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 peripherative changes from pre-existing MR findings, our systematic search strategy focused on identifying original research studies reporting both presurgery and post-surgery 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 post-surgery. 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 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 post-surgery. 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
Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines\textsuperscript{10} 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 postsurgical 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\textsuperscript{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\textsuperscript{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.\textsuperscript{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 prep scan occurred at a median (IQR) of 5 (IQR: 4.6–6) days. Of these, 203 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 specified\textsuperscript{6} (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 350 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.\textsuperscript{9} Note that, for some subjects, more
Table 1 Summary of main patient and operative characteristics

| Author (year)       | Study design | N (male: female) | CHD diagnosis | Gestational age at birth (weeks) | Age at surgery (days) | Age at preoperative MRI (days) | Age at postoperative MRI |
|---------------------|--------------|------------------|---------------|---------------------------------|-----------------------|-------------------------------|--------------------------|
| McConnel (1990) USA | Cohort (pro) | 28 (15: NR)      | CHD           | NR                              | NR                    | NR                            | NR                       |
| Mahle (2002) USA    | Cohort (pro) | 24 (16:8)        | CHD           | NR                              | NR                    | NR                            | NR                       |
| Partridge (2006) USA| Cohort (pro) | 25 (16:9)        | CHD           | NR                              | NR                    | NR                            | NR                       |
| Dent (2006) USA     | Cohort (pro) | 22 (15:7)        | CHD           | 39 (36–41)                      | 4 (1, 8)              | Operation day 4 (1, 8)         | 9.5 (5–14) days          |
| McQuillen (2007) USA| Cohort (pro) | 62 (NR)          | CHD           | NR                              | NR                    | NR                            | NR                       |
| Miller (2007) USA   | Case-control (pro) | 41 (29:12) | CHD           | 39.1 (38.2–40.0)                | NR                    | 5 (3–6)                       | NR                       |
| Block (2010) USA    | Cohort (pro) | 92 (59:33)       | CHD           | NR                              | NR                    | NR                            | NR                       |
| Kwak (2010) Korea   | Cohort (pro) | 11 (10:1)        | CHD           | NR                              | NR                    | 11 (5, 46)                    | NR                       |
| Beca (2013) New Zealand | Cohort (pro) | 153 (98:55)     | CHD           | 38.8±1.6                        | 7 (4–11)             | NR                            | NR                       |
| Drury (2013) New Zealand | Cohort (pro) | 18 (11:7)       | CHD           | NR                              | NR                    | NR                            | NR                       |
| Mulkey (2013) USA   | Cohort (pro) | 73 (46:27)       | CHD           | NR                              | NR                    | NR                            | 46±11                    |
| Algra (2014) The Netherlands | RCT | 37 (30:7) | CHD           | NR                              | NR                    | NR                            | NR                       |
| Andropoulos (2014) USA | Cohort (retro) | 59 (34:25) | CHD           | 38.4±1.2                        | NR                    | NR                            | NR                       |
| Bertholdt (2016) Switzerland | Case-control (pro) | 30 (22:8) | CHD           | 39.3 (36.7–41.9)               | NR                    | 6 (1, 12)                     | 13 (6–30)                |
| Lynch (2014) USA    | Cohort (pro) | 37 (18: 19)      | CHD           | 38.9±0.8                        | 4.2±1.9              | NR                            | 1 week after surgery     |
| Claessens (2018) The Netherlands | Cohort (pro) | 40 (27:13) | CHD           | NR                              | NR                    | 9 (7–10)                      | NR                       |
| Peyvandi (2018) USA  | Cohort (pro) | 79 (55:24)       | CHD           | NR                              | NR                    | 5 (3–7)                       | 8 (7–10)                 |
| Claessens (2019) The Netherlands | Cohort (pro) | 74 (49:25) | CHD           | 39.5 (38.7–40.6)               | NR                    | NR                            | NR                       |

Continued
Quantitative brain lesion scores

Four studies adopted an MRI brain lesion scoring system to quantify both the location and severity of findings. \(^9\) \(^13\) \(^22\) \(^26\) 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 months\(^27\) 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 tool\(^21\) 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 72–13 days, providing 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

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 CSVIT\(^17\) \(^22\) \(^23\) 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 acquire new lesions; 32% (48/149) of paediatric patients with pre-existing lesions had additional new brain MRI findings following surgery.

