*Cardiology in the Young*

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# Prospective evaluation of acute neurological events after paediatric cardiac surgery

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## Original Article

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## Abstract

*Objectives:* Children with CHD are at heightened risk of neurodevelopmental problems; however, the contribution of acute neurological events specifically linked to the perioperative period is unclear. *Aims:* This secondary analysis aimed to quantify the incidence of acute neurological events in a UK paediatric cardiac surgery population, identify risk factors, and assess how acute neurological events impacted the early post-operative pathway. *Methods:* Post-operative data were collected prospectively on 3090 consecutive cardiac surgeries between October 2015 and June 2017 in 5 centres. The primary outcome of analysis was acute neurological event, with secondary outcomes of 6-month survival and post-operative length of stay. Patient and procedure-related variables were described, and risk factors were statistically explored with logistic regression. *Results:* Incidence of acute neurological events after paediatric cardiac surgery in our population occurred in 66 of 3090 (2.1%) consecutive cardiac operations. 52 events occurred with other morbidities including renal failure (21), re-operation (20), cardiac arrest (20), and extracorporeal life support (18). Independent risk factors for occurrence of acute neurological events were CHD complexity 1.9 (1.1–3.2), $p = 0.025$, longer operation times 2.7 (1.6–4.8), $p < 0.0001$, and urgent surgery 3.4 (1.8–6.3), $p < 0.0001$. Unadjusted comparison found that acute neurological event was linked to prolonged post-operative hospital stay (median 35 versus 9 days) and poorer 6-month survival (OR 13.0, 95% CI 7.2–23.8). *Conclusion:* Ascertainment of acute neurological events relates to local measurement policies and was rare in our population. The occurrence of acute neurological events remains a suitable post-operative metric to follow for quality assurance purposes.

Given that survival rates following even complex paediatric cardiac surgery are excellent, there is greater focus on the optimisation of longer-term functional outcomes. Children with CHD who undergo cardiac surgery face an elevated risk of neurological injury and developmental delays for a wide range of reasons, and it is challenging to delineate these complex and often inter-related factors as separate entities.[1] Aetiological mechanisms include genetics,[2] abnormalities of brain perfusion before birth,[3,4] brain immaturity,[5,6] low oxygen levels, poor condition after birth,[7] complex heart conditions,[8] a difficult post-operative course after cardiac surgery,[9,10] and socio-economic factors.[11] Then in many previous studies, a down-stream neurodevelopmental outcome may be attributed to a range of these different and inter-related factors.[12–14]

We previously undertook a prospective multi-centre study in five of the ten paediatric cardiac centres in the UK, in which we monitored children after 3090 consecutive cardiac surgeries[15] and diagnosed post-operative morbidities based on defined criteria.[16] We used the term morbidity to characterise these post-operative clinical conditions, which were extracorporeal life support, acute neurological event, unplanned re-intervention, feeding problems, major adverse event, prolonged pleural effusion, post-surgical infection morbidity, renal support, and necrotising enterocolitis, because we recognise that although they may be referred to as complications, the causal pathway involves a combination of pre-, intra-, and post-operative variables. A clinically important morbidity (or complication), that is potentially linked to elevated rates of neurodevelopmental delay amongst paediatric cardiac surgery patients, is acute neurological event, when a newly acquired brain injury is identified after surgery. Our wider research study, which involved a prospective monitoring process and data collection, enabled us to undertake this separate sub-study to focus specifically on the diagnosis and characterisation of acute neurological events that came to light in the immediate post-operative period, within the post-operative hospitalisation. In this sub-study, we aimed to describe the incidence of acute neurological event in the complex setting of paediatric cardiac surgery, to describe the association of acute neurological event with other important post-operative morbidities (or complications), and to explore clinical risk factors linked with the study outcome of acute neurological event.

