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Research Article

REGENERATIVE MEDICINE REPORTS
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Arterial switch and neurological outcomes: a retrospective study of medical records

Ekta G. Shah[†], Sarah ML. Wilson[1], Yi Yao[2], Wen Li[3], Pauline A. Filipek[1], Taylor S. Koerner[4], Jorge D. Salazar[5], Tina O. Findley[6], Antonio F. Corno[7, 8, *]

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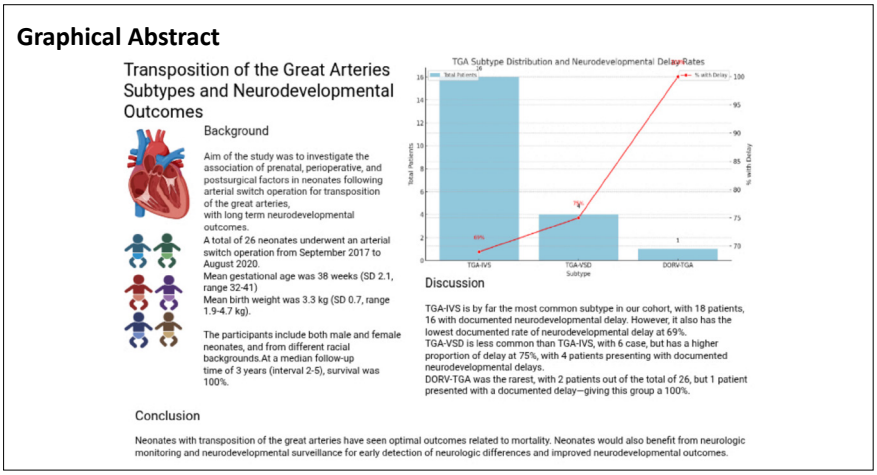
Graphical Abstract



Abstract

Despite being uncommon, survivors of neonatal cardiac surgery for complex congenital heart defects may face delays in various developmental domains, along with persistent subtle neurological deficits throughout their lifetime. Research is ongoing to determine the full extent and scope of these impairments. This study was performed to investigate neonatal and perioperative factors associated with neurodevelopmental differences in neonates who underwent arterial switch operation for transposition of the great arteries. Data collected retrospectively from neonates undergoing arterial switch operation from September 2017 to August 2020 at a single, quaternary institution, included perinatal history, perioperative data, and outpatient documentation. Primary outcome measures were neurological outcomes. The results showed that 26 neonates (65% male, 17/26) were included in this study, with a mean gestational age of 38 weeks (range 32–41 weeks) and a median birth weight of 3.3 kg (range 1.86–4.74 kg). Racial demographics included Caucasian in 8/26 (30.8%), Black in 2/26 (7.7%), Asian in 1/26 (3.8%), biracial in 9/26 (34.6%), and unspecified in 6/26 (23.1%). 46% (12/26) were of Hispanic ethnicity. No participant had a genetic diagnosis. Cardiac diagnoses included transposition of the great arteries with intact ventricular septum (17/26, 65%), with ventricular septal defect (8/26, 31%), and with double outlet right ventricle (1/26, 4%). Prenatal detection occurred in 12/26 (46%) patients. High-risk mortality risk factors, as categorized by Society of Thoracic Surgery Congenital Heart Surgery Database, were present in 22/26 (85%). Balloon atrio-septostomy was performed in 16/26 (62%). Arterial switch operation was performed at a mean age of 7.7 days (range 3–39 days). The average oxygen saturation 24 hours before BAS was 69% (range 50–87%), and the average oxygen saturation 24 hours before the arterial switch operation was 85% (range 75–92%). The mean cardiopulmonary bypass duration was 252 minutes (range 125–460 minutes), and the mean aortic cross-clamp duration was 138 minutes (range 61–266 minutes). No neonates required extracorporeal membrane oxygenation perioperatively. A shorter duration of cardiopulmonary bypass ($P = 0.004$) and cross-clamp time ($P = 0.015$) and the need for BAS ($P = 0.043$) were significantly associated with developmental delay in early childhood. The Apgar score, birth weight, microcephaly, need for preoperative mechanical ventilation, and age at the time of the arterial switch operation were not associated with developmental delay. The survival rate was 100% at a median follow-up of 3 years (range 2–5 years). These findings suggest that an arterial switch for transposition of the great arteries can be performed with satisfactory outcomes; however, this study supports the need for more neurodevelopmental-focused care through both the neonatal period and long-term follow-up. Neurodevelopmental monitoring of high-risk neonates with transposition of the great arteries before and after cardiac interventions is critically important, as it guides decisions on the need for advanced neuroimaging and the risk for neurodevelopmental impairments in the long term.

