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Paediatric brain MRI findings following congenital heart surgery: a systematic review

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ABSTRACT

Objective This systematic review aimed to establish the relative incidence of new postoperative brain MRI findings following paediatric congenital cardiac surgery.

Design To distinguish perioperative changes from pre-existing MR findings, our systematic search strategy focused on identifying original research studies reporting both presurgery and postsurgery brain MRI scans. Patient demographics, study methods and brain MR findings were extracted.

Results Twenty-one eligible publications, including two case-control and one randomised controlled trial, were identified. Pre-existing brain MRI findings were noted in 43% (513/1205) of neonates prior to surgery, mainly white matter injuries (WMI). Surgery was performed at a median age of 8 days with comparison of preoperative and postoperative MR scans revealing additional new postoperative findings in 51% (550/1075) of patients, mainly WMI. Four studies adopted a brain injury scoring system, but the majority did not indicate the severity or time course of findings. In a subgroup analysis, approximately 32% of patients with pre-existing lesions went on to develop additional new lesions postsurgery. Pre-existing findings were not found to confer a higher risk of acquiring brain lesions postoperatively. No evidence was identified linking new MR findings with later neurodevelopmental delay.

Conclusion This systematic review suggests that surgery approximately doubles the number of patients with new brain lesions.

INTRODUCTION

It has long been recognised that delivery, congenital heart disease (CHD) and open heart surgery all carry a risk to the brain, potentially negatively impacting neurodevelopmental outcomes.¹ The estimated prevalence of CHD is 9 per 1000 infants,² of which 3 per 1000 require surgical or catheter-based interventions early in life.³ Due to advances in diagnostic imaging, surgical treatment and intensive care, more children with CHD now reach adulthood.⁴ However, the impact of brain lesions on long-term developmental outcomes remains a cause for concern. Up to 50% of CHD infants go on to experience developmental or psycho-social issues, but whether these are linked to perioperative brain injury remains unclear.⁵

Paediatric brain MRI is gaining in popularity and is already being performed routinely at many centres, especially in the USA. Brain MR scans obtained before and after surgery have the potential to provide unique insights into the nature, severity

Key messages

What is already known on this topic?

- ⇒ Paediatric cardiac surgery patients are at high risk of brain lesions but the clinical significance of these, and potential impacts on neurodevelopment are unclear.
- ⇒ Comparison of presurgery and postsurgery MRI scans provides an important tool for distinguishing new from pre-existing MR findings.

What this study adds?

- ⇒ Our results suggest that preoperative MR findings are present in approximately 43% of paediatric patients with congenital heart disease (CHD) prior to surgery.
- ⇒ Approximately 51% of patients undergoing surgery experience new findings postoperatively.
- ⇒ Pre-existing lesions were not found to be a significant risk factor for acquiring new postoperative findings.

and timing of brain lesions acquired around the time of surgery. Comparison of presurgery and postsurgery brain images provides a means of confidently separating surgery-induced changes from other sources of injury, especially where surgery is performed soon after delivery.⁶

MRI findings are commonly classified as focal ischaemic infarcts (including stroke), white matter injury (WMI) (including periventricular leukomalacia), cerebral sinovenous thrombosis (CSVT) and haemorrhage.⁷ The nature, location and severity of brain MRI findings can be quantified using scoring systems that include both qualitative and quantitative image assessment.^{8,9} The primary aim of this systematic review was to quantify the incidence of, and risk of acquiring, new MRI findings postsurgery. Secondary objectives included a preliminary exploration of factors associated with new MR findings, and whether surgery-related changes were associated with lower neurodevelopmental test scores. As the impact of surgery can only be determined by comparing presurgery and postsurgery MRI scans our inclusion criteria were limited to studies comparing presurgery and postsurgery MRI to identify new findings.

METHODS

A systematic search and data extraction was conducted and reported in accordance with the



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Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines¹⁰ to identify all studies reporting paired presurgery and postsurgery MRI scans in paediatric patients undergoing congenital cardiac surgery.