## Methods

### Design

This is a secondary analysis of a prospectively collected dataset pertaining to a United Kingdom cohort of children who underwent paediatric cardiac surgery.[17]

### Data collection

As described previously,[15] patients were monitored prospectively following cardiac procedures for the occurrence of defined nine morbidities (or complications)[16] each of which was assigned to an index preceding cardiac procedure. These were extracorporeal life support, acute neurological event, unplanned re-intervention, feeding problems, major adverse event, prolonged pleural effusion, post-surgical infection morbidity, renal support, and necrotising enterocolitis (See Supplementary Materials Table A). Each of these complications was prospectively diagnosed in the same hospitalisation, excluding unplanned re-operation which was identified within one month and mediastinitis which was diagnosed as linked to the preceding surgery by the operating surgeon. The ascertainment of each complication was undertaken locally, and discrepancies or complex cases were discussed in monthly team meetings involving study team members from all centres, with decisions being made by consensus.

### Patient population

All children aged 17 years and below who underwent open, closed, and hybrid cardiac surgery across 5 United Kingdom centres between 01/10/2015 – 30/06/2017 were included. Exclusions were premature babies undergoing patent ductus arteriosus ligation and children having cardiothoracic transplants/tracheal procedures. Participating centres were Great Ormond Street Hospital for Children, Evelina London Children's Hospital, Birmingham Children's Hospital, Bristol Royal Children's Hospital, and the Royal Hospital for Children in Glasgow.

### Outcome

#### Primary outcome

The primary outcome of this study was the complication of acute neurological event occurring as a new finding post-operation within the same hospitalisation as cardiac surgery, defined as[17] "any occurrence of the following: seizures, focal neurological deficit, intracranial haemorrhage, stroke, brain death, hypoxic ischaemic encephalopathy, spinal cord ischaemia, basal ganglia damage, or brainstem injury."

The acute neurological events were identified by prospective evaluation and clinical scrutiny daily per the study protocol by a dedicated research nurse and clinician for the study. However, the measurement methods were intended for future routine use, and therefore, investigation with electroencephalogram and cross-sectional imaging was only undertaken when there were clinical concerns for an acute neurological event. Children considered to be at high risk of acute neurological event based on clinical history and or emerging clinical signs such as focal neurological signs, altered consciousness not explained by therapies including brain death, seizures, and abnormal movement disorders underwent brain scan (CT or MRI) and electroencephalogram as per usual clinical care. It was recognised that when patients were extremely ill and on life support and sedative medications prior to surgery, exclusion of pre-operative neurological injury is challenging; however, patients who were deemed at risk of this were assessed prior to surgery following local protocols. All detected acute pre-operative neurological injuries and long-standing neurological comorbidities were captured in the study dataset.

#### Secondary outcomes

Secondary outcomes of the study were length of hospital stay and 6-month survival rates.

### Case-mix variables

The candidate variables collected on our study cohort were sex, age band (neonate, infant, child), patient weight, cardiac diagnosis, functionally univentricular heart (yes/no), specific procedure type category, operation type (bypass, non-bypass or hybrid), bypass time, urgency of operation, acquired comorbidity, congenital comorbidity excluding Down syndrome, Down syndrome, additional cardiac risk factors, prematurity, and a pre-operative requirement for critical care supports (severity of illness indicator). For the variables of cardiac diagnosis and cardiac surgical procedure, we noted that there were many variables leading to some categories being sparsely populated. Therefore, these two variable groups were collapsed further to help with clinical interpretation (See Supplementary Table B).[15] All risk variables and sub-categorisations were selected with reference to empiric data on risk of early mortality.[18–22]

### Descriptive analysis

We describe the criteria by which acute neurological event was first diagnosed, and we describe the associations between acute neurological events and other complications such as need for extracorporeal life support. We describe the study population by the stated case-mix variables by presence of acute neurological event.

