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# Early identification of autism spectrum disorder in children with CHD attending a Cardiac Developmental Outcomes Program

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## Original Article

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## Abstract

*Objective:* To determine the prevalence and timing of autism spectrum disorder diagnosis in a cohort of congenital heart disease (CHD) patients receiving neurodevelopmental follow-up and identify associated risk factors. *Method:* Retrospective single-centre observational study of 361 children undergoing surgery for CHD during the first 6 months of life. Data abstracted included age at autism spectrum disorder diagnosis, child and maternal demographics, and medical history. *Results:* Autism spectrum disorder was present in 9.1% of children with CHD, with a median age at diagnosis of 34 months and 87.9% male. Prematurity, history of post-operative extracorporeal membrane oxygenation, and seizures were higher among those with autism ($p = 0.013$, $p = 0.023$, $p = 0.001$, respectively). Infants with autism spectrum disorder were older at the time of surgery (54 days vs 13.5 days, $p = 0.002$), and infants with surgery at ≥ 30 days of age had an increased risk of autism spectrum disorder (OR 2.31; 95% CI =1.12, 4.77, $p = 0.023$). On multivariate logistic regression analysis, being male (OR 4.85, $p = 0.005$), surgery ≥ 30 days (OR 2.46, $p = 0.025$), extracorporeal membrane oxygenation (OR 4.91, $p = 0.024$), and seizures (OR 4.32, $p = 0.003$) remained associated with increased odds for autism spectrum disorder. Maternal age, race, ethnicity, and surgical complexity were not associated. *Conclusions:* Children with CHD in our cohort had more than three times the risk of autism spectrum disorder and were diagnosed at a much earlier age compared to the general population. Several factors (male, surgery at ≥ 30 days, post-operative extracorporeal membrane oxygenation, and seizures) were associated with increased odds of autism. These findings support the importance of offering neurodevelopmental follow-up after cardiac surgery in infancy.

There are currently estimated to be more than 2 million children and adults living in the United States with congenital heart disease (CHD).[1,2] As a result of advances in diagnostic tools, surgical approaches, perioperative care, and longitudinal follow-up, survival after cardiac surgery has improved dramatically over the past few decades.[3] Alongside this increased survival, there is now a greater recognition that children with CHD are at significant risk of long-term neurodevelopmental impairment.[4] In addition to the well-described neurodevelopmental (cognitive, learning, and motor)[5] and neurobehavioral (anxiety, depression, attention-deficit/hyperactivity disorder)[6,7] impairments, there has been increasing concern regarding deficits in social cognition and symptoms of autism spectrum disorder in children with CHD.[8–11] Autism spectrum disorder is a neurodevelopmental disorder marked by deficits in social interaction and social communication, as well as the presence of restricted interests and/or repetitive behaviours.[12] Several factors have been associated with increased risk for autism spectrum disorder such as decreased gestational age, prematurity, and seizures.[13]

In the most recent report from the Centers for Disease Control and Prevention autism surveillance programme (Autism and Developmental Disabilities Monitoring Network), autism spectrum disorder prevalence was 17.0 per 1,000 (1 in 59, or 1.7%) for children 4 years of age and 23.0 per 1,000 (1 in 44 or 2.3%) for 8 years of age.[14,15] Recent research on children with CHD reveals that they are more likely to have a positive screening (3.2%), receive a diagnosis (2.6%), or be identified as 'at risk' (8.2%) for autism spectrum disorder than children without CHD.[10,16,17] Furthermore, larger studies using international diagnostic codes to define autism spectrum disorder diagnosis showed higher incidence rates of autism spectrum disorder in CHD patients than in a control (non-CHD, matched for age, sex, and enrolled time) group of patients in Taiwan (3%), while in the United States, a study showed that patients diagnosed with autism spectrum disorder had higher odds of having CHD compared to controls (matched for date of birth, sex, and time of enrolment in the health system – OR

1.85 95% 1.65–2.10 n = 1063).[18,19] Autism spectrum disorder can be reliably diagnosed as early as 18–24 months of age; however in the United States, autism spectrum disorder diagnosis generally tends to occur later and varies by site (e.g. between 36 m and 63 m depending on the geographic location), possibly due to the timing of routine screening.[12,14,20,21] Limited data in the CHD population have suggested a much later age at diagnosis of 60 months.[19] We hypothesised that children with CHD would be at risk of developmental delays including autism than children without CHD. The aim of our current study was to investigate the prevalence, age at diagnosis, and potential risk factors for autism spectrum disorder in a cohort of children who have undergone surgery for CHD at the same medical centre and are followed in a specialised multi-disciplinary cardiac developmental outcomes clinic.

