUS findings. Comparison with a control group was only reported in one of the seven preoperative CUS studies [15] and CUS was frequently performed weeks or months after birth [16–18]. Therefore the results of these studies cannot be applied to fetuses with a prenatally detected CHD.

* Corresponding author at: Leiden University Medical Centre, K6-P, Postbus 9600, 2300 RC Leiden, the Netherlands.
E-mail addresses: f.a.r.jansen@lumc.nl (F.A.R. Jansen), m.c.haak@lumc.nl (M.C. Haak), a.d.j.ten_harkel@lumc.nl (A.D.J.D.-J. ten Harkel), j.m.m.van_lith@lumc.nl (J.M.M. van Lith), n.a.blom@lumc.nl (N.A. Blom), s.j.steggerda@lumc.nl (S.J. Steggerda).

https://doi.org/10.1016/j.earlhumdev.2020.105097
Received 23 December 2019; Received in revised form 5 May 2020; Accepted 27 May 2020

We performed a prospective CUS study in neonates with prenatally detected, isolated CHD and compared the findings to a group of healthy controls. The primary aim was to investigate whether neonates with prenatally detected CHD demonstrate cerebral abnormalities on early preoperative CUS. The secondary aim was to measure several brain structures to assess brain growth and development in both groups. Our hypothesis was that neonates with CHD more frequently display CUS abnormalities and present with smaller brain structures and wider cerebrospinal fluid (CSF) compartments.

2. Material and methods

We performed a prospective cohort study with controls. The institutional ethical committee approved the study protocol. Consecutive cases of neonates with prenatally detected and postnatally confirmed CHD, born between September 2013 and May 2016 in the Leiden University Medical Centre (LUMC) were included, after informed consent from both parents. Severe CHD was defined as the need of a therapeutic catheter intervention or cardiac surgery in the first year of life. An unmatched healthy control group of pregnant women with a normal second trimester anomaly scan was recruited after informed consent in midwifery practices between August 2014 and May 2016. Exclusion criteria were additional structural or genetic anomalies and birth before 35 weeks gestational age (GA). To be ascertained of a healthy control group, we included only neonates that were appropriately sized for GA (birth weight above the 2.3rd percentile), that did not suffer from pregnancy complications influencing placental function (pre-eclampsia, hypertension) or perinatal complications (such as asphyxia or neonatal infection). Besides the postnatal CUS, both groups had monthly prenatal neurosonography (up to 36 weeks of GA) which revealed no suspected abnormalities. Additional maternal and perinatal data were collected, including mode of delivery, GA at birth, head circumference (HC) and birth weight (BW, both expressed in z-scores), type of CHD and type of surgery or endovascular intervention. Follow-up data regarding neurodevelopment were distilled from clinical charts.

Postnatal CUS was performed shortly after birth, preferably in the first postnatal week, but not on the first day of life, to allow the ventricles to open [22]. In the CHD group, the CUS was performed as part of the standard neonatal assessment in the intensive care unit. All scans were assessed for various ultrasound findings as listed below. All noted ultrasound findings were categorized in three categories: as a significant abnormality, a minor abnormality, or as a physiological variant (described in Box 1). CUS was always performed before surgery. Because the aim was to study the intrauterine effects on the brain in CHD, cases in which CUS was performed *after* early endovascular interventions, such as balloon atrioseptostomy (BAS), were excluded from the primary analysis, but analysed separately.

2.1. CUS assessment and findings

All scans were assessed for the presence of: periventricular echogenicity (PVE) of the white matter; cystic periventricular leucomalacia (cPVL) [23]; peri- and intraventricular hemorrhage (P/IVH; Fig. 2) [24,39]; non-physiologic echogenicity in the deep grey matter; suspected stroke; changes in echogenicity in the cerebellum and supra- and infratentorial congenital malformations. Lenticulostriate vasculopathy (LSV; Fig. 3) and subependymal or choroid plexus cysts (CPC) were also noted. For the classification of PVE we used grade 1 (moderately increased echogenicity, (almost) as bright as the choroid plexus) and grade 2 ((smaller areas of) increased echogenicity, being obviously brighter than the choroid plexus) [38]. CUS was performed with an Aloka α 10 ultrasound system (Hitachi Medical Systems Holding AG, Switzerland) or a Toshiba Aplio 400 system (Toshiba Medical Systems B.V., the Netherlands). Scanning was performed routinely by the attending neonatologist or one of the investigators (FJ/SS), according to a standardised protocol through the anterior and mastoid fontanelles [38]. Images were digitally stored (Clinical Assistant, RVC B.V., the Netherlands) and reviewed at least 2 months after the initial recording by two separate investigators (FJ/SS), blinded to the patients' names and the presence or absence of CHD. Discrepancies were solved by consensus.

Cerebral measurements were performed offline (see Supplement 1) and included the lateral ventricles, interhemispheric fissure, sinocortical and cavum septum pellucidum width, corpus callosum length, corpus callosum to fastigium distance, transcerebellar diameter and basal ganglia dimensions. An estimated intracranial volume was calculated according to the method of Graca [25].The volume of the basal ganglia area was calculated according to the same method (see Supplement 1).