### Risk factor selection for statistical analysis

We considered the number of acute neurological events, which was 66 out of the population of 3090, and as such we planned to analyse risk variables involving 7-10 degrees of freedom.[23] We considered related literature on risks for neurodevelopmental problems in paediatric cardiac surgery[1–9] as well as the clinical importance of both patient-related and procedure-related factors before selecting risk variables as predictors. We used the following risk variables in our statistical analyses: CHD complexity based on category A-C (more complex diagnoses) versus D–E[15] (less complex diagnoses), neonatal age versus non-neonatal age, critical illness at the time of surgery based on presence or not of a severity of illness factor (ventilation, inotropes or mechanical support),[24] no or short bypass versus bypass time > 90 minutes, and elective surgery versus all types of urgent surgery (urgent, emergency or salvage operations).[24]

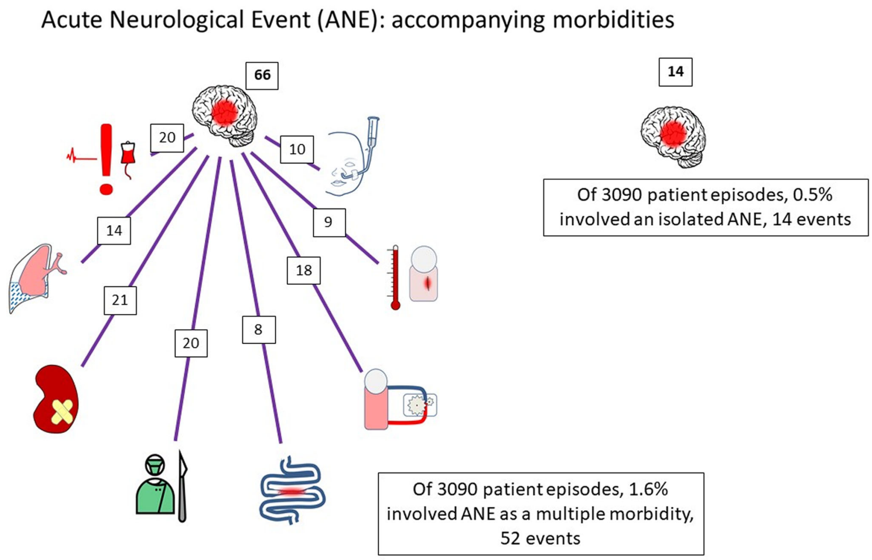


**Figure 1.** There were only 14 of 66 (0.5%) ANE that occurred as an isolated morbidity and 52 (1.6%) occurred as part of a multiple morbidity. The figure shows the co-occurrence of ANE with ECLS in 18, major adverse event in 20, feeding problems in 10, necrotising enterocolitis in 8, renal support in 21, prolonged pleural effusion in 14, surgical site infection in 9, and unplanned re-operation in 20.

### *Primary outcomes*

The distribution of each risk variable was evaluated with a Chi-squared analysis. Analysis of risk variables was carried out at procedure level for the complication of acute neurological event (yes or no). Both, a univariate and a multivariable logistic regression, were used to analyse the relationship of prespecified risk variables to acute neurological event.

### *Secondary outcomes*

We undertook univariate comparisons of the secondary outcomes by presence of acute neurological event. Length of hospital stay was analysed as a median with a Kruskal-Wallis statistic. Six-month mortality was assessed at patient level with univariate odds ratio.

Analysis was carried out using Stata.v.16.

## Results

### *The study population*

In total, 3090 index cardiac procedures met the inclusion criteria. We noted and excluded 10 misclassified procedures, 63 planned procedures occurring within one month and 143 unplanned reoperations within one month as reported previously.[15,25] The 3090 included procedures included 2861 patients, with 2648 undergoing one procedure, 197 undergoing 2 and 16 having 3 procedures. The median age at procedure was 228 days with an interquartile range of patients in the study of 77–1390 days, and 1671 (54.1%) of the patients were male. The incidence of complications was 675 (21.8%) of which 197 (6.4%) were multiple complications. Acute neurological event was the rarest complication, with total incidence 66 (2.1%). The other complications had overall rates as follows (any occurrence): pleural effusion (6.5%), feeding problems (6.0%), unplanned re-intervention (5.2%), renal support (4.6%), major adverse event (4.3%), post-surgical infection (2.8%), and necrotising enterocolitis (2.4%).