Key Words: arterial switch operation; cardiopulmonary bypass; congenital heart defects; developmental delay; neonatal heart surgery; neurodevelopmental impairment; neuroimaging; regenerative medicine; seizures; transposition of the great arteries

Introduction

Background

Congenital heart defects are the leading cause of death in infancy among all congenital malformations.[1,2] Advanced prenatal and postnatal diagnostic methodologies have improved perinatal and perioperative managements, and enhanced intensive care management has led to lower mortality rates following neonatal heart surgery over the last few decades,[3,4] including arterial switch operations.[5] Over the last 20 years, most children born with complex congenital heart defects have reached adulthood.[4] The substantial improvement in survival rates after neonatal cardiovascular surgery has resulted in a shift in research focus from short-term survival to long-term outcomes related to morbidity and quality of life defined by neurological and developmental outcomes.[6,7]

[1]Division of Child & Adolescent Neurology, Department of Pediatrics, McGovern Medical School at the University of Texas Health Science Center at Houston, Houston, TX, USA; [2]School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA; [3]Division of Clinical and Translational Sciences, Department of Internal Medicine, McGovern Medical School at the University of Texas Health Science Center at Houston, Houston, TX, USA; [4]Division of Pediatric Cardiology and Cardiac Critical Care, Connecticut Children's Hospital, Hartford, CT, USA; [5]Children Heart Institute, McGovern Medical School at the University of Texas Health Science Center at Houston and Children Memorial Hermann Hospital, Houston, TX, USA; [6]Division of Neonatal-Perinatal Medicine, Department of Pediatrics, McGovern Medical School at the University of Texas Health Science Center at Houston, Houston, TX, USA; [7]Faculty of Science and Engineering, Manchester Metropolitan University, Manchester, UK; [8]School of Engineering, University of Leicester, Leicester, UK
[†]Current address: Division of Neurology, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA
***Correspondence to:** Antonio F. Corno, MD, FRCS, FETCS, FACC, FHEA, t.corno@mmu.ac.uk or tonycorno2@gmail.com.
https://orcid.org/0000-0003-4374-0992 (Antonio F. Corno)

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Rationale and knowledge gap

Neurological and developmental impairments are recognized in children with complex congenital heart defects and contribute to lifelong morbidities.[6,8-12] The prevalence and severity of these impairments are associated with the degree of complexity of congenital heart defects, affecting up to 50% of children.[6,13] Children who require surgical correction or palliation in the neonatal period are at considerably high risk for developmental delays. Research spanning the prenatal and neonatal periods, preoperative events, perioperative management, and both early and long-term follow-up has shown that the etiologies of neurodevelopmental impairments are multifactorial, cumulative, and synergistic.[7,9,14-16]

The single most important risk factor for neurodevelopmental impairment is the type of congenital heart defect, driven by fetal pathophysiology and specific morphology. The most severe brain lesions during fetal life are cyanotic congenital heart defects, namely, transposition of the great arteries, single-ventricle physiology, and hypoplastic left heart syndrome.[17-26]

Transposition of the great arteries is a cono-truncal defect with ventriculo-arterial discordance and is considered the most common cyanotic heart defect, affecting 5%–7% of neonates with congenital heart disease.[27,28] Improved prenatal diagnosis has enabled anticipation of early intervention to increase systemic oxygen saturation either medically or through interventions, mitigating the negative effects of prolonged hypoxemia.[29-31] In the first few weeks of life, neonates undergo a crucial palliative surgery known as the arterial switch operation, and approximately 90% survive into adulthood.[28] In patients with critical preoperative hypoxemia due to impaired intracardiac mixing, balloon atrio-septostomy (Rashkind procedure) is an option.[28] The perioperative period constitutes another potential source of neurological insult from general anesthesia, stressors of surgery, and cardiopulmonary bypass with potential changes in homeostasis due to variations in temperature, blood flow, and hematocrit values, resulting in hypoxia/reoxygenation and ischemia/reperfusion injuries.[5-6,9,17,32-34] Furthermore, the postoperative period is complicated by low cardiac output and the associated systemic inflammatory state, as well as complications related to intensive care and prolonged hospitalizations, all of which may contribute to neurologic morbidities in the early[35-37] as well as late[38-40] follow-up periods.