2.2. Data management and statistical analysis

Categorical variables were summarized with frequency counts and percentages and compared using a Chi-square or Fischer's exact test. Continuous variables were summarized with means/SD and compared using *t*-test or one-way ANOVA. To check for normality, we plotted outcome measures in a histogram. If data were not distributed normally we performed a Mann-Whitney-U non-parametrical test. In case of a linear correlation of a measurement with age, regression coefficients were compared in a generalized linear model. In these models we included the postmenstrual age (PMA) at CUS and the presence of CHD as covariates, as well as the interaction between age and CHD. Using a generalized linear model, the mean + SD at the PMA of 40 weeks was calculated. The inter- and intra-observer variations of the measurements were estimated with the interclass correlation coefficient. Analyses were performed with SPSS (version 23.0, SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered significant.

3. Results

Isolated severe fetal CHD was suspected in 100 healthy women in the mentioned time period. The exclusion process is shown in Fig. 1, resulting in 58 infants with prenatally detected CHD and an early postnatal pre-operative CUS in whom data were available for analysis. In 36 of 58 CHD cases (62%) prenatal ($n = 29$) or postnatal ($n = 7$) genetic testing (usually microarray) confirmed the absence of a genetic syndrome. There were no neonates with CHD excluded due to low birth weight. The types of CHD are listed in Table 1. The CHD group included

Box 1
Categorisation of ultrasound findings.

Significant abnormalities were defined as: any grade of P/IVH (Fig. 2), persistent grade 2 PVE, cPVL, intraparenchymal lesions suspect for stroke and structural brain abnormalities.

Minor abnormalities were defined as: any variant or combination of variants with need for further assessment or CUS follow up, not included in the significant abnormalities group, such as a combination of large/multiple pseudocysts suspect for (congenital) infection or transient lesions (cysts, focal echodensities) with spontaneous regression.

Physiological variants were defined as: LSV (Fig. 3), subependymal and choroid plexus cysts, grade 1 PVE in the first postnatal week and CSF space variations (asymmetric or plump; size within normal limits).

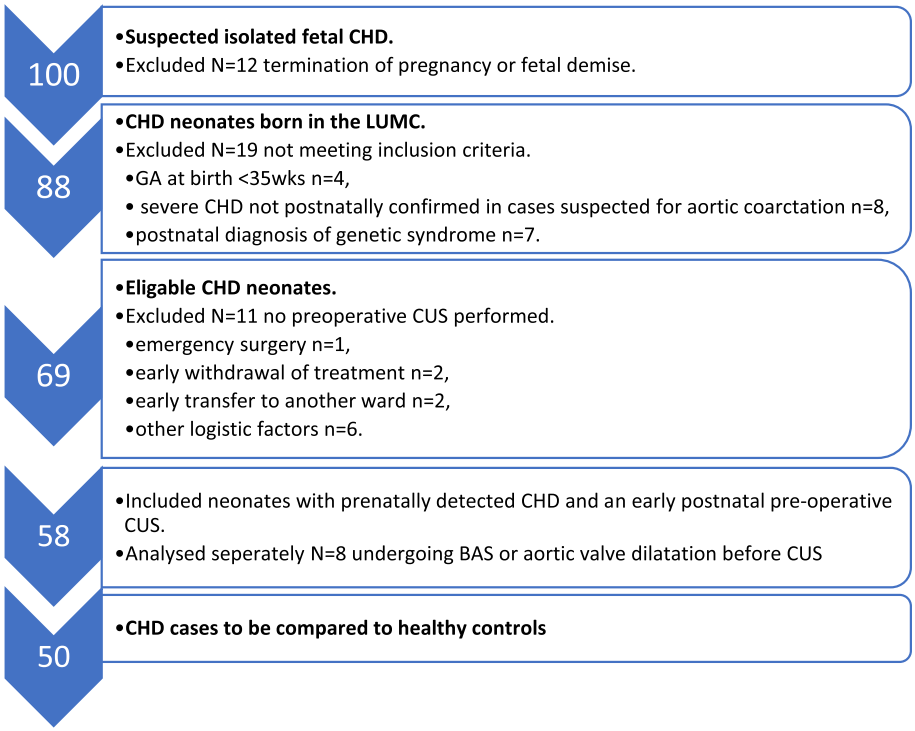

Fig. 1. Flow diagram of inclusion process of CHD neonates.

4 neonates who were part of a twin pregnancy: all were term born dichorionic twins with otherwise uneventful pregnancies. Eight CHD cases underwent (emergency) endovascular intervention before CUS was performed. These cases were analysed separately, resulting in 50 CHD cases to be compared with controls. In the control group of 65 healthy singleton pregnancies, 6 neonates were excluded due to maternal morbidity (hypertension/HELLP syndrome, $n = 2$) or neonatal factors (small for GA $n = 1$, GA at birth < 35wks n = 2, pneumonia n = 1), resulting in 59 healthy controls. The characteristics of cases and controls are displayed in Table 1. CHD cases were younger at birth and at CUS, and had a significantly lower HC z-score.