Search strategy

Our systematic review protocol was prospectively designed and registered with the PROSPERO database (Registration number: CRD42019158886). A comprehensive, systematic literature search was conducted in MEDLINE OVID and SCOPUS by two independent researchers (FA and HSAC). The search was limited to original peer-reviewed research conducted in humans and published in English between January 1990 and June 2021 (see supplemental file for search strategy).

Study eligibility criteria

After automated removal of duplicates, two researchers (FA and HSAC) independently screened study titles and abstracts for eligibility. Eligibility was assessed according to a PICO (patient-intervention-comparator-outcome) framework to extract all studies reporting preoperative and new postoperative brain MRI findings in paediatric patients (≤ 16 years) undergoing congenital heart surgery (online supplemental table 1). Articles identified as eligible by either reviewer were progressed to full text review with eligibility agreed by consensus. Reference lists and citations associated with eligible articles were searched by hand for additional relevant publications. All primary peer-reviewed original research studies, including randomised controlled trials, cohort, case-control studies and case reports, were eligible for inclusion. Conference abstracts were excluded.

Data extraction and quality assessment

Quality assessment and data charting were independently conducted by two reviewers (FA and HSAC) and agreed by consensus. Data were extracted from the full text of each article using a predefined checklist. Full details of data extraction, including parameters that were not reported, and an indication of heterogeneity, are provided in online supplemental tables 2 and 3. A total of seven studies were excluded due to their cohorts representing a subset of patients published elsewhere. We were careful to ensure that patients were not 'double-counted' due to multiple publications. For the case-control study, only the CHD group was included (ie, not healthy controls). For the randomised controlled trial (RCT), both groups involved patients with CHD, so were included.

A modified version of the Newcastle-Ottawa Scale (NOS) for observational studies, and a five-item scale developed by Jadad *et al*¹¹ for the RCT, were used to support quality assessment. Full details of our quality assessment and extraction methods are provided as an online supplemental file.

Due to the paired nature of the data, it was not appropriate to conduct a meta-analysis; findings are reported in a narrative format. Statistical analyses were performed using Prism GraphPad (V.7).

RESULTS

Our systematic search criteria returned a total of 2244 papers across two databases (online supplemental figure 1). Ten additional studies were identified by reviewing full text bibliographies. After removal of duplicate entries, and screening of abstracts and full text, 21 studies involving a total of 1277 patients were eligible for inclusion. Studies were methodologically diverse as well involving differences in patient's CHD

conditions and surgical interventions. In terms of information directly addressing our primary review aims relating to MR findings, 6 out of 21 studies provided a full set of relevant information^{12–17} (online supplemental table 3). Quality assessment scores suggested studies were of variable quality, ranging from a minimum of 3/7 to maximum of 7/7 for the NOS, and 3/5 based on the Jadad *et al* score. In six of the cohort studies, MR outcomes were not clearly reported. In two studies, it was unclear whether findings had been present preoperatively (online supplemental tables 4 and 5). For the RCT, the handling of withdrawals was not described. It was also unclear whether the person reviewing the MR images had been blinded to the intervention. However, as the aim of the RCT differed from that of our review, these issues would not have affected our findings.

Study and patient characteristics

Patient demographics, CHD condition, details of preoperative and postoperative MRI, and operative details are summarised in table 1. Data from a total of 1277 independent paediatric patients with CHD were identified for further analysis. Of these, the sex of the baby was specified for 1155 subjects, with 67% of babies reported as male. A summary of patient population characteristics shows that 35% of children were diagnosed with single ventricle abnormalities, 38% with transposition of the great arteries (TGA), 10% with two-ventricle abnormalities, 14% with other cardiac lesions and 3% with coarctation of the aorta. One study did not report the population CHD type.⁹ Most studies included patients with multiple types of cardiac abnormality. The majority (76%) of included patients underwent surgery involving CPB with a median CPB time of 147 (range 47–200) min.

MRI protocol

MR scan sequences exhibited significant heterogeneity between studies, as can be seen in table 2. T1-weighted and T2-weighted imaging are used in up to 90% of studies, diffusion-weighted imaging and volumetric imaging in 60% of studies, while other sequences are performed non-routinely (5%–30% of studies). Non-sedated brain MRI was performed in approximately 23% (297/1277) of patients across six studies using the 'feed and sleep' technique, with most patients still receiving a sedative or anaesthetic drug during their scan.