### *Missing data*

Nine patients discharged from hospital alive lacked 30-day life status information, and a further seven patients had missing 6-month life status information. Seven patients had missing length of hospital stay data. Four patients had missing surgery urgency data, and nine patients had missing weight information. All other variables were complete.

### *Criteria by which acute neurological event was initially diagnosed*

There were missing acute neurological event details in four patients. The criteria by which acute neurological event was diagnosed were clinical features in 26/62 including seizures and abnormal movements in 14/62, abnormal electroencephalogram in 23/62, abnormal CT scan in 29/62, abnormal MRI in 24/62. In addition to this, 26 were treated with anticonvulsants. None of the patients in our study met the criteria for brain death. Of the 66 children with acute neurological event, 18 patients had 1 of these features, 19 had 2, 18 had 3, 2 had 4, 3 had 5, and 2 had 6. Of note, cranial ultrasound findings were not in our dataset, although this modality is widely used in the UK.

### *Association of acute neurological event with other morbidities*

There were only 14 (0.5%) acute neurological events that occurred as an isolated complication (Fig. 1) and 52 (1.6%) occurred with multiple complications (18 patients had two, 13 had three, 11 had 4, 7 had 5 and 3 had 6 complications).

### *Acute neurological event patient features*

The features of patients by presence of acute neurological events are shown in Table 1, and here we focus on the most obvious differences between the two groups. Acute neurological event patients were younger than non-event patients with many more in the neonatal age category (39% versus 16.3%, $p < 0.001$). Congenital heart conditions were more complex in acute neurological event patients, with a higher proportion having the most severe diagnosis category A (16.7% versus 8.8%, $p < 0.001$). Acute neurological event patients were more likely to be critically ill prior to surgery: 18 (27.3%) versus 356 (11.8%) of the non-event patients ($p < 0.001$). Longer cardiopulmonary bypass times were seen in patients who developed acute neurological events with

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**Table 1.** Demographic, diagnostic, and surgical variables related to case mix by occurrence of acute neurological event.

| Demographic and diagnostic factors ascertained at the time of surgery | Acute neurological event N = 66 | No acute neurological event N = 3024 | Chi-squared value $X^2$ (p-value) |
|---|---|---|---|
| Male | 38 (57.5%) | 1633 (54.0%) | 0.3 (p = 0.56) |
| Female | 28 (42.4%) | 1391 (46.0%) | |
| **Antenatal diagnosis** | | | |
| Yes | 34 (51.5%) | 1217 (40.2%) | 3.4 (p = 0.18) |
| No | 31 (47.0%) | 1749 (57.8%) | |
| Unknown | 1 (1.5%) | 57 (1.9%) | |
| **Congenital abnormality non-Downs** | | | |
| Yes | 21 (31.8%) | 695 (23.0%) | 2.8 (p = 0.09) |
| No | 45 (68.2%) | 2329 (77.0%) | |
| **Acquired comorbidity** | | | |
| Yes | 13 (19.7%) | 443 (14.6%) | 1.3 (p = 0.25) |
| No | 53 (80.3%) | 2581 (85.4%) | |
| **Down's Syndrome** | | | |
| Yes | 4 (6.1%) | 273 (9.0%) | 0.7 (p = 0.40) |
| No | 62 (93.9%) | 2751 (91.0%) | |
| **Congenital heart diagnosis category** | | | |
| A (most complex) | 11 (16.7%) | 266 (8.8%) | 33.6 (p < 0.0001) |
| B | 9 (13.6%) | 332 (11.0%) | |
| C | 17 (25.8%) | 308 (10.2%) | |
| D | 23 (34.8%) | 1000 (33.0%) | |
| E (least complex) | 6 (9.1%) | 1118 (37.0%) | |
| **Premature** | | | |
| Yes | 11 (16.7%) | 293 (9.7%) | 3.6 (p = 0.06) |
| No | 55 (83.3%) | 2731 (90.3%) | |
| **Weight (<2.5 Kg)** | | | |
| Low weight | 22 (33.3%) | 1026 (34.0%) | 0.01 (p = 0.91) |
| Normal weight | 44 (66.6%) | 1989 (66.0%) | |
| **Age category** | | | |
| Neonate | 26 (39.4%) | 493 (16.3%) | 29.1 (p < 0.0001) |
| Infant | 28 (42.4%) | 1272 (42.1%) | |
| Child | 12 (18.2%) | 1259 (41.6%) | |
| **Top rank congenital heart diagnosis category** | | | |
| 1: Hypoplastic left heart syndrome | 9 (13.6%) | 188 (6.2%) | |
| 2: Functionally univentricular heart | 5 (7.6%) | 182 (6.0%) | |
| 3: Common arterial trunk | 0 (0.0%) | 55 (1.8%) | |
| 4: Complex transposition of the great arteries | 13 (19.7%) | 179 (5.9%) | |
| 5: Interrupted aortic arch | 1 (1.5%) | 43 (1.4%) | |
| 6: Transposition of the great arteries | 1 (1.5%) | 44 (1.5%) | |
| 7: Pulmonary atresia | 6 (9%) | 173 (5.8%) | |
| 9: Miscellaneous primary congenital diagnosis | 11 (16.7%) | 275 (9.1%) | |
| 10: Atrioventricular septal defect | 4 (6.0%) | 290 (9.6%) | |
| 11: Tetralogy of Fallot | 7 (10.6%) | 304 (10.0%) | |