Frequencies of CUS findings are listed in Table 2. No differences were found between the two groups regarding physiological variants. Abnormal CUS findings were present in 5 neonates with CHD (10%) (all singletons) and in 4 of controls (7%) ($p = 0.1$; *RR* 1.5; 95% *CI* 0.4–5.2)). Of these, in 1 neonate with CHD (2%) and in 4 controls (7%) the CUS finding was considered a minor abnormality. Significant abnormalities were considered in 4 CHD cases (8%), but not in controls ($p = 0.04$; *RR* 10.6 (95% *CI* 0.6–192)). Table 3 describes the patient and ultrasound characteristics of neonates with abnormal CUS findings. Two CHD cases (aortic arch hypoplasia, double outlet right ventricle (DORV)-Fallot type) displayed persistent grade 2 PVE and 2 left-sided CHD cases displayed grade 1 IVH. In Table 4, CUS findings of the 50 neonates before intervention, are compared to 8 CHD neonates who underwent CUS after an endovascular intervention, showing a higher prevalence of CUS abnormalities after endovascular intervention (10% vs 37%, $p = 0.07$; RR 3.7 (95% CI 1.1–12.7)). Arterial stroke, confirmed by MRI, only occurred in the post-intervention group ($p = 0.02$; RR 28 (95% CI 1.5–543)). The two cases with stroke had a transposition of the great arteries (TGA) and underwent emergency BAS on their first postnatal day.

For the analysis of measurements of the intracranial and basal ganglia area volumes we used 54 singleton CHD cases and 59 controls, see Table 5. Most cerebral structures were smaller in neonates with CHD, when corrected for age at CUS. However, the TCD and CSF measurements did not differ significantly. To assess the influence of postnatal age at CUS and re-opening of the ventricles [22], measurements of the CSF compartments were also corrected for postnatal day at CUS. These analyses (data not shown) did not differ from the results shown in Table 5, and the measurements did not show a change with advancing (postnatal or postmenstrual) age.

4. Discussion

Previous studies have implicated CHD neonates to have smaller head sizes and to be more vulnerable for sustaining cerebral damage. This study is the first to prospectively assess early neonatal, pre-operative CUS findings in a cohort of neonates with prenatally detected CHD, and to compare the findings with CUS in healthy term born neonates. Significant CUS abnormalities, including IVH and grade 2 PVE, occurred in 8% of CHD neonates and not in controls. Although the confidence interval is wide, the difference is statistically significant. The prevalence of CUS abnormalities in our study is however much lower than the previously reported rates of 15–59% [14–18]. This can be explained by our strict definition of pathological findings, excluding physiological and minor variants. Another reason is that we only included prenatally detected, isolated CHD, (near) term born, without additional (genetic) pathology, as well as the separate analysis of cases with CUS after endovascular interventions. This avoids the inclusion of cases with externa inflicted neurological injury, for example due to hypoxia after birth in undetected cases. We therefore state that prenatal detection of CHD may at least partially prevent cerebral damage in the early postnatal, pre-operative period, and therefore may positively influence the (neurodevelopmental) outcome [26]. Strengthening this statement is the fact that our cohort had a favorable global long term outcome as distilled from clinical charts.

The timing of the identified significant CUS abnormalities remains difficult to determine. In all cases extensive prenatal CUS up to 36 weeks of gestation revealed no abnormalities, but abnormalities were already visible within 1–4 days after birth. The neonates with grade 2 PVE had CHD with different hemodynamic effects (aortic hypoplasia, DORV), and the sample size is too small to assess a possible effect of the specific type of CHD. The two cases with grade 1 IVH both had a left sided CHD. Both cases were stable during transition and the

Table 1
basic characteristics of study population.

	Controls n = 59	CHD n = 58	p-Value
Neonatal characteristics			
Male gender, n (%)	25 (42%)	34 (58%)	0.06
GA weeks at birth, mean ± SD	39.7 ± 1.3	39.0 ± 1.4	**0.02**
Range GA at birth, weeks + days	35 + 6 to 42 + 0	35 + 3 to 41 + 5	
PMA weeks at CUS, mean ± SD	40.3 ± 1.3	39.3 ± 1.4	**0.00**
Range PMA at CUS, weeks + days	36 + 1 to 43 + 2	35 + 4 to 43 + 2	
Postnatal age at CUS*, mean days ± SD	3.5 ± 2.5	2.1 ± 2.0	**0.00**
Range postnatal age, days	1–11	0–13	
CUS after endovascular intervention‡, n (%)	n/a	8 (14%)	
HC cm, mean ± SD	35.2 ± 1.1	34.1 ± 1.5	0.00
HC z-score, mean ± SD	0.18 ± 0.84	−0.33 ± 0.96	**0.02**
BW grams, mean ± SD	3479 ± 415	3166 ± 524	0.00
BW z-score, mean ± SD	−0.03 ± 0.87	−0.33 ± 1.06	0.1
Maternal characteristics			
Age years, mean ± SD	31.8 ± 4.6	30.9 ± 4.6	0.3
Smoking, n (%)	2 (4%)	5 (9%)	0.1
Induced labour, n (%)	19 (32%)	32 (55%)	**0.01**
Vaginal unassisted delivery, n (%)	47 (80%)	39 (67%)	0.07
First line/home delivery (midwife), n (%)	19 (32%)	n/a	