Outcomes

Qualitative brain MRI findings

Of 1205 patients who received a preoperative brain MRI in the early days of life, 513 patients (43%) had at least one pre-existing brain MRI finding at the time of their first scan. The preop scan occurred at a median (IQR) of 5 (IQR: 4.6–6) days. Of these, 205 patients were reported with WMI (40%) and 153 patients with infarcts (30%). A further 58 haemorrhage (11%) and 63 CSVT (12%) neonates were reported. In one study, 'lesions' in 34 patients were reported but the severity and type were not specified⁹ (see table 3).

A total of 1124 out of 1277 (88%) patients received a postoperative brain MRI conducted at a median (IQR) age of 13 (IQR: 7–19) days. This generated comparable paired presurgery and postsurgery MRI scans in 1075 patients, which were compared to identify new findings. Comparison of paired preop and postop MRI revealed 550 patients (49%) with new postoperative MRI findings: 301 WMI (55%), 161 infarct (29%), 50 haemorrhage (9%) and 28 with CSVT (5%). In 10 patients, the type of findings was unspecified.⁹ Note that, for some subjects, more

Table 1 Summary of main patient and operative characteristics

Author (year) country	Study design	N (male: female)	CHD diagnosis TV 2V TGA AC OL	1	NR	1	1	12	NR	Gestational age at birth (weeks)	Age at surgery (days)	Age at preoperative MRI (days)	Age at postoperative MRI
McComel (1990) USA ²⁸	Cohort (pro)	15 (NR)	1	NR	1	1	1	12	NR	NR	NR	NR	NR
Mahle (2002) USA ¹²	Cohort (pro)	24 (16:8)	13	11	NR	NR	NR	NR	NR	39.4 (36.0, 41.1)	4 (1, 24)	Day of surgery	8.5 (5–12) days after surgery Late scan: 4.5 (3–6) months
Partridge (2006) USA ¹³	Cohort (pro)	25 (16:9)	3	NR	18	1	3	3	NR	▶ No brain injury: 39.6 (37.7–41) days ▶ Preop injury: 39.3 (36.3–39.6) ▶ Postop injury: 39.3 (38–41)	≤6	▶ No brain injury: 6 (2, 36) ▶ Preop injury: 4 (2, 13) ▶ Postop injury: 3.5 (1, 7)	▶ No brain injury: 16 (12–56) days ▶ Preop injury: 20 (16–36) ▶ Postop injury: 18.5 (14–43)
Dent (2006) USA ¹⁸	Cohort (pro)	22 (15:7)	22	NR	NR	NR	NR	NR	NR	39 (36–41)	4 (1, 8)	Operation day 4 (1, 8)	9.5 (5–14) days
McQuillen (2007) USA ¹⁴	Cohort (pro)	62 (NR)	18	12	32	NR	NR	NR	NR	NR	NR	▶ No brain injury: 5.5 ▶ With brain injury: 5	▶ No brain injury: 18.5 ▶ With brain injury: 19
Miller (2007) USA ¹⁹	Case-control (pro)	41 (29:12)	12	NR	29	NR	NR	NR	NR	39.1 (38.2–40.0)	NR	5 (3–6)	NR
Block (2010) USA ¹⁵	Cohort (pro)	92 (59:33)	62	NR	30	NR	NR	NR	NR	▶ At UBC: 39 (38–40) ▶ At UCSF: 39 (38–40)	▶ With preop injury: 9 (7–11) ▶ No preop injury: 7 (5–11)	5 (3–7)	21 (16–27)
Kwak (2010) Korea ²⁹	Cohort (pro)	11 (10:1)	NR	NR	NR	11	NR	NR	NR	NR	11 (5, 46)	NR	NR