## Materials and methods

### Patients

This was a retrospective, single-centre cohort study of patients born between January 1st 2013 and December 31st, 2016 who were followed at the Cardiac Developmental Outcomes Programme clinic. For purposes of this study, only clinic visits until July 2022 were included in the analysis. Given that part of the period of follow-up included the early phase of the COVID-19 pandemic, clinic visits were a combination of telemedicine and in-person. For those patients for which concerns for autism spectrum disorder were reported or observed during a telemedicine visit, an in-person assessment was offered. The study was approved (with a waiver of consent) by the Institutional Review Board. The Cardiac Developmental Outcomes Programme Clinic was established in 2013 and offers routine longitudinal neurodevelopmental assessments at 6, 12, 18, and 24 months of age and yearly thereafter for children (from infancy to adolescence) who underwent cardiac procedures during the first 6 months of life.[22] In addition, the clinic offers a routine follow-up to all infants and children with a history of extracorporeal membrane oxygenation or ventricular assist device (VAD) support; children undergoing transplant; and other children with CHD and developmental/learning/behavioural concerns. Before the patient is discharged from the hospital, the Cardiac Developmental Outcomes Programme clinic coordinator visits the patient, provides information to the parents about the programme, and offers to schedule the 6 months evaluation. Outpatient evaluations are completed by a team of dedicated developmental-behavioural paediatricians and a psychologist. Patient demographic, diagnostic, clinical data relating to the infant's hospitalisation, and the results of their neurodevelopmental assessments are all recorded in a dedicated Institutional Review Board-approved Cardiac Developmental Outcomes Programme clinical database. During the study period, there were 657 patients referred to the Cardiac Developmental Outcomes Programme clinic. Of those, 240 (37%) did not attend the programme and thus were not included in the study and 417 (63%) attended the programme. The main criteria for inclusion *in this study* were surgery during the first 6 months of life and at least one clinic assessment at 24 months of age or older. Patients were excluded from the study if they did not have surgery or if surgery occurred after the age of 6 months (56 patients excluded). We identified 361 who fulfilled the inclusion criteria for this study.

### Demographic and clinical data

Data were collected from the Cardiac Developmental Outcomes Programme outcome database and from the Electronic Medical Record (EPIC Systems Corporation, November 2019). Data included age, sex, gestational age, maternal age, prenatal diagnosis, prematurity (<37 weeks), race, ethnicity, language, insurance type, surgical complexity (The Society of Thoracic Surgeon-European for Cardiothoracic Surgery (STAT) score) for index surgery, history of non-febrile seizures or a diagnosed seizure disorder, stroke, and history of extracorporeal membrane oxygenation.

### Autism diagnosis

The diagnoses of autism spectrum disorder were made through the clinical neurodevelopmental assessments that are a component of the routine clinical care provided in the Cardiac Developmental Outcomes Programme clinic. During the routine clinical care visit, each infant undergoes a comprehensive clinical and neurological examination with standardised developmental testing. Experienced clinicians based their autism spectrum disorder diagnosis on **Diagnostic and Statistical Manual of Mental Disorders**-5 criteria[23] and by either the Childhood Autism Rating Scale 2-Standard[24] or the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2).[25,26] Developmental-behavioural paediatricians utilised the Childhood Autism Rating Scale 2-Standard for their diagnosis and if further evaluations were needed, patients were referred to a neuropsychologist and the Autism Diagnostic Observation Schedule, 2nd Edition was utilised.