Type of CHD	N	Intervention
Left sided: AS/Ao hypoplasia/small left heart/CoAo/ PLVCS with small LV	18 (31%)	1
Left sided: hypoplastic left heart syndrome	4 (7%)	–
Tetralogy of Fallot or DORV-Fallot type	6 (10%)	–
TGA	17 (29%)	6
Right sided: Ebstein's anomaly/PS/PA-IVS/tricuspid atresia	5 (9%)	–
Other: common arterial trunk, ccTGA, AVSD, DORV	8 (14%)	1

Abbreviations: GA gestational age; PMA postmenstrual age; HC head circumference; BW birth weight; CHD congenital heart defects; CUS cranial ultrasound; CS caesarian section; AS aortic stenosis; Ao aorta; CoAo Coarctation; DORV double outlet right ventricle; LV left ventricle; PS pulmonary stenosis; PA-IVS pulmonary atresia with intact ventricular septum; PLVCS persistent left vena cava superior; ccTGA congenitally corrected TGA; AVSD atrioventricular septal defect.

* Mann Whitney nonparametric test.

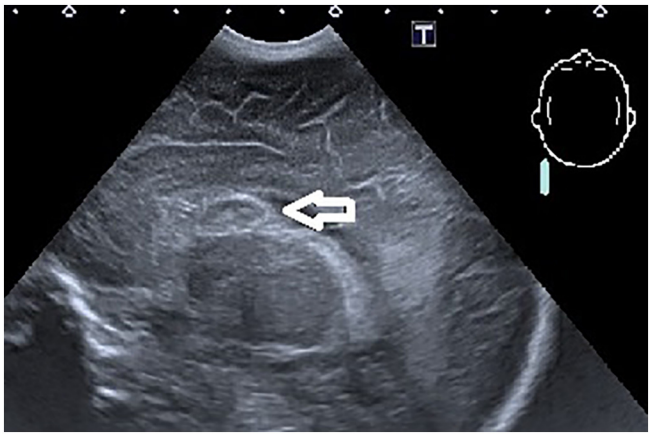

Fig. 2. Intraventricular hemorrhage in case 57.
The arrow marks the place of the grade 1 IVH in CHD case 57.

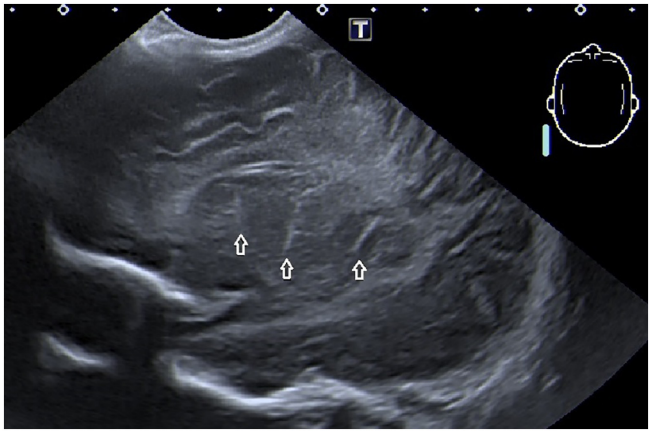

Fig. 3. Example of lenticulostriate vasculopathy.
The arrows mark the places of LSV in one of the control cases.

Table 2
Frequencies (numbers and percentages) of CUS findings in cases and controls.

	Controls n = 59	CHD n = 50	p-Value
Abnormal CUS finding	4 (7%)	5 (10%)	0.4
- Significant CUS abnormality	–	4 (8%)	0.04
- Minor CUS finding	4 (7%)	1 (2%)	0.1
No variations[a]	23 (39%)	19 (38%)	0.5
Physiological variants total[b]	32 (54%)	26 (52%)	0.5
- Grade 1 PVE	12 (20%)	12 (24%)	0.4
- Lenticulostriate vasculopathy	16 (27%)	14 (28%)	0.5
- Choroid plexus cyst(s)	12 (20%)	10 (20%)	0.6
- Subependymal cyst(s)	8 (14%)	8 (16%)	0.5
- Any cyst(s)	16 (27%)	18 (36%)	0.3
- 2 or more variations present	13 (22%)	11 (22%)	0.6
Wide/plump ventricles[c]	1 (2%)	4 (7%)	0.1
Asymmetric ventricles[c]	–	3 (6%)	0.1
Wide extra-axial spaces[c]	3 (5%)	5 (10%)	0.3

[a] Normal CUS.
[b] Including cases with variants coinciding with CUS abnormalities;
[c] Subjective finding as interpreted by the reviewer; categorized as normal CUS variant CUS cranial ultrasound; CHD congenital heart defects; PVE periventricular echogenicicity.

early postnatal period. A higher prevalence of low grade IVH in newborns with various types of CHD has recently been described, and may be explained by a combination of cerebral immaturity and hypoxia and/or impaired perfusion [27]. Arterial stroke was diagnosed in two neonates that underwent BAS; this association has been reported previously [28,29].