(*Continued*)

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**Table 1.** (*Continued*)

| Demographic and diagnostic factors ascertained at the time of surgery | Acute neurological event N = 66 | No acute neurological event N = 3024 | Chi-squared value $X^2$ (p-value) |
|---|---|---|---|
| 12: Aortic valve stenosis (isolated) | 2 (3.0%) | 141 (4.7%) | |
| 13: Tricuspid valve including Ebstein's anomaly | 1 (1.5%) | 63 (2.1%) | |
| 14: Mitral valve abnormality | 1 (1.5%) | 79 (2.6%) | |
| 15: Total anomalous pulmonary venous connection | 2 (3.0%) | 42 (1.4%) | |
| 16: Aortic arch obstruction +/− septal defect | 3 (4.5%) | 201 (6.6%) | |
| 17: Pulmonary stenosis | 0 (0.0%) | 60 (2.0%) | |
| 18: Subaortic stenosis (isolated) | 0 (0.0%) | 28 (0.9%) | |
| 19: Aortic regurgitation | 0 (0.0%) | 32 (1.1%) | |
| 20: Ventricular septal defects | 0 (0.0%) | 335 (11.1%) | |
| 21: Atrial septal defects | 0 (0.0%) | 185 (6.1%) | |
| 22: Patent ductus arteriosus | 0 (0.0%) | 36 (1.2%) | |
| 23: Other (Acquired, arrhythmia, miscellaneous congenital terms and comorbidities) | 0 (0.0%) | 89 (3.0%) | |
| **Univentricular status** | | | |
| Univentricular | 14 (21.2%) | 400 (13.2%) | 3.6 (p = 0.06) |
| Non-univentricular | 52 (78.8%) | 2624 (86.8%) | |
| **Patient condition at surgery/surgical factors** | | | |
| **Additional cardiac risk factor** | | | |
| Yes | 7 (10.6%) | 223 (7.4%) | 1.0 (p = 0.32) |
| No | 59 (89.4%) | 2801 (92.6%) | |
| **Severity of illness** | | | |
| Yes | 18 (27.3%) | 356 (11.8%) | 14.6 (p < 0.0001) |
| No | 48 (72.7%) | 2668 (88.2%) | |
| **Procedure category** | | | |
| Palliative/Staged | 17 (25.8%) | 493 (16.3%) | 4.2 (p = 0.12) |
| Reparative/Corrective | 32 (48.5%) | 1693 (56.0%) | |
| Ambiguous | 17 (25.8%) | 838 (7.7%) | |
| **No bypass** | | | |
| **Bypass time** | 7 (10.6%) | 486 (16.1%) | 24.0 (p < 0.0001) |
| up to 90 minutes | 12 (18.2%) | 1286 (42.5%) | |
| Bypass time 90 minutes or over | 47 (71.2%) | 1252 (41.4%) | |
| **Pre-operative ANE** | | | |
| Yes | 1 (1.5%) | 10 (0.3%) | 2.6 (p = 0.11) |
| No | 65 (98.5%) | 3014 (99.7%) | |
| **Urgency of surgery** | | | |
| Elective | 21 (31.8%) | 2046 (67.7%) | 53.6 (p < 0.0001) |
| Urgent | 37 (56.1%) | 897 (29.7%) | |
| Emergency and Salvage | 8 (12.1%) | 77 (2.6%) | |