### Statistical analysis

All baseline characteristics were summarised using mean (standard deviation), median (25th and 75th percentiles), or frequency (percentage). The prevalence of autism spectrum disorder was calculated with an exact binomial 95% confidence interval. Characteristics were summarised by autism spectrum disorder and compared using an independent two-sided *t*-test, Wilcoxon rank-sum test, chi-squared test, or Fisher's exact test as appropriate. Logistic regression was used to assess the association between characteristics and the odds of autism spectrum disorder. A multivariable logistic regression model included all characteristics that were associated with the odds of autism spectrum disorder with a p-value less than 0.1 in univariable analysis. Any variable with greater than 10% missing data was not included in the logistic regression analysis. Due to collinearity between the timing variables, only age at surgery was included in the final multivariable model but not age at the first Cardiac Developmental Outcomes Programme visit and time between surgery and the first Cardiac Developmental Outcomes Programme visit. All statistical analyses were performed using Stata v 15.1 (StataCorp). A p-value of less than 0.05 was considered statistically significant.

## Results

The median (IQR) age of the 361 children in this cohort at the time of the study analysis was 7.7 (6.6, 8.6) years. The median (IQR) age at first cardiac surgery was 15 (7.0, 51.0) days, median (IQR) age at the time of the first clinic visit was 7 (6.2, 9.4) months, and the median (IQR) number of visits to the clinic was 4 (2.0, 6.0) (Table 1). The majority of patients were male (59.8%); 42.9% were

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**Table 1.** Summary statistics of all Cardiac Developmental Outcomes Programme clinic patients.

| Variable | All CDOP patients (n = 361) |
|---|---|
| | Median (IQR) (IQR) |
| Gestational age (weeks), N = 360 | 38 (37.0,39.0) |
| Age at 1st surgery (days) | 15 (7.0,51.0) |
| Age at first CDOP visit (months) | 7 (6.2,9.4) |
| Days between surgery and first visit | 190 (167.0,259.0) |
| Number of CDOP visits | 4 (2.0,6.0) |
| | |
| | N (%) |
| Autism | 33 (9.1) |
| Male | 216 (59.8) |
| Hispanic | 150 (41.6) |
| Non-Hispanic White | 155 (42.9) |
| English language | 303 (83.9) |
| Private insurance | 171 (47.4) |
| Premature (< 37 wks GA at birth) | 60 (16.7) |
| Antenatal diagnosis | 194 (53.7) |
| Age at surgery | |
| < 30 days | 231 (64.0) |
| >= 30 days | 130 (36.0) |
| STAT category | |
| 1-3 (low complexity) | 139 (38.5) |
| 4-5 (high complexity) | 222 (61.5) |
| ECMO | 13 (3.6) |
| Stroke | 19 (5.3) |
| Seizures | 27 (7.5) |

ECMO=Extracorporeal membrane oxygenation; GA=gestational age; IQR=interquartile range; STAT category=the Society of Thoracic Surgeon-European for cardiothoracic surgery score.

non-Hispanic Whites; 83.9% were English-speaking, and 47.4% had private insurance. Furthermore, less than 20% of patients were premature, and more than half had an antenatal diagnosis of CHD (53.7%). The majority (61.5%) of the patients in this cohort showed major surgical complexity (The Society of Thoracic Surgeon-European for Cardiothoracic Surgery 4–5) for first surgery and had surgery occurring < 30 days of age (64%). A history of seizures, stroke, or the need for extracorporeal membrane oxygenation was seen in less than 10% of patients in this cohort (Table 1).