Risk factors related to presurgery and new postsurgery MRI brain findings were reported in 11 studies.\(^12\) \(^14\)–\(^18\) \(^21\)–\(^23\)
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 25% of patients postoperatively. Haemorrhage and CSVT were investigated less frequently among studies. Maturational changes in the brain, clinical significance is unclear. As many MRI findings represent minor lesions, which can resolve with time, or be mitigated through neuronal plasticity and adaptions 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 2  Summary of MRI protocols adopted by the included studies

| MRI protocol | Outcome of interest | Studies |
|--------------|---------------------|---------|
| GE           | McConnell, Partridge, Dent, McQuillen, Block, Mulkey, Berthold, Peyvandi, Guo |
| Philips      | Mulkey, Algra, Andropoulos, Claessens, Claessens, Claessens |
| Siemens      | Mahle, Block, Beca, Drury, Lynch, Lim, Guo |
| Not reported  | Miller, Kwak |
| Field strength | 1.5 T | McConnell, Mahle, Partridge, Dent, McQuillen, Block, Beca, Drury, Mulkey, Algra, Andropoulos, Lynch, Claessens, Peyvandi, Claessens, Lim, Guo |
| 3 T          | Beca, Berthold, Claessens, Peyvandi, Claessens, Claessens, Guo |
| Not reported  | Miller, Kwak |
| Immobilisation | General anaesthetic | Mahle, Dent, Andropoulos, Lynch |
| Sedation     | Block, Berthold, Claessens, Peyvandi, Claessens |
| Feed and sleep | Block, Berthold, Claessens, Peyvandi, Claessens, Lim |
| Not reported  | Miller, Partridge, McQuillen, Miller, Kwak, Beca, Drury, Mulkey, Algra, Guo |
| Image review | Single blinded observer (O), radiologist (R) or neuroradiologist (N) | McConnell, Mahle, Partridge, Dent, McQuillen, Miller, Block, Kwak, Drury, Andropoulos, Peyvandi, Claessens |
| Not reported  | |
| T1 weighted  | Structural imaging (suppresses water and high signal intensity of fat) | McConnell, Mahle, Partridge, Dent, McQuillen, Block, Beca, Drury, Mulkey, Algra, Andropoulos, Berthold, Lynch, Claessens, Peyvandi, Claessens, Lim, Guo |
| T2 weighted  | Detect pathology associated with oedema/fluid (high signal intensity of water) | McConnell, Mahle, Partridge, Dent, McQuillen, Block, Beca, Drury, Mulkey, Algra, Andropoulos, Berthold, Lynch, Claessens, Peyvandi, Claessens, Lim |
| DWI and DTI  | Acute cerebral infarct and haemorrhage (Brownian motion of water molecules) | Mahle, Dent, Beca, Drury, Mulkey, Andropoulos, Berthold, Lynch, Claessens, Peyvandi, Claessens, Lim |
| FLAIR        | High signal for lacunar Infarcts and subarachnoid haemorrhage. | Beca, Drury, Mulkey, Algra |
| SWI          | Detects microhaemorrhages and calcium | Beca, Mulkey, Andropoulos, Lynch, Claessens, Claessens, Claessens, Lim |
| Proton density | Evaluates grey/white matter abnormalities (grey matter has a higher signal intensity than the white matter) | McConnell |
| MP-RAGE      | Useful for brain tissue classification by offering excellent contrast for brain cortical segmentation | Lynch |
| MR-venography | Examines the veins without the overlying tissues being visible (requires contrast material to enhance the visibility of the veins). | Claessens |
| DWI, diffusion-weighted imaging. | | |
Table 3  Number of patients with preoperative and postoperative brain MRI findings