Missing weight information for nine non-acute neurological event patients (N = 3015), missing urgency information for four non-acute neurological events patients (N = 3020).

71.1% having bypass > 90 minutes versus only 41.4% in those without acute neurological events. Of acute neurological event patients, 21 (31.8%) had elective procedures, 37 (56.1%) urgent, 8 (12.1%) emergency or salvage whereas non-event patients were more likely to be elective 2046 (67.7%) with only 897 (29.7%) urgent and 77 (2.6%) emergency or salvage procedures ($p < 0.001$).

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**Table 2.** Univariate and multivariable risk factor analysis in relation to the occurrence of acute neurological event.

| Risk factor analysis | Acute neurological event N = 66 | No acute neurological event N = 3024 | Univariate odds ratio (95% confidence interval), p-value | Multivariable odds ratio (95% confidence interval), p-value |
|---|---|---|---|---|
| **Diagnosis category** | | | | |
| A-C (more complex) | 37 (56.1%) | 906 (30.0%) | 3.0 (1.8–4.9), p < 0.0001 | 1.9 (1.1–3.2), p = 0.025 |
| D-E (less complex) (ref) | 29 (43.9%) | 2118 (70.0%) | | |
| **Severity of illness indicator** | | | | |
| Yes | 18 (27.3%) | 356 (11.8%) | 2.8 (1.6–4.9), p < 0.0001 | 1.4 (0.7–2.5), p = 0.315 |
| No (ref) | 48 (72.7%) | 2668 (88.2%) | | |
| **Cardiopulmonary bypass time** | | | | |
| Over 90 minutes | 47 (71.2%) | 1252 (41.4%) | 3.5 (2.0–6.0), p < 0.0001 | 2.7 (1.6–4.8), p < 0.0001 |
| None/under 90 minutes (ref) | 19 (28.8%) | 1772 (58.6%) | | |
| **Age category** | | | | |
| Neonate | 26 (39.4%) | 502 (16.6%) | 3.3 (2.0–5.4), p < 0.0001 | 1.0 (CI 0.5–1.8), p = 0.963 |
| Not neonate **(ref)** | 40 (60.6%) | 2522 (83.4%) | | |
| **Urgency** | | | | |
| Non-elective | 45 (68.2%) | 974 (32.3%) | 4.5 (2.7–7.6), p < 0.0001 | 3.4 (1.8–6.3), p < 0.0001 |
| Elective (ref) | 21 (31.8%) | 2046 (67.7%) | | |

Missing urgency information for four non-acute neurological event patients (N = 3020).

### *Risk factor analysis*

#### *Univariate analysis*

All of our selected risk variables were associated with the complication outcome of acute neurological event on univariate analysis (See Table 2). Neonatal age increased the risk of acute neurological event compared to older ages, with OR 3.3 (95% CI 2.0–5.4) $p < 0.0001$. The more complex CHD categories of A to C were linked to higher risk of acute neurological event compared to the less complex CHD categories (D and E), with OR 3.0 (95% CI 1.8–4.9) $p < 0.0001$. Critical illness at the time of surgery (compared to none) was associated with an increased risk of acute neurological event with OR 2.8 (95% CI 1.6–4.9) $p < 0.0001$. A cardiopulmonary bypass time over 90 minutes compared to shorter or no bypass was linked to increased risk of acute neurological event, with OR 3.5 (95% CI 2.0–6.0) $p < 0.0001$ and having urgent / non-elective surgery also increased risk of acute neurological event compared with elective surgery OR 4.5 (95% CI 2.7–7.6) $p < 0.0001$.