Objective

While severe disability is quite uncommon, survivors of neonatal cardiac surgery for complex congenital heart defects may exhibit delays across various developmental domains, including subtle neurologic deficits that persist throughout their life. The extent and range of these impairments continue to be researched.[6-7,9,11,13-14,16,32,36,37] This retrospective study of children with transposition of the great arteries was performed to (1) investigate the association of prenatal, perioperative, and postsurgical factors at our institution with long-term neurodevelopmental differences and (2) compare findings to neurodevelopmental differences reported in the literature.

Methods

Study population

In this retrospective study, the medical records were examined for all consecutive neonates who underwent arterial switch operation for transposition of the great arteries from September 2017 to August 2020 at a single, quaternary institution.

Data collection

Data were collected during the prenatal and postnatal periods through the last analysis (May 30, 2022), with special consideration of the perioperative period. Factors that were analyzed included pregnancy complications, genetic testing, gestational age, Apgar scores, anthropometric measurements, demographic information (race, ethnicity), subtype of transposition of the great arteries, neurologic diagnostic studies (head ultrasound, scalp electroencephalography, head computerized tomography, brain magnetic resonance imaging, head ultrasound), and neurologic history (seizures, epilepsy, cerebrovascular injuries, developmental delay).

Outcome variables

The factors associated with the perioperative period were also analyzed, including the need for mechanical ventilation before surgery, balloon atrio-septostomy, systemic oxygen saturation, duration of cardiopulmonary bypass and aortic cross clamp, use of selective cerebral perfusion, total duration of mechanical ventilation, and length of stay in the intensive care unit and hospital. Two pediatric neurologists reviewed the medical records for data collection in the inpatient and outpatient settings. The primary outcome measures were neurologic conditions diagnosed by a clinician or based on the results of neurologic diagnostic studies. No standardized developmental evaluations were used.

Statistical analysis

The analytical approach examined the relationship between each variable and the occurrence of "developmental delay." Association analyses employed Fisher's exact test for categorical variables and t-test (analysis of variance for binary outcome) for continuous variables, applying a significance threshold of $P \leq 0.05$. Hypothesis testing was not performed for the subgroup of patients who underwent brain magnetic resonance imaging because of the small sample size ($n = 8$). Measures of central tendency were reported in median (interquartile range), with the threshold for statistical significance of $P \leq 0.05$.

Results

Patient characteristics

A total of 26 neonates underwent an arterial switch operation from September 2017 to August 2020 (**Table 1**), among which 17/26 (65%) were male. The mean gestational age was 38 weeks (SD 2.1, range 32–41), and the mean birth weight was 3.3 kg (SD 0.7, range 1.9–4.7 kg). Racial demographics included Caucasian in 8/26 (30.8%), Black in 2/26 (7.7%), Asian in 1/26 (3.8%), biracial in 9/26 (34.6%), and unspecified in 6/26 (23.1%). 46% (12/26) were of Hispanic ethnicity. Demographics, gestational age, APGAR scores, birth weight, and the presence of microcephaly were not associated with developmental differences. Pregnancy complications of gestational diabetes mellitus, gestational hypertension, polyhydramnios, oligohydramnios, and other complications, as categorized by the Society of Thoracic Surgery, were present in 7/26 (27%), and, after analysis with multiple interpolations, none of them was associated with developmental delay ($P = 0.656$). Genetic testing through a chromosomal microarray was obtained in 13/26 (50%) of patients; no variants associated with cardiac defects were detected. At a median follow-up time of 3 years (interval 2–5), the survival rate was 100%.