Beca (2013) New Zealand ¹⁶	Cohort (pro)	153 (98:55)	72	81	NR	NR	NR	NR	NR	38.8±1.6	7 (4–11)	NR	▶ Early MRI ≈ 7 days after surgery ▶ Late MRI ≈ 3 months of age
Drury (2013) New Zealand ³⁰	Cohort (pro)	18 (11:7)	NR	NR	NR	18	NR	NR	NR	▶ DHCA: 39 (37, 41) ▶ No DHCA: 40 (39–41)	NR	NR	NR
Mulkey (2013) USA ⁹	Cohort (retro)	73 (46:27)	NR	NR	NR	NR	73	NR	NR	▶ No brain injury: 39 (38–39) ▶ With brain injury: 38 (37–39)	▶ No brain injury: 7 (4–10) ▶ With brain injury: 8 (4–12)	No brain injury: 4 (2–10) With brain injury: 8 (4–13)	46±41
Algra (2014) The Netherlands ²³	RCT	37 (30:7)	12	5	2	1	17	NR	NR	▶ No new WMI: 39.5 (37.6–41.0) ▶ New WMI: 39.0 (35.3–41.0)	▶ No new WMI: 9 (8, 15) ▶ New WMI: 9 (5, 34)	8 (4, 34)	▶ No new WMI: 6 days ²⁷ ▶ New WMI: 7 (2–12)
Andropoulos (2014) USA ¹⁰	Cohort (retro)	59 (34:25)	27	12	20	NR	NR	NR	NR	38.4±1.2	NR	NR	NR
Bertholdt (2014) Switzerland ²¹	Case-control (pro)	30 (22:8)	8	NR	22	NR	NR	NR	NR	39.3 (36.7–41.9)	NR	6 (1, 12)	13 (6–30)
Lynch (2014) USA ²⁴	Cohort (pro)	37 (18:19)	37	NR	NR	NR	NR	NR	NR	38.9±0.8	4.2±1.9	NR	1 week after surgery
Claessens (2018) The Netherlands ¹⁷	Cohort (pro)	40 (27:13)	16	NR	12	2	10	NR	NR	▶ CSVT negative: 39.1 (38.8–40.1) ▶ CSVT positive: 39.3 (37.6–40.4)	▶ CSVT negative: 9 (8–15) ▶ CSVT positive: 9 (7–10)	▶ CSVT negative: 7 (6–12) ▶ CSVT positive: 6 (4–8)	CSVT negative: 6 (5–8) CSVT positive: 7 (6–9)
Peyvandi (2018) USA ³¹	Cohort (pro)	79 (55:24)	30	NR	49	NR	NR	NR	NR	▶ d-TGA: 39.2 (38.8–39.6) * ▶ HLHS: 38.9 (38.4–39.3) *	▶ d-TGA: 8 (5.5–11) ▶ HLHS: 8 (6–11)	▶ d-TGA: 5 (3–6) ▶ HLHS: 5 (3–6)	▶ d-TGA: 17.5 (15–25) ▶ HLHS: 24 ^{10–30}
Claessens (2019) The Netherlands ²⁶	Cohort (pro)	74 (49:25)	17	NR	26	NR	NR	31	NR	39.5 (38.7–40.6)	NR	5 (3–7)	8 (7–10)

Continued

Table 1 Continued

Author (year) country	Study design	N (male: female)	CHD diagnosis 1V 2V TGA AC OL	N	NR	NR	NR	NR	NR	NR	Gestational age at birth (weeks)	Age at surgery (days)	Age at preoperative MRI (days)	Age at postoperative MRI
Claessens (2019) The Netherlands ²²	Cohort (pro)	124 (92:32)	33	14	77	NR	NR	NR	NR	NR	HSC: 39.1 (38.1–39.9) ▲▲ WKZ: 39.4 (38.7–40.4)	~60 days	▲ HSC: 4 (2–5) ▲▲ WKZ: 5 (3–7)	▲ HSC: 12 ^{7–18} ▲▲ WKZ: 7 (7–10)
Lim (2019) Canada ²⁷	Cohort (pro)	45 (NR)	NR	NR	45	NR	NR	NR	NR	NR	39 (35–41)	▲ Early repair: 7 (3, 13) ▲ Late repair: 17 (14, 54)	5 (1, 26)	21 (4–70)
Guo (2019) USA ²⁵	Cohort (pro)	216 (144:72)	64	NR	118	NR	NR	NR	NR	NR	▲ UBC: 39 (38–40) ▲ UCSF: 39 (38–40) ▲ UCZ: 39.2 (38.8–40.1)	40 weeks (38.6–41.2)	41.9 weeks (40.5–43.2)	
Total		1277	447	135	481	34	34	180						

Age and time values presented as median (IQR) or median (min, max), median, mean±SD, mean (95% CI)* NR.