Of the 361 children in the cohort, 33 (9.1%) of the patients have been diagnosed with autism spectrum disorder (95% CI: 6.48, 12.60) by the end of the follow-up period, at a median age of diagnosis of 34 (25.0, 52.0) months. Table 2 summarises demographic and patient characteristics during infancy. Median gestational age was lower among those with autism spectrum disorder ($p = 0.035$). The majority of those diagnosed with autism spectrum disorder were male (n = 29; 87.9%) and the proportion of males with autism spectrum disorder is higher compared to those without ($p \leq 0.001$). Patients with autism spectrum disorder were older at first surgery, 54 days versus 13.5 days ($p = 0.002$), and were older at their first clinic visit, 10.4 versus 6.8 months ($p \leq 0.001$). Further stratification, according to first surgery before 30 days of age (64% of the cohort) or older (36%), revealed that the majority of those with autism spectrum disorder (54.5%) underwent cardiac surgery ≥ 30 days of age ($p = 0.023$). Furthermore, there was an increased likelihood of an autism spectrum disorder diagnosis for those born premature (i.e. < 37 weeks, $p = 0.013$), who were placed on extracorporeal membrane oxygenation ($p = 0.023$), or had history of non-febrile seizures ($p = 0.001$). There were no significant differences in maternal age, race, ethnicity, language, insurance type, antenatal diagnosis, the Society of Thoracic Surgeon-European for Cardiothoracic Surgery category, or history of stroke between patients with or without autism spectrum disorder.

Unadjusted logistic regression analysis showed that the odds of autism spectrum disorder were 5.5 times higher for males compared to females (95% CI 1.88, 15.93; $p = 0.002$). The odds of autism spectrum disorder were 2.31 higher in infants who had surgery at ≥ 30 days of age (95% CI 1.12, 4.77; $p = 0.023$) than < 30 days. Furthermore, the odds of autism spectrum disorder were 2.8 times higher for babies who were born prematurely (95% CI 1.29, 6.22; $p = 0.009$), 4.89 times higher in those on extracorporeal membrane oxygenation (95% CI 1.42, 16.88; $p = 0.012$), and 5.20 times higher (95% CI 2.07, 13.09 p=<0.001) in patients with a history of non-febrile seizures. Multivariate logistic regression analysis including only variables associated with autism spectrum disorder showed that adjusting for sex (OR 4.85; 95% CI 1.62, 14.53; $p = 0.005$), age at surgery ≥ 30 days of age (OR = 2.46; 95% CI 1.12, 5.59; $p = 0.025$), extracorporeal membrane oxygenation (OR = 4.91; 95% CI 1.23, 19.57; $p = 0.024$), and seizures (OR = 4.32; 95% CI 1.63, 11.44; $p = 0.003$) odds of autism spectrum disorder were still significantly higher (Table 3).

## Discussion

Our study demonstrates that early, routine neurodevelopmental follow-up after cardiac surgery in infancy can lead to earlier identification of autism spectrum disorder than has previously been described. The average age of diagnosis in the general population is 4 years, and in previous reports of children with CHD – the age at diagnosis was 60 months.[19] In our patients, who were seen in the Cardiac Developmental Outcomes Programme clinic from infancy onwards, the median age at diagnosis was 34 months. It is important to note that for telemedicine visits during the pandemic due to the need for a second (in-person) visit to make or confirm a diagnosis, this may have added to the age at diagnosis for some patients. Furthermore, in our clinic population, we found a higher rate of autism spectrum disorder diagnosis that has been previously reported in the general population as well as in studies limited to children with CHD. We also have identified several important risk factors for this including prematurity, the need for extracorporeal membrane oxygenation, and a history of seizures. Additionally, in contrast with the accepted 'norm' regarding neurodevelopmental delay after surgery for CHD in infancy, autism spectrum disorder was not more prevalent in children who had undergone more complex cardiac surgery and/or surgery at a younger age. In this cohort, only 36% of the patients had their first surgery ≥ 30 days; nevertheless, they had a significantly higher autism spectrum disorder diagnosis than those with first surgery

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**Table 2.** Demographics and infant characteristics of CHD patients.