#### *Multiple risk factor analysis*

Upon multivariable analysis (See Table 2), after adjustment for other variables, neonatal (compared to older) age (OR 1.0, 95% CI 0.5–1.8, $p = 0.963$) and critical illness at surgery (OR 1.4, 95% CI 0.7–2.5, $p = 0.315$) became less important with statistically insignificant results. However, adjusted for other variables in the model, urgent compared to elective surgery (OR 3.4, 95% CI 1.8–6.3, $p < 0.0001$) and bypass over 90 minutes compared to shorter or no bypass (OR 2.7, 95% CI 1.6–4.8, $p < 0.0001$) remained very strongly linked to the risk of acute neurological event, and the more complex CHD categories of A-C remained at somewhat higher risk of acute neurological event than less complex conditions (OR 1.9, 95% CI 1.1–3.2, $p = 0.025$)

### *Secondary outcomes*

Acute neurological event patients had significantly poorer 6-month survival than non-event patients (74.2% versus 97.4%), which equates to an unadjusted odds ratio of 13.0, (95% CI 7.2–23.8, $p < 0.001$) for acute neurological event. The length of stay for acute neurological event patients was significantly higher than non-event patients (median 35 [IQR 19,44]) days versus 9 (IQR [6,18] days) ($p < 0.001$).

## Discussion

### *Summary of findings*

We used a prospectively collected multi-centre dataset related to 3090 consecutive cardiac operations, and found 66 acute neurological events, providing an incidence rate of 2.1%. Only 14 acute neurological events were isolated post-operative complications, whereas the majority, 52, occurred alongside other types of complication, indicating a very challenging post-operative course. We found that children with acute neurological events were initially detected based on a range of methods (brain scan, electroencephalogram, and clinical assessment), often involving more than one of these at the point of diagnosis. This reflects the complex nature of acute neurological events, which may be clinically challenging to identify in critically ill children, requiring a range of diagnostic tools. Consideration of case complexity for interpretation of our findings was limited given the need to collapse variables (e.g. congenital heart diagnosis), into very broad categories because of small numbers of acute neurological event. Nonetheless, we were interested to note that the most important variables in our multiple risk factor analysis were surgical factors of longer cardiopulmonary bypass time and urgency of the operation. Given our study focuses on the prospective evaluation of post-operative acute neurological event, the specific flagging up of surgical risk factors as most important has face validity. Our study supports the inclusion of acute neurological event as a post-operative metric for paediatric cardiac surgery.

### Results in context

There are relatively few studies that specifically explore post-operative acute neurological event as an entity, in part because there are so many other factors implicated in determining neurodevelopmental outcome for children with CHD.[1,13,14,26,27] In animal cardiopulmonary bypass models, brain injury was demonstrated with cardiopulmonary bypass-associated hypoxic/ischemic effects on oligodendrocyte precursor cells, and these impacts were worsened by preceding hypoxaemia as compared to normal oxygen levels.[28,29] These observations are in line with our observational findings in children after paediatric cardiac surgery given the strongest risk factors that we found were urgent heart surgery/longer bypass times. Furthermore, the findings of the Boston Circulatory Arrest Trial demonstrated that prolonged cardiopulmonary bypass times are linked to increased incidence of seizures and additional abnormalities in motor and speech function, as well as cognitive abilities supporting our findings and potentially indicating future sequelae of our patient group.[30–35] In addition to the length of bypass time, the optimal bypass strategy in this patient group is an area of interest when considering measures to reduce post-operative complications. Tadphale et al, identified reduced rates of acute kidney injury with a higher cardiopulmonary bypass flow rate, higher haematocrit target on bypass, higher terminal haematocrit and no reduction in flow rate during hypothermia.[36] A further study explored the relationship between this bypass strategy and neurological events, but did not find a link perhaps because of the low event rate (0.8%).[37]