AC, aorta coarctation; ACP, antegrade cerebral perfusion; DHCA, deep hypothermic circulate; HSC, Hospital for Sick Children Toronto; NR, not reported; TGA, transposition of the great arteries; 1V, single ventricle abnormalities; 2V, two-ventricle abnormalities; WKZ, Wilhelmina Children's Hospital Utrecht.

than one category of MR finding was present. Although most studies reported the number of new WMI, or acute or chronic infarcts, fewer reported findings of haemorrhage^{12 15 16 18–22} or CSVT^{17 22 23} and the location and severity of new findings were rarely described in detail.

As most papers only reported totals and averages, the paired relationship between pre-existing and new findings was often unclear. Based on a more detailed analysis of 390 pairs of scans, from a subset of 7 papers providing sufficient information to deduce how many patients with pre-existing lesions went on to acquired new lesions; 32% (48/149) of paediatric patients with pre-existing lesions had additional new brain MRI findings following surgery.^{9 12–17}

Risk factors related to presurgery and new postsurgery MRI brain findings were reported in 11 studies.^{12 14–18 21–25}

Quantitative brain lesion scores

Four studies adopted an MRI brain lesion scoring system to quantify both the location and severity of findings.^{9 15 22 26} Mulkey *et al*⁹ developed a detailed brain MRI score to predict patients with CHD likely to be at greatest risk of neurodevelopmental delay. The scoring system ascribes a numerical value to each of 11 categories of brain lesion, and accounts for severity by considering the approximate number and size of areas affected. They concluded that brain lesion scores of 7/11 or higher would be concerning for neurodevelopmental delay. Full details of other scoring systems are provided as online supplemental file.

Neurodevelopmental assessment

A total of 232 infants across 7 studies underwent neurodevelopmental assessment between 1 and 2 years by either a paediatrician or psychologist. Most studies (five studies, n=207) used the third edition of the Bayley Scales of Infant and Toddler Development, when infants reached 2 years (three studies),^{16 17 23} 18 months²⁷ or 12 months of age.²⁰ Based on these studies it is unclear whether there is any link between new postoperative MRI findings and low neurodevelopmental test scores. Neurodevelopmental risk factors are reported in a single study by Andropoulos *et al*²⁰ and full details are provided as an online supplemental file.

One study used a modified standardised assessment tool²¹ to examine posture, general movements, tone, primitive reflexes and muscle stretch reflexes, cranial nerves and reactivity/behaviour in 22 neonates. Preoperative neuromotor assessment was performed at a median age of 7^{2–13} days, providing a median sum score of 2 (range 0–6) out of a maximum score of 18. Postoperatively, 30 neonates with a median age of 15 (9–86) days had a median score of 2.5 (range 0–7). Children with preoperative brain MR lesions were found to have significantly poorer neuromotor preoperative score than neonates without brain lesions. There were no significant differences in postoperative neurodevelopment between neonates with and without either preoperative (p=0.55, Mann–Whitney U-test) or new postoperative brain lesions (p=0.96, Mann–Whitney U-test).²¹ However, these findings need to be interpreted with caution, as one study, with only 22 patients is likely to be underpowered.

DISCUSSION

To the best of our knowledge, this is the first systematic review to focus on understanding the incidence of perioperative brain MRI findings associated with paediatric congenital cardiac surgery. Our findings suggest that CHD is consistently associated with a high proportion of patients experiencing both presurgery