| Variable | ASD - (n = 328) | ASD + (n = 33) | p-value |
|---|---|---|---|
| Maternal age, yrs, Mean (SD) (n = 326, 33) | 29.2 (6.1) | 28.7.2 (6.6) | 0.623 |
| Patient's current age, yrs, median (IQR) | 7.7 (6.6,8.6) | 7.6 (6.7,8.6) | 0.641 |
| Gestational age, weeks, median (IQR) (n = 327, 33) | 39 (37,39) | 38 (36,39) | **0.035** |
| Age at 1st surgery, days, median (IQR) | 13.5 (7,48) | 54 (10,122) | **0.002** |
| Age at 1st CDOP visit, months, median (IQR) | 6.8 (6.1,9) | 10.4 (7,16) | < **0.001** |
| Number of CDOP visits, median (IQR) | 4 (2, 6) | 5 (4,6) | **0.008** |
| Age at surgery | | | **0.023** |
| < 30 days | 216 (65.9) | 15 (45.5) | |
| >= 30 days | 112 (34.1) | 18 (54.4) | |
| Gender, N (%) Male | 187 (57) | 29 (87.9) | < **0.001** |
| Race, N (%) | | | 0.398 |
| Caucasian | 278 (84.8) | 28 (84.8) | |
| African American | 32 (9.8) | 2 (6.1) | |
| American Indian; Native Hawaiian | 2 (0.6) | 0 (6.1) | |
| Asian | 13 (4.0) | 2 (6.1) | |
| Ethnicity, N (%) Hispanic/Latino | 134 (40.9) | 16 (48.5) | 0.555 |
| Language, N (%) | | | 0.214 |
| English | 277 (84.5) | 26 (78.8) | |
| Spanish | 49 (14.9) | 6 (18.2) | |
| Other | 2 (0.6) | 1 (3.0) | |
| Insurance, N (%) | | | 0.102 |
| Public/no insurance | 168 (51.2) | 22 (66.7) | |
| Private | 160 (48.8) | 11 (33.3) | |
| Premature, N (%) (N = 327, 33) | 49 (15) | 11 (33.3) | **0.013** |
| Antenatal Diagnosis, N (%) | 173 (52.7) | 21 (63.6) | 0.274 |
| STAT, N (%) | | | 0.352 |
| 1-3 (low complexity) | 129 (39.3) | 10 (30.3) | |
| 4-5 (high complexity) | 199 (60.7) | 23 (69.7) | |
| ECMO | 9 (2.7) | 4 (12. 1) | **0.023** |
| Seizure | 19 (5.8) | 8 (24.2) | **0.001** |
| Stroke | 17 (5.2) | 2 (6.1) | 0.689 |

ASD=autism spectrum disorder; ECMO=extracorporeal membrane oxygenation; IQR=interquartile range; SD=standard deviation; STAT category=the Society of Thoracic Surgeon-European for cardiothoracic surgery score.

**Table 3.** Multivariable logistic regression for autism.

| | Odds ratio | 95% CI | p-value |
|---|---|---|---|
| **Age at surgery ≥ 30 days** | 2.46 | (1.12–5.39) 5.39) | 0.025 |
| **Male** | 4.85 | (1.62–14.53) | 0.005 |
| **Premature** | 2.12 | (0.90–5.00) | 0.087 |
| **ECMO** | 4.91 | (1.23–19.57) | 0.024 |
| **Seizure** | 4.32 | (1.63–11.44) | 0.003 |

CI=confidence interval.

< 30 days (54% versus 45.5%, respectively). This underscores the message that an outcome programme that limits follow-up to traditionally 'high-risk patients' (undergoing surgery during the neonatal period) would miss the opportunity for early diagnosis of autism spectrum disorder in an important proportion of patients. In our Cardiac Developmental Outcomes Programme clinic, the median age of autism spectrum disorder diagnosis in children with CHD was 34 months, significantly earlier than the 60 months of age reported in children with CHD,[19] and this offers the opportunity for earlier intervention before typical school age. A national survey of parents caring for children with autism showed

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that obtaining an autism spectrum disorder diagnosis is often delayed, despite parents often having concerns early on but then experiencing long wait times and in some cases multiple appointments with several specialists before receiving a diagnosis.[27] Our findings are consistent with recommendations from the Cardiac Neurodevelopmental Outcomes Collaborative, which recommends routine screening for autism from infancy through adolescence.[17] Furthermore, an earlier diagnosis of autism spectrum disorder can facilitate the introduction of therapeutic interventions that may lead to improved developmental outcomes for these children.[28–31]