Cardiac characteristics

Cardiac diagnoses included transposition of the great arteries with intact ventricular septum (18/26, 69%), with ventricular septal defect (6/26, 23%), and with double outlet right ventricle (2/26, 8%). Cardiac diagnoses were identified prenatally in 46% (12/26). Mortality risk factors, as categorized by the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database, were present in 22 neonates (85%). Balloon atrial septostomy was performed in 16/26 (62%) and was associated with developmental delay ($P = 0.043$); however, average percutaneous oxygen saturation (SpO_2) prior to the balloon atrial septostomy was not associated with developmental differences ($P = 0.695$). The arterial switch operation was performed at a mean age of 7.7 days (SD 7.2, range 3–39), associated with either pulmonary artery reconstruction ($n = 5$), aortic arch reconstruction ($n = 3$), and Konno aorto-ventriculoplasty procedure ($n = 1$). The average age for the arterial switch operation was 7.7 days (SD 7.2, range 3–39 days), and 24/26 (92%) underwent this procedure within the first 2 weeks of life. Among the different subtypes of transposition of the great arteries, the mean age for the arterial switch with transposition of the great arteries with an intraventricular septum was 6.3 days (SD 3.89, range 3–20), and with transposition of the great arteries with a ventricular septal defect was 10.8 days (SD 11.5, range 5–39). Only one patient had transposition of the great arteries with a double outlet right ventricle; the age of the arterial switch was 6 days. Neither the timing of the arterial switch nor the average SpO_2 24 hours prior to the procedure was associated with developmental delay ($P = 0.234$ and $P = 0.574$, respectively). The average cardiopulmonary bypass duration was 251.9 minutes (SD 84.6, range 125–460 minutes), and the average aortic cross-clamp duration was 137.6 minutes (SD 52.9, range 61–266 minutes), with 3/26 (11%) neonates undergoing selective cerebral perfusion. When cardiopulmonary bypass and aortic cross-clamp variables were assessed, shorter durations were associated with developmental delay ($P = 0.004$ and $P = 0.015$, respectively). No neonates required extracorporeal membrane oxygenation during the perioperative or postoperative period.

Neurodevelopmental characteristics

Through their initial admission, occupational and speech therapy worked with

Table 1 | **Descriptive variables**

Variable	Developmental delay (*n* = 15)	Total (*N* = 26)	Note
Sex			
Female	5/15 (33)	9/26 (35)	
Male	10/15 (67)	17/26 (65)	
Ethnics			
Hispanic	7/15 (47)	12/26 (46)	
Not Hispanic	8/15 (53)	14/26 (54)	
Subtype of TGA			
TGA-VSD	3/15 (20)	6/26 (23)	
TGA-DORV	1/15 (7)	2/26 (8)	
TGA-IVS	11/15 (73)	18/26 (69)	
Perinatal factors			
Antenatal diagnosis	8/15 (53)	12/26 (46)	
Preterm (< 37 wk)	3/15 (20) Mean: 36 wk Range: 36 wk	5/26 (19) Mean: 34 wk Range: 32–36 wk	
Term (> 37 wk)	12/15 (80) Mean: 38 wk Range: 37–40 wk	21/26 (81) Mean: 38 wk Range: 37–41 wk	
APGAR 1 min	15/15 Mean: Apgar: 7 Range: 3–9	26/26 Mean: Apgar: 7 Range: 3–9	
APGAR 5 min	15/15 Mean: Apgar: 8 Range: 7–9	26/26 Mean: Apgar: 8 Range: 7–9	
Birthweight (kg)	15/15 Mean: 3.43 Range: 2.12–4.37	26/26 Mean: 3.3 Range: 1.86–4.74	
Intrauterine growth restriction	1/15 (6.7)	1/25 (4)*	**1 of the 26 patients with unknown IUGR status*
Pregnancy complications	5/12 (42)*	7/19 (37)**	**3 of 15 patients with developmental delay had unknown pregnancy demographics* ***7 of the 26 patients had unknown pregnancy demographic*
Neurodiagnostic			
Normal head ultrasound	13/14 (93)*	24/25 (96)**	**1 of the 15 patients with HUS results was unknown* ***1 of the 26 patients with HUS was results unknown*
Brain MRI obtained	6/15 (40)	8/26 (31)	
Abnormal MRI brain	3/6 (50)*	5/8 (63)**	**6/15 patients with developmental delay had brain MRI, 3/6 were abnormal* ***8/26 patients had brain MRI, 5/26 were abnormal*
EEG obtained	2/15 (7.7)	3/26 (11.5)	
Other diagnosis			
Seizures	1/15 (6.7)	2/26 (8)	
Epilepsy	1/15 (6.7)	1/26 (3.8)	
Dysphagia/concern for dysphagia	8/15 (53)	9/26 (35)	
Therapy			
OT assessment inpatient	12/15 (80)	23/26 (88)	
PT assessment inpatient	8/15 (53)	11/26 (42)	
Abnormal physical exam on therapy evaluation	8/15 (53)	11/26 (42)	
Genetics			
Chromosomal microarray completed	8/15 (53)	13/26 (50)	
Normal chromosomal microarray	6/8 (75)	11/26 (42)	
Abnormal chromosomal microarray	2/8* (25)	2/26* (7.7)	**Findings of 2 CMA were not thought to be associated with congenital heart defect. Patient 1 had a loss of 15q15.3, associated with autosomal recessive deafness-infertility syndrome. Patient 2 had a GAIN 2q31.1 with no clear clinical correlation.*
Perisurgical information			
Preoperative mechanical ventilation	13/15 (87)	20/26 (77)	
ECMO	0/15 (0)	0/26 (0)	
CBP time (minutes)	213	251	
X clamp time (minutes)	116	137	
Age of ASO (Days)	6	7	