Table 2 Summary of MRI protocols adopted by the included studies

MRI protocol	Outcome of interest	Studies
Scanner manufacturer	GE	McConnell, ²⁸ Partridge, ¹³ Dent, ¹⁸ McQuillen, ¹⁴ Block, ¹⁵ Mulkey, ⁹ Bertholdt, ²¹ Peyvandi, ³¹ Guo ²⁵
	Philips	Mulkey, ⁹ Algra, ²³ Andropoulos, ²⁰ Claessens, ¹⁷ Claessens, ²⁶ Claessens ²²
	Siemens	Mahle, ¹² Block, ¹⁵ Beca, ¹⁶ Drury, ³⁰ Lynch, ²⁴ Lim, ²⁷ Guo ²⁵
	Not reported	Miller, ¹⁹ Kwak ²⁹
Field strength	1.5 T	McConnell, ²⁸ Mahle, ¹² Partridge, ¹³ Dent, ¹⁸ McQuillen, ¹⁴ Block, ¹⁵ Beca, ¹⁶ Drury, ³⁰ Mulkey, ⁹ Algra, ²³ Andropoulos, ²⁰ Lynch, ²⁴ Claessens, ¹⁷ Peyvandi, ³¹ Claessens, ²² Lim, ²⁷ Guo ²⁵
	3 T	Beca, ¹⁶ Bertholdt, ²¹ Claessens, ¹⁷ Peyvandi, ³¹ Claessens(19), Guo ²⁵
	Not reported	Miller, ¹⁹ Kwak ²⁹
Immobilisation	General anaesthetic	Mahle, ¹² Dent, ¹⁸ Andropoulos, ²⁰ Lynch ²⁴
	Sedation	Block, ¹⁵ Bertholdt, ²¹ Claessens, ¹⁷ Peyvandi, ³¹ Claessens ²⁶
	Feed and sleep	Block, ¹⁵ Bertholdt, ²¹ Claessens, ¹⁷ Peyvandi, ³¹ Claessens, ²⁶ Lim ²⁷
	Not reported	McConnell, ²⁸ Partridge, ¹³ McQuillen, ¹⁴ Miller, ¹⁹ Kwak, ²⁹ Beca, ¹⁶ Drury, ³⁰ Mulkey, ⁹ Algra, ²³ Guo ²⁵
Image review	Single blinded observer (O), radiologist (R) or neuroradiologist (N)	McConnell, ²⁸ Mahle, ¹² Partridge, ¹³ Dent, ¹⁸ McQuillen, ¹⁴ Miller, ¹⁹ Block, ¹⁵ Kwak, ²⁹ Drury, ³⁰ Andropoulos, ²⁰ Peyvandi, ³¹ Claessens ²²
	Pair of blinded observers (O), radiologist (R) or neuroradiologist (N)	Beca, ¹⁶ Mulkey, ⁹ Algra, ²³ Bertholdt, ²¹ Lynch, ²⁴ Claessens, ¹⁷ Claessens, ²⁶ Guo ²⁵
	Not reported	Lim ²⁷
T1 weighted	Structural imaging (suppresses water and high signal intensity of fat)	McConnell, ²⁸ Mahle, ¹² Partridge, ¹³ Dent, ¹⁸ McQuillen, ¹⁴ Block, ¹⁵ Beca, ¹⁶ Drury, ³⁰ Mulkey, ⁹ Algra, ²³ Andropoulos, ²⁰ Bertholdt, ²¹ Lynch, ²⁴ Claessens, ¹⁷ Peyvandi, ³¹ Claessens, ²⁶ Claessens, ²² Lim, ²⁷ Guo ²⁵
T2 weighted	Detect pathology associated with oedema/fluid (high signal intensity of water)	McConnell, ²⁸ Mahle, ¹² Partridge, ¹³ Dent, ¹⁸ McQuillen, ¹⁴ Block, ¹⁵ Beca, ¹⁶ Drury, ³⁰ Mulkey, ⁹ Algra, ²³ Andropoulos, ²⁰ Bertholdt, ²¹ Lynch, ²⁴ Claessens, ¹⁷ Peyvandi, ³¹ Claessens, ²⁶ Claessens, ²² Lim ²⁷
DWI and DTI	Acute cerebral infarct and haemorrhage (Brownian motion of water molecules)	Mahle, ¹² Dent, ¹⁸ Beca, ¹⁶ Drury, ³⁰ Mulkey, ⁹ Andropoulos, ²⁰ Bertholdt, ²¹ Lynch, ²⁴ Claessens, ¹⁷ Peyvandi, ³¹ Claessens, ²⁶ Claessens, ²² Lim ²⁷
	Tractography (Brownian motion along direction of nerve fibres)	McQuillen, ¹⁴ Miller, ¹⁹ Block ¹⁵
FLAIR	High signal for lacunar infarcts and subarachnoid haemorrhage.	Beca, ¹⁶ Drury, ³⁰ Mulkey, ⁹ Algra ²³
SWI	Detects microhaemorrhages and calcium	Beca, ¹⁶ Mulkey, ⁹ Andropoulos, ²⁰ Lynch, ²⁴ Claessens, ¹⁷ Claessens, ²⁶ Claessens ²²
3D/Volumetric	Detects abnormal brain region volumes	Partridge, ¹³ McQuillen, ¹⁴ Block, ¹⁵ Beca, ¹⁶ Drury, ³⁰ Claessens, ¹⁷ Peyvandi, ³¹ Claessens, ²⁶ Claessens, ²² Lim, ²⁷ Guo, ²⁵ Lynch ²⁴
MRS	Diagnoses metabolic brain disorders	Dent, ¹⁸ Miller ¹⁹
Proton density	Evaluates grey/white matter abnormalities (grey matter has a higher signal intensity than the white matter)	McConnell ²⁸
MP-RAGE	Useful for brain tissue classification by offering excellent contrast for brain cortical segmentation	Lynch ²⁴
MR-venography	Examines the veins without the overlying tissues being visible (requires contrast material to enhance the visibility of the veins).	Claessens ²²