In addition to our study demonstrating that autism spectrum disorder can be diagnosed earlier in children with CHD, we also found that the rate of autism spectrum disorder was significantly higher compared to the general population. In the most recent report from the CDC autism surveillance programme, autism spectrum disorder prevalence was between 1.7% and 2.3% for children 4 years of age and 8 years of age, respectively.[14,15] Although several studies suggest that children with CHD are at a higher risk of having autism spectrum disorder,[9,10,16–19] our single-centre study relied on confirmed autism spectrum disorder diagnosis by clinic providers using autism spectrum disorder diagnostic assessments and found that 9.1% of the CHD patients attending the clinic have autism spectrum disorder. Consistent with studies in the general population, we found several factors associated with higher odds of autism spectrum disorder in the CHD population. For instance, studies in pre-term infants have shown a higher prevalence of autism spectrum disorder, with each week of shorter gestation associated with higher risk.[13] In our premature group (17%), we found higher odds for autism spectrum disorder in the unadjusted analysis; however, when adjusting for several factors, this association was no longer significant. One possible explanation could be that our cohort consisted mostly of moderate to late pre-term (32– < 37 weeks) infants. As infants with CHD are at risk of being born prematurely and prematurity is a known risk factor for neurodevelopmental impairment, this population should be longitudinally followed.[32,33] Several co-occurring medical conditions, including seizures, are common in children with autism spectrum disorder.[12] A population-based study found that prevalence of autism spectrum disorder is higher in children with a history of seizures than in the general population.[34] Furthermore, in the general population, it has been reported that 20% of individuals with epilepsy have autism and thus this association is not surprising.[35] We found odds of autism spectrum disorder higher in patients with history of seizures, and it has been well documented that the occurrence of seizures in patients with CHD is consistent with worse neurodevelopmental outcomes, again demonstrating the importance of continuous surveillance.[36,37] Although the group of patients placed on extracorporeal membrane oxygenation in our cohort was small, the odds of autism spectrum disorder were still significant after adjusting for several factors. Extracorporeal membrane oxygenation is lifesaving for many critically ill cardiac patients; however, there is an increased risk for neurologic complications (i.e. stroke, seizures) and long-term neurodevelopmental delays associated with it.[38,39] To our knowledge, this is the first study demonstrating an association between extracorporeal membrane oxygenation and autism spectrum disorder in the CHD population, and thus, it will be of importance to corroborate in a larger cohort of patients.

The association between autism spectrum disorder and older age at surgery deserves further discussion, particularly given that surgery during the neonatal period has generally been considered to be associated with a higher risk of developmental impairment. Sigmon et al (2019) compared autism spectrum disorder with multiple CHD subtypes and found a higher risk of autism spectrum disorder among children with less severe forms of CHD, such as atrial septal defects and ventricular septal defects, than more complex types of CHD. Although we did not find a relationship between a diagnosis of autism spectrum disorder and surgical complexity according to the Society of Thoracic Surgeon-European for Cardiothoracic Surgery category, our clinic population is currently limited to patients who had surgery for CHD during early infancy, the majority of whom were of higher surgical complexity. However, our finding that those undergoing surgery beyond 30 days of age had a threefold increased risk for autism spectrum disorder supports the observation of Sigmon et al.[18]

There are some important limitations that should be considered. First, although we have a relatively large sample size, this is a single-centre cohort that may not be representative of other outcomes programmes. Second, it is possible that our higher-than-expected incidence of autism spectrum disorder could be related to sampling biases as patients with concerns for possible delays or existing impairments may be more likely to participate than patients who appear to be developmentally appropriate and whose parents are not concerned. However, our clinic schedule, with the initial visit being scheduled at a relatively early stage in development (6 months of age), may make this less likely. Third, data regarding the rate of autism diagnosis in patients who did not attend our follow-up programme were not available for review. Fourth, although a genetic link between autism spectrum disorder and CHD has been suggested, it was beyond the scope of this study.[40] Finally, further studies will be needed in order to postulate a mechanism for our findings or for the apparent relationship with age at surgery.

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