Physiological variants and minor CUS abnormalities occurred as frequently in CHD neonates as in healthy controls. Examples of physiological variants are CPC, LSV and homogeneous grade 1 PVE within the first postnatal week. Previous studies found similar or lower frequencies of physiological variants in high-risk neonates, admitted to the neonatal ward for various reasons: Shin et al. found 22% LSV (vs 27% in our healthy cohort) and Norton et al. found 12% CPC (vs 20% in our healthy cohort) [30,31]. Our slightly higher prevalence of physiological CUS variants may be due to the fact that we specifically searched for these findings, and used new CUS equipment with high resolution. In contrast to previous studies we did not consider these variants as significant or clinically relevant.

With respect to the cerebral measurements, we found a slightly smaller head circumference, a smaller intracranial volume and a smaller size of several brain structures in CHD neonates, when corrected for age, as found in previous studies [10,11,32,33]. In contrast to previous reports we did not find wider CSF spaces in CHD neonates. This may be explained by the fact that we scanned the CHD cases closer

Table 3
Characteristics of cases and controls with identified abnormal cranial ultrasound findings.

Case	Sex	CHD	GA at birth*	Postnatal age at CUS (days)	CUS physiological variants	CUS finding + follow up
CHD cases						
11	M	Borderline HLHS	35 + 6	2	LSV	Significant: grade 1 IVH, no major NDD (4 years old)
57	M	Aortic arch hypoplasia	37 + 0	4	SEP, grade 1 PVE	Significant: grade 1 IVH (Fig. 2), no major NDD (2 years old)
93	F	Aortic arch hypoplasia	41 + 0	2	LSV (bilateral), SEP	Significant: persistent grade 2 PVE, no cPVL on follow up CUS, loss to follow up.
65	M	DORV - fallot type	40 + 5	1	–	Significant: persistent grade 2 PVE, no c PVL on follow up CUS, no major NDD (1,5 years old).
43	M	Aortic stenosis	39 + 3	2	CPC, SEP	Minor: multiple (large) CPCs/SEP, CMV excluded. Deceased when 2 months old after perisurgical cardiac arrest with severe neurological damage.
Controls						
4	F	–	40 + 1	3	CPC, SEP, LSV	Minor: multiple CPCs/SEP/LSV, CMV excluded, no further follow up.
19	M	–	39 + 4	1	SEP, LSV	Minor: small (transient) focal abnormality in the basal ganglia, suspect for stroke, but normal on follow up CUS, no further follow up.
26	M	–	41 + 1	2	Large pericerebral CSF spaces	Minor: mildly dilated lateral ventricles and possible IVH, but no pathological findings on follow up CUS using both anterior and posterior fontanel.
42	M	–	37 + 1	4	Large pericerebral CSF spaces	Minor: cavum velum interpositum cyst (12 mm), spontaneous regression after 6 weeks, no further follow up.
CHD cases after endovascular intervention						
17	M	TGA, restrictive FO. Postpartum immediate BAS.	38 + 5	1	–	Significant: stroke in basal ganglia (MRI confirmation). Second incident: asphyxia after perisurgical cardiac arrest when 3 months old. Has global NDD (3 years old).
24	M	TGA. Postpartum immediate BAS.	36 + 4	1	Large pericerebral CSF spaces	Significant: middle cerebral artery stroke, persistent grade 2 PVE (MRI confirmation). No NDD (3 years old).
77	F	TGA, restrictive FO. Postpartum immediate BAS	39 + 1	3	LSV (bilateral)	Minor: small (transient) focal abnormality in the basal ganglia, suspect for stroke but normal on follow up. No NDD (2 years old).

Abbreviations: BAS balloon atrioseptostomy; CUS cranial ultrasound; DORV double outlet right ventricle; FO foramen ovale; GA gestational age *(weeks + days); HLHS hypoplastic left heart syndrome; TGA transposition of the great arteries; CMV cytomegalovirus; CPC choroid plexus cyst; CSF cerebrospinal fluid; SEP subepenydymal cyst; LSV lenticulostriate vasculopathy; PVE periventricular echodensity, grade 1 or 2; NDD neurodevelopmental delay.

Table 4
Frequencies and percentages of ultrasound abnormalities before and after catheter intervention.