DWI, diffusion-weighted imaging.

and postsurgery brain MRI lesions. Based on comparison of pairs of images, just over half of neonates (51%) were reported with new brain MRI findings post-surgery, compared to 43% with pre-existing findings.

WMI was the dominant finding in both preoperative (40%) and new postoperative (55%) MRI scans. Focal infarcts were seen in 30% of patients preoperatively with additional new infarcts found in 29% of patients postoperatively. Haemorrhage and CSVT were investigated less frequently among studies. Haemorrhage was reported in 11% of patients preoperatively, with 9% of patients experiencing new lesions postoperatively. Some patients exhibited more than one type of finding and were represented in multiple categories.

Based on paired data, 32% (48/149) of patients with pre-existing lesions went on to acquire new lesions following surgery. This is lower than the 49% incidence overall and concurs with the results of a multivariable logistic regression analysis conducted by Block *et al* (n=92), suggesting that pre-existing lesions are not a significant risk factor for acquiring

new postoperative findings.¹⁵ Significant risk factors identified by previous studies are summarised in online supplemental figure 2.

It is important to note that these are radiological rather than clinically relevant diagnoses and some findings may simply reflect maturational or other differences. As many MRI findings represent minor lesions, which can resolve with time, or be mitigated through neuronal plasticity and adaptations of the growing brain, clinical significance is unclear.

It is worth noting that there have been significant improvements in MR imaging equipment and image quality over the last 30 years. Only one eligible paper was published in the 1990s, limited to 15 patients; this would not have contributed strongly to the review findings. Seven papers were published up to 2010 (inclusive) and 13 papers between 2011 and 2021. When we prospectively filed the review with PROSPERO, we were keen to capture all papers relevant to the topic regardless of publication date. In future reviews it may be beneficial to limit the search to recent publications to reduce heterogeneity.

Table 3 Number of patients with preoperative and postoperative brain MRI findings