| Study          | MRI scans Pre | MRI scans Post | MRI scans Paired | WMI Pre | Infarct Pre | Haemorrhage Pre | CSVT Pre | Total Pre | WMI Post | Infarct Post | Haemorrhage Post | CSVT Post | Total Post | With preop findings |
|----------------|---------------|---------------|------------------|---------|-------------|-----------------|----------|-----------|----------|-------------|-------------------|----------|-----------|-------------------|
| McConnel et al | 15            | 15            | 15               | NR      | 1           | NR              | NR       | 1         | NR       | 1           | NR                | NR       | 1         | NR                |
| Mahenteal      | 24            | 21            | 21               | 4       | 2           | 1               | NR       | 7         | 9        | 4           | 7                 | NR       | 20        | 3/12              |
| Partridge et al| 25            | 25            | 25               | 4       | 3           | 2               | NR       | 7         | 5        | 1           | NR                | NR       | 6         | 2/7               |
| Dent et al     | 22            | 15            | 15               | 1       | 4           | 2               | NR       | 7         | 7        | 8           | 1                 | NR       | 11        | NR                |
| McQuillen et al| 62            | 53            | 53               | 11      | 13          | 5               | NR       | 29        | 14       | 5           | NR                | NR       | 19        | 3/29              |
| Miller et al   | 41            | 36            | 36               | 4       | 10          | 2               | NR       | 14        | 9        | 3           | 0                 | NR       | 11        | NR                |
| Block et al    | 92            | 78            | 78               | 21      | 23          | 7               | NR       | 40        | 24       | 8           | 1                 | NR       | 32        | 13/33             |
| Knorre et al   | 11            | 11            | 11               | NR      | NR          | NR              | NR       | NR        | NR       | NR          | NR                | NR       | NR        | NR                |
| Bocca et al    | 153           | 125           | 135              | 30      | 7           | 6               | NR       | 38        | 57       | 5           | 3                 | NR       | 59        | 3/21              |
| Dreyer et al   | 18            | 18            | 18               | 5       | NR          | NR              | NR       | 5         | NR       | NR          | NR                | NR       | 5         | NR                |
| Mulkey et al   | 73            | 38            | 38               | NR      | NR          | NR              | NR       | 34        | (16 type is NS) | NR        | NR        | 5                 | NR       | 28        | (23 type is NS)   |
| Alper et al    | 37            | 36            | 36               | 18      | 3           | 5               | NR       | 29        | 22       | 9           | 2                 | 38       | 71        | NR                |
| Andriopoulos et al, USA | 59    | 59            | 59               | 12      | 9           | 4               | NR       | 18        | 14       | 10          | 10                | NR       | 28        | NR                |
| Backholder et al, Switzerland | 30 | 30            | 30               | 6       | 3           | NR              | NR       | 7         | 2        | NR          | NR                | NR       | 2         | NR                |
| Lynder et al   | 37            | 33            | 33               | 8       | NR          | NR              | NR       | 8         | 16       | NR          | NR                | NR       | 16        | NR                |
| Claessen et al | 40            | 40            | 40               | NR      | NR          | NR              | NR       | 3         | 30        | 26       | 8           | NR                | 11        | 45        | 3/3               |
| Peyvandi et al | 79            | 73            | 73               | 16      | 18          | NR              | NR       | 34        | 22       | 8           | NR                | NR       | 30        | NR                |
| Claessen et al | 56            | 71            | 53               | 12      | 5           | NR              | NR       | 17        | 25       | 15          | NR                | NR       | 40        | NR                |
| Claessen et al | 100           | 120           | 100              | 16      | 48          | 8               | 57       | 100       | 37       | 74          | 21                | 12        | 124       | NR                |
| Lim et al      | 45            | 45            | 45               | 14      | 4           | 1               | NR       | 19        | NR       | 1           | NR                | NR       | 1         | NR                |
| Guo et al      | 186           | 172           | 161              | 23      | NR          | NR              | NR       | 23        | 7         | NR          | NR                | NR       | 2         | NR                |
| Total          | 1205          | 1124          | 1075             | 205     | 153         | 58              | 63       | 442       | 301      | 161         | 50                | 28       | 519       | 48/140             |

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, 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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