	CUS without/before intervention n = 50	CUS after intervention n = 8	p-Value
Significant CUS abnormality total	4 (8%)	2 (25%)	0.2
• Intraventricular hemorrhage	2 (4%)	–	0.7
• Grade 2 PVE	2 (4%)	1** (13%)	0.4
• Stroke	–	2** (25%)	**0.02**
Abnormal CUS finding (including minor)	5 (10%)	3 (37%)	0.06

** One case had both grade 2 PVE and stroke; CUS cranial ultrasound; CHD congenital heart defects; PVE periventricular echodensity.

Table 5
CUS measurements and estimations of intracranial and basal ganglia volumes.[a, b, c]

	Controls n = 59		CHD n = 54		
	Mean	SD	Mean	SD	p-Value
Cerebrospinal fluid assessment					
Sinocortical width (mm)	0.4	± 0.4	0.3	± 0.4	0.2[a]
Interhemispheric fissure (mm)	0.8	± 0.5	0.7	± 0.6	0.3[a]
Cavum septum pellucidum width (mm)[c]	1.7	± 2.0	2.4	± 1.5	0.8[c]
Ventricular index (mm)[c]	12.3	± 2.1	12.6	± 1.5	0.3[c]
Anterior horn width (mm)	0.8	± 0.5	0.7	± 0.5	0.1[a]
Thalamo-occipital distance (mm)	14.4	± 2.2	14.3	± 2.6	0.7[b]
Cerebral growth assessment					
Basal ganglia volume (cm3)[c]	10.1	± 1.7	9.6	± 1.2	**0.00**[c]
Cranial volume (cm3)[c]	437	± 67	398	± 48	**0.00**[c]
CC length (mm)[c]	44.0	± 4.3	42.5	± 3.1	**0.01**[c]
CC to fastigium length (mm)[c]	50.3	± 3.6	49.1	± 2.5	**0.01**[c]
Pons diameter (mm)[c]	17.1	± 2.1	16.5	± 1.5	**0.05**[c]
Vermis height (mm)[c]	24.0	± 3.0	23.1	± 2.0	**0.01**[c]
TCD (mm)[c]	54.6	± 3.6	54.0	± 2.5	0.2[c]

CUS cranial ultrasound; CHD congenital heart defects; SD standard deviation; CC corpus callosum; TCD transcerebellar diameter.
[a] Mann Whitney nonparametric test.
[b] Independent sample *t*-test.
[c] At 40 weeks of postmenstrual age; linear correlation; estimated with generalized linear regression model.

to birth and included prenatally detected CHD only. A longer interval between birth and surgery and lower oxygenation levels after birth are associated with cerebral lesions just before surgery [29,34]; the same (hemodynamic) factors might also affect the development of cerebral atrophy and widened CSF spaces.

Previous authors have suggested that hemodynamic factors in fetal life already cause susceptibility for cerebral damage in CHD [21]. Our findings neither confirm nor deny this. Left sided CHD are over-represented in our group with abnormal CUS findings (cases 11, 57 and 93), indicating a possible effect of prenatal aortic flow. However, in our cohort, grade 2 PVE also occurred in DORV with uncompromised fetal and neonatal aortic flow. Previous studies could not identify a possible effect of prenatal cerebral oxygenation or aortic flow on fetal head circumference growth [35,36]. We therefore are not convinced that prenatal hemodynamics are a major cause for fetal or early neonatal cerebral damage. Other factors, such as (*epi*)genetic changes, might also be involved in the susceptibility for cerebral damage and/or NDD.

Strengths of our study are the prospective inclusion of unselected, consecutive, isolated, prenatally detected CHD cases, and the comparison with healthy controls, recruited in non-clinical midwifery practices. The most important CUS abnormalities were confirmed by MRI. Furthermore, we used regression models to correct for age.

An important limitation of our study is the small sample size. Due to logistic reasons we were only able to include 50 of 69 eligible CHD cases. Inherent to critical CHD, some cases were too ill to prioritise a CUS before other, life-saving, procedures or transfer. This may have introduced some selection bias in the results. Secondly, we were not always able to perform (structured and ND) follow-up. The evolution of several CUS findings, including PVE grade 1 in the first postnatal week, is unknown in most cases. Since PVE grade 1 occurred similarly in CHD cases and in healthy controls, we felt it confirmed that this should not be seen as abnormality, but more likely as a physiological variant. Also, in cases with (possible) significant abnormalities, we did perform CUS follow-up to see whether these abnormalities persisted. Thirdly, our study design resulted in a slightly younger postnatal age of the CHD group, which could result in an overestimation of cerebral abnormalities. As described before, we corrected cerebral measurements for gestational age at CUS to correct for the age difference. Finally, CUS may not be the optimal tool to detect all types of cerebral injury, such as maturational delay or diffuse mild white matter injury [13,16,18]. However, CUS is a cheap, non-invasive and bedside method to detect clinically relevant abnormalities and perform growth measurements [37]. The use of CUS instead of MRI in our study made it possible to perform very early postnatal imaging in healthy controls and in CHD neonates who were often too unstable to leave the neonatal intensive care unit.