Descriptive statistics are listed for variables among patients with developmental delay and all 26 patients. Categorical variables are presented as count (percentage). ASO: Arterial switch operation; CBP: cardiopulmonary bypass; DORV: double-outlet right ventricle; ECMO: extracorporeal membrane oxygenation; IVS: intact ventricular septum; MRI: magnetic resonance imaging; TGA: transposition of the great arteries; VSD: ventricular septal defect; X clamp: aortic cross clamp.

23/26 (89%) patients; physical therapy worked with 11/26 (42%) patients. By the time of discharge, abnormal neurologic exams were detected by physical therapy in all patients they evaluated. By the conclusion of the study period, developmental delay was documented in 15/26 (58%) patients. Of those with developmental delays, 5/15 (33%) had speech delays, and 4/15 (27%) had motor delays. Motor delays were classified as gross motor delays in 2/15 (13%) and 2/15 (13%) presented with both fine and gross motor delays. Dysphagia was documented in 9/26 (35%) patients. Non-specified developmental delay was documented in 5/15 (33%) patients. No patient had documented global developmental delay, autism spectrum disorder, or cerebral palsy (**Table 2**).

Of patients with TGA-IVS, developmental outcomes were documented in 16/18 (89%) of patients and developmental delay was identified in 11/16 (69%); specifically, speech delay in 3/11 (27%), gross motor delay in 2/11 (18%), mixed fine and gross motor delay in 1/11 (9%), and non-specified delay in 5/11 (45%). Of patients with transposition of the great arteries (TGA)-