Study	MRI scans			Preoperative MRI findings					New postoperative MRI findings					Total	With preop findings
	Pre	Post	Paired	WMI	Infarct	Haemorrhage	CSVT	Total	WMI	Infarct	Haemorrhage	CSVT			
McConnell <i>et al</i> ²⁸	15	15	15	NR	1	NR	NR	1	NR	1	NR	NR	NR	1	NR
Mahle <i>et al</i> ¹²	24	21	21	4	2	1	NR	7	NR	7	NR	NR	NR	20	3/12
Partridge <i>et al</i> ¹³	25	25	25	4	3	2	NR	7	NR	7	NR	NR	NR	6	2/7
Dent <i>et al</i> ¹⁸	22	15	15	1	4	2	NR	7	NR	7	NR	NR	NR	11	NR
McQuillen <i>et al</i> ¹⁴	62	53	53	11	13	5	NR	29	NR	29	NR	NR	NR	19	7/29
Miller <i>et al</i> ⁹	41	36	36	4	10	2	NR	14	NR	14	NR	NR	NR	11	NR
Block <i>et al</i> ¹⁵	92	78	78	21	23	7	NR	40	NR	40	NR	NR	NR	32	13/33
Kwak <i>et al</i> ²⁹	11	11	11	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1	NR
Beca <i>et al</i> ¹⁶	153	135	135	30	7	6	NR	38	NR	38	NR	NR	NR	59	7/27
Drury <i>et al</i> ³⁰	18	18	18	5	NR	NR	NR	5	NR	5	NR	NR	NR	5	NR
Mulkey <i>et al</i> ⁶	73	38	38	NR	NR	15	NR	34 (16 type is NS)	NR	NR	5	NR	NR	28 (23 type is NS)	13/38
Algra <i>et al</i> ²³	37	36	36	18	3	5	3	29	NR	29	NR	NR	NR	71	NR
Andropoulos <i>et al</i> ^{20, 26} USA	59	59	59	12	9	4	NR	18	NR	18	NR	NR	NR	28	NR
Bertholdt <i>et al</i> ²¹ Switzerland	30	30	30	6	3	NR	NR	7	NR	7	NR	NR	NR	2	NR
Lynch <i>et al</i> ⁴	37	33	33	8	NR	NR	NR	8	NR	8	NR	NR	NR	16	NR
Claessens <i>et al</i> ¹⁷	40	40	40	NR	NR	NR	NR	30	NR	30	NR	NR	NR	45	3/3
Peyvandil <i>et al</i> ³¹	79	73	73	16	18	NR	NR	34	NR	34	NR	NR	NR	30	NR
Claessens <i>et al</i> ¹⁶	56	53	53	12	5	NR	NR	17	NR	17	NR	NR	NR	40	NR
Claessens <i>et al</i> ³²	100	120	100	16	48	8	NR	100	NR	100	NR	NR	NR	124	NR
Lim <i>et al</i> ²⁷	45	45	45	14	4	1	NR	19	NR	19	NR	NR	NR	1	NR
Guo <i>et al</i> ²⁵	186	172	161	23	NR	NR	NR	23	NR	23	NR	NR	NR	7	NR
Total	1205	1124	1075	205	153	58	63	442	301	161	50	28	519	48/149	

CSVT, cerebral sinovenous thrombosis; NR, not reported; WMI, white matter injury.

Heterogeneity among studies is clearly present. Although most studies reported totals for cohorts including more than one type of CHD condition, single ventricle abnormalities and TGA represented 73% of subjects. The altered neurovascular physiology in these conditions is likely to have a more significant impact on prenatal brain development than other forms of CHD, which are under-represented. Several eligible studies limited recruitment to patients with specific CHD conditions. Furthermore, our analysis did not distinguish between patients who had received cardiopulmonary bypass compared with non-bypass interventions.

Diagnostic accuracy levels are likely to differ between the selected papers due to the use of differing methods for lesion detection and classification. Few studies used a brain lesion scoring system, which makes accurate comparisons difficult without a consistent approach across studies. As MR findings may resolve with time,^{12,21} variations in study design, sequences adopted, and the timing of postoperative brain MRI may also be responsible for differences in brain MR findings between studies.

Future work should be directed towards systematically examining different CHD subgroups, with robust ascertainment of brain lesions to enable improved risk stratification of patients with CHD. Development of a standardised MRI brain lesion scoring system for paediatric CHD would also be beneficial. Structured neurodevelopmental follow-up programmes may be useful to help improve developmental outcomes integrated with clinical care. However, we found no evidence to support a link between either preoperative or new postoperative MR findings around the time of surgery and neurodevelopmental delay. In conclusion, this systematic review confirms the presence of preoperative brain MR findings in approximately 43% of neonates, with 51% of babies found to have additional new MR findings postoperatively.

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