In conclusion, neonates with prenatally detected CHD display CUS abnormalities more frequently, and have smaller cerebral volume, compared to healthy neonates. The prevalence of significant cerebral abnormalities in our cohort is much lower than previously reported in mixed pre- and postnatally detected CHD groups. Therefore, abnormal neurodevelopment may only partly be explained by pre- and perinatal cerebral injury in CHD. Acute severe hypoxia and/or chronic mild hypoxia in the period between birth and surgery may be important factors as well, and prenatal diagnosis of CHD may have a guarding effect.

Declaration of competing interest

None.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2020.105097.

References

[1] D. van der Linde, E.E. Konings, M.A. Slager, M. Witsenburg, W.A. Helbing, J.J. Takkenberg, et al., Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis, J. Am. Coll. Cardiol. 58 (21) (2011) 2241–2247.
[2] D.C. Bellinger, R.A. Jonas, L.A. Rappaport, D. Wypij, G. Wernovsky, K.C. Kuban, et al., Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass, N. Engl. J. Med. 332 (9) (1995) 549–555.
[3] J. Stieh, H.H. Kramer, P. Harding, G. Fischer, Gross and fine motor development is impaired in children with cyanotic congenital heart disease, Neuropediatrics 30 (2) (1999) 77–82.
[4] B. Marino, M.C. Digilio, Congenital heart disease and genetic syndromes: specific correlation between cardiac phenotype and genotype, Cardiovasc. Pathol. 9 (6) (2000) 303–315.