The high proportion of children who had acute neurological events that also had other post-operative complications linked to low cardiac output syndrome (e.g. the need for extracorporeal life support and renal support, cardiac arrest, and necrotising enterocolitis) might imply that in some cases, low cardiac output syndrome could be on the causal pathway. This would be supported by data from the single ventricle reconstruction trial, which found that children who had low cardiac output syndrome associated events (extracorporeal life support and cardiac arrest) had worse neurodevelopmental outcomes after adjustment for other factors.[38] A single centre study that reported electroencephalography amongst children who had extracorporeal life support reported that seizures were more common with low cardiac output syndrome.[39] Low cardiac output syndrome is more likely with a poorer technical result from surgery and poorer technical results are also linked to worse neurodevelopmental outcome.[40,41] Our dataset also demonstrated a 0.45% incidence of post-operative seizures which may be a significant marker for future neurodevelopment of these patients due to established links with poorer developmental outcomes.[30–35,42–49] Strokes were observed in small proportion of our patients but is another key predictor of subsequent poor neurodevelopmental and reduced quality of life.[52–54]

### Limitations

Assessment of the brain amongst children requiring cardiac surgery is most challenging in the youngest and sickest children since over and above the inherent difficulties in assessing very young children, they may be sedated and ventilated. In the setting of an imminent urgent cardiac operation, patient evaluation can take advantage of cerebral imaging and electroencephalogram, but none of these modalities is perfect.[55] Whilst we prospectively focussed on these assessment challenges, both pre- and post-operative evaluations are not standardised in the UK, hence the assessment will have been imperfect and could have confounded both the pre- and the post-operative evaluation. All participating teams used a dedicated research nurse and physician to assess children prospectively based on the same definition of acute neurological event; however, there was no prospective screening with either electroencephalogram or cross-sectional imaging in all children, in line with routine practice in the UK.

The rarity of acute neurological events and the small number of events in our study mean that the case-mix variables we considered were very broad, which is a particular barrier when trying to understand the inter-relationship between case complexity, the duration of an operation and the occurrence of acute neurological event. We note that children with more complex heart disease require more complex operations, which may require longer periods of cardiopulmonary bypass, and amongst the surgeries that had higher rates of acute neurological event, operations required at neonatal ages dominated. Neonatal operations with an above average rate of acute neurological events in our cohort included: arterial switch 5/85 (6%), complex arterial switch 2/12 (15%), Norwood operation 5/73 (7%), systemic to pulmonary arterial shunt 4/50 (8%), repair of TAPVC 3/43 (7%), and these mixed age operations featured, Rastelli 1/10 (10%), repair of pulmonary atresia 1/18 (6%), repair of anomalous coronary artery from the pulmonary artery 2/14 (14%), and repair of Cor triatriatum 1/10 (10%). The link between acute neurological events and the secondary outcomes of mortality and length of stay will have been influenced by case mix and also by the co-occurrence of other morbidities in 52 of 66 children affected.

### Future directions

Our study supports the use of acute neurological event as a post-operative metric for paediatric cardiac surgery and we note that this metric is captured in the Society of Thoracic Surgery and the Paediatric Cardiac Critical Care Consortium (PC4). The definition and evaluation of patients for possible acute neurological events need to be carried out with utmost care and consistency. Additional monitoring methods such as routine use of electroencephalogram[56] might improve capture of events. Capture of in-hospital data on acute neurological events may contribute to wider efforts to study neurodevelopment in children with heart disease, including crucially, long-term clinical evaluation.

## Conclusions

The study of neurological function and detection of acute neurological event is extremely challenging in the context of paediatric cardiac surgery. Further work is required in order to ensure that this important metric is adequately captured. Prospective monitoring for acute neurological events will be helpful to future quality improvement initiatives in paediatric cardiac surgery.

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