[5] B.S. Marino, P.H. Lipkin, J.W. Newburger, G. Peacock, M. Gerdes, J.W. Gaynor, et al., Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association, Circulation 126 (9) (2012) 1143–1172.
[6] McQuillen PS, S.P. Miller, Congenital heart disease and brain development, Ann. N. Y. Acad. Sci. 1184 (2010) 68–86.
[7] H.H. Hovels-Gurich, Factors influencing neurodevelopment after cardiac surgery during infancy, Front. Pediatr. 4 (2016) 137.
[8] A.J. du Plessis, Mechanisms of brain injury during infant cardiac surgery, Semin. Pediatr. Neurol. 6 (1) (1999) 32–47.
[9] S.P. Miller, McQuillen PS, S. Hamrick, D. Xu, D.V. Glidden, N. Charlton, et al., Abnormal brain development in newborns with congenital heart disease, N. Engl. J. Med. 357 (19) (2007) 1928–1938.
[10] M. Owen, M. Shevell, A. Majnemer, C. Limperopoulos, Abnormal brain structure and function in newborns with complex congenital heart defects before open heart surgery: a review of the evidence, J. Child Neurol. 26 (6) (2011) 743–755.
[11] A. Khalil, N. Suff, B. Thilaganathan, A. Hurrell, D. Cooper, J.S. Carvalho, Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis, Ultrasound Obstet. Gynecol. 43 (1) (2014) 14–24.
[12] D.J. Licht, D.M. Shera, R.R. Clancy, G. Wernovsky, L.M. Montenegro, S.C. Nicolson, et al., Brain maturation is delayed in infants with complex congenital heart defects, J. Thorac. Cardiovasc. Surg. 137 (3) (2009) 529–536.
[13] N.H. Claessens, P. Moeskops, A. Buchmann, B. Latal, W. Knirsch, I. Scheer, et al., Delayed cortical gray matter development in neonates with severe congenital heart disease, Pediatr. Res. 80 (5) (2016) 668–674.
[14] A.B. Te Pas, G. van Wezel-Meijler, R. Bokenkamp-Gramann, F.J. Walther, Preoperative cranial ultrasound findings in infants with major congenital heart disease, Acta Paediatr. 94 (11) (2005) 1597–1603.
[15] J.P. van Houten, A. Rothman, R. Bejar, High incidence of cranial ultrasound abnormalities in full-term infants with congenital heart disease, Am. J. Perinatol. 13 (1) (1996) 47–53.
[16] D.R. Rios, S.E. Welty, J.K. Gunn, J. Beca, C.G. Minard, M. Goldsworthy, et al., Usefulness of routine head ultrasound scans before surgery for congenital heart disease, Pediatrics 131 (6) (2013) e1765–e1770.
[17] F. Krull, K. Latta, P.F. Hoyer, G. Ziemer, H.C. Kallfelz, Cerebral ultrasonography before and after cardiac surgery in infants, Pediatr. Cardiol. 15 (4) (1994) 159–162.
[18] B. Latal, C. Kellenberger, A. Dimitropoulos, C. Hagmann, C. Balmer, I. Beck, et al., Can preoperative cranial ultrasound predict early neurodevelopmental outcome in infants with congenital heart disease? Dev. Med. Child Neurol. 57 (7) (2015) 639–644.
[19] V.Y. Chock, V.M. Reddy, D. Bernstein, A. Madan, Neurologic events in neonates treated surgically for congenital heart disease, J. Perinatol. 26 (4) (2006) 237–242.
[20] W.I. El-Naggar, M. Keyzers, McNamara PJ, Role of amplitude-integrated electroencephalography in neonates with cardiovascular compromise, J. Crit. Care 25 (2) (2010) 317–321.
[21] M.T. Donofrio, A.J. Duplessis, C. Limperopoulos, Impact of congenital heart disease on fetal brain development and injury, Curr. Opin. Pediatr. 23 (5) (2011) 502–511.
[22] M.D. Nelson Jr., C.J. Tavare, L. Petrus, P. Kim, F.H. Gilles, Changes in the size of the lateral ventricles in the normal-term newborn following vaginal delivery, Pediatr. Radiol. 33 (12) (2003) 831–835.
[23] L.S. de Vries, P. Eken, L.M. Dubowitz, The spectrum of leukomalacia using cranial ultrasound, Behav. Brain Res. 49 (1) (1992) 1–6.
[24] J.J. Volpe, Intraventricular hemorrhage and brain injury in the premature infant. Diagnosis, prognosis, and prevention, Clin. Perinatol. 16 (2) (1989) 387–411.
[25] A.M. Graca, K.R. Cardoso, J.M. da Costa, F.M. Cowan, Cerebral volume at term age: comparison between preterm and term-born infants using cranial ultrasound, Early Hum. Dev. 89 (9) (2013) 643–648.
[26] S. Peyvandi, V. De Santiago, E. Chakkarapani, V. Chau, A. Campbell, K.J. Poskitt, et al., Association of prenatal diagnosis of critical congenital heart disease with postnatal brain development and the risk of brain injury, JAMA Pediatr. 170 (4) (2016) e154450.
[27] C.M. Ortinau, J.S. Anadkat, C.D. Smyser, P. Eghtesady, Intraventricular hemorrhage in moderate to severe congenital heart disease, Pediatr. Crit. Care Med. 19 (1) (2018) 56–63.
[28] McQuillen PS, S.E. Hamrick, M.J. Perez, A.J. Barkovich, D.V. Glidden, T.R. Karl, et al., Balloon atrial septostomy is associated with preoperative stroke in neonates with transposition of the great arteries, Circulation 113 (2) (2006) 280–285.
[29] C.J. Petit, J.J. Rome, G. Wernovsky, S.E. Mason, D.M. Shera, S.C. Nicolson, et al., Preoperative brain injury in transposition of the great arteries is associated with oxygenation and time to surgery, not balloon atrial septostomy, Circulation 119 (5) (2009) 709–716.
[30] H.J. Shin, M.J. Kim, H.S. Lee, R. Namgung, K.I. Park, M.J. Lee, Imaging patterns of sonographic lenticulostriate vasculopathy and correlation with clinical and neurodevelopmental outcome, J. Clin. Ultrasound 43 (6) (2015) 367–374.
[31] K.I. Norton, B. Rai, H. Desai, D. Brown, M. Cohen, Prevalence of choroid plexus cysts in term and near-term infants with congenital heart disease, AJR Am. J. Roentgenol. 196 (3) (2011) W326–W329.
[32] N.B. Matthiesen, T.B. Henriksen, J.W. Gaynor, P. Agergaard, C.C. Bach, V.E. Hjortdal, et al., Congenital heart defects and indices of fetal cerebral growth in a nationwide cohort of 924 422 liveborn infants, Circulation 133 (6) (2016) 566–575.
[33] M. von Rhein, A. Buchmann, C. Hagmann, H. Dave, V. Bernet, I. Scheer, et al., Severe congenital heart defects are associated with global reduction of neonatal brain volumes, J. Pediatr. 167 (6) (2015) 1259–63 e1.
[34] J.M. Lim, T. Kingdom, B. Saini, V. Chau, M. Post, S. Blaser, et al., Cerebral oxygen delivery is reduced in newborns with congenital heart disease, J. Thorac. Cardiovasc. Surg. 152 (4) (2016) 1095–1103.
[35] M.J. Mebius, S.A.B. Clur, A.S. Vink, E. Pajkrt, W.S. Kalteren, E.M.W. Kooi, et al., Growth patterns and cerebro-placental hemodynamics in fetuses with congenital heart disease, Ultrasound Obstet. Gynecol. (2018).
[36] F.A. Jansen, E.W. van Zwet, M.E. Rijlaarsdam, E. Pajkrt, C.L. van Velzen, H.R. Zuurveen, et al., Head growth in fetuses with isolated congenital heart defects: lack of influence of aortic arch flow and ascending aorta oxygen saturation, Ultrasound Obstet. Gynecol. 48 (3) (2016) 357–364.
[37] G. van Wezel-Meijler, S.J. Steggerda, L.M. Leijser, Cranial ultrasonography in neonates: role and limitations, Semin. Perinatol. 34 (1) (2010) 28–38.
[38] G. Meijler, S.J. Steggerda, Neonatal Cranial Ultrasound, 3rd edition, Springer, 2019.
[39] J.J. Volpe, Neurology of the Newborn, W.B. Saunders, London, 2000.