Table 2 | **Test for association with developmental delay**

	Developmental delay			
Variable	No (*n* = 11)	Yes (*n* = 15)	Total (*N* = 26)	***P* value**
Sex				1.000[1]
Female	4 (36.4)	5 (33.3)	9 (34.6)	
Male	7 (63.6)	10 (66.7)	17 (65.4)	
Hispanic ethnicity				1.000[1]
No	6 (54.5)	8 (53.3)	14 (53.8)	
Yes	5 (45.5)	7 (46.7)	12 (46.2)	
Caucasian race				0.683[1]
No	3 (27.3)	6 (40.0)	9 (34.6)	
Yes	8 (72.7)	9 (60.0)	17 (65.4)	
Black race				1.000[1]
No	9 (81.8)	13 (86.7)	22 (84.6)	
Yes	2 (18.2)	2 (13.3)	4 (15.4)	
TGA-VSD or TGA-DORV				0.683[1]
No	7 (63.6)	11 (73.3)	18 (69.2)	
Yes	4 (36.4)	4 (26.7)	8 (30.8)	
TGA-IVS				0.683[1]
No	4 (36.4)	4 (26.7)	8 (30.8)	
Yes	7 (63.6)	11 (73.3)	18 (69.2)	
Associated cardiac lesions				1.000[1]
No	8 (72.7)	12 (80.0)	20 (76.9)	
Yes	3 (27.3)	3 (20.0)	6 (23.1)	
Pregnancy complications				0.656[1]
N-Miss	4	3	7	
No	5 (71.4)	7 (58.3)	12 (63.2)	
Yes	2 (28.6)	5 (41.7)	7 (36.8)	
Gestational age				0.438[2]
Mean (SD)	37.5 (2.8)	38.2 (1.4)	37.9 (2.1)	
Range	32–41	36–40	32–41	
1 min Apgar score				0.761[2]
Mean (SD)	7.4 (1.3)	7.5 (1.5)	7.5 (1.4)	
Range	5.0–9.0	3.0–9.0	3.0–9.0	
5 min Apgar score				0.361[2]
Mean (SD)	8.5 (0.7)	8.3 (0.8)	8.4 (0.8)	
Range	7.0–9.0	7.0–9.0	7.0–9.0	
Birth weight (kg)				0.371[2]
Mean (SD)	3.2 (0.8)	3.4 (0.6)	3.3 (0.7)	
Range	1.9–4.7	2.1–4.4	1.9–4.7	
Microcephaly				0.492[1]
No	11 (100.0)	13 (86.7)	24 (92.3)	
Yes	0 (0.0)	2 (13.3)	2 (7.7)	
Preoperative mechanical ventilation				0.348[1]
No	4 (36.4)	2 (13.3)	6 (23.1)	
Yes	7 (63.6)	13 (86.7)	20 (76.9)	
BAS performed				0.043[1]
No	7 (63.6)	3 (20.0)	10 (38.5)	
Yes	4 (36.4)	12 (80.0)	16 (61.5)	
Time to BAS (hours)				0.864[2]
N-Miss	7	3	10	
Mean (SD)	24.8 (32.5)	29.8 (53.6)	28.5 (48.2)	
Range	3.0–73.0	2.0–144.0	2.0–144.0	
Average SpO_2 prior to BAS (%)				0.695[2]
Mean (SD)	71.0 (12.2)	67.9 (13.6)	68.7 (13.0)	
Range	54–83	50–87	50–87	
Age at ASO (days)				0.234[2]
Mean (SD)	9.6 (10.9)	6.2 (1.3)	7.7 (7.2)	
Range	3.0–39.0	4.0–9.0	3.0–39.0	
Average SpO_2 24 hours prior to ASO (%)				0.574[2]
Mean (SD)	85.3 (5.1)	84.3 (4.0)	84.7 (4.4)	
Range	75.0–91.0	79.0–92.0	75.0–92.0	
CBP time (minutes)				0.004[2]
Mean (SD)	304.6 (80.1)	213.3 (66.5)	251.9 (84.6)	
Range	229.0–460.0	125.0–321.0	125.0–460.0	
X clamp time (minutes)				0.015[2]
Mean (SD)	166.2 (55.2)	116.7 (41.3)	137.6 (52.9)	
Range	102.0–266.0	61.0–190.0	61.0 –266.0	

Descriptive statistics of variables and their test of association with developmental delay among all 26 patients. Categorical variables are presented as count (percentage), and continuous variables are presented in mean (SD) and range. The number of missing values is shown in N-Miss. [1]Fisher's exact test for count data. [2]Linear model analysis of variance. ASO: Arterial switch operation; BAS: balloon atrioseptostomy; CPB: cardiopulmonary bypass; DORV: double-outlet right ventricle; IVS: intact ventricular septum; SpO_2: percutaneous oxygen saturation; TGA: transposition of the great arteries; VSD: ventricular septal defect; X clamp: aortic cross clamp.

ventricular septal defect (VSD), developmental outcomes were documented in 4/6 (67%); specifically, developmental delay was identified in 3/4 (75%), 2/4 (50%) with speech delay and 1/4 (25%) with non-specified motor delay. Of patients with double-outlet right ventricle (DORV)-TGA, developmental outcomes were documented in 1/2 (50%). Although the sample size was small between the subtypes, developmental delay among patients with documented developmental outcomes was identified in 3/4 (75%) of TGA-VSD patients and 11/16 (69%) of TGA-IVS patients.

Neurodiagnostic studies

Neurological investigations were performed at the discretion of the clinical team and included cranial ultrasounds (25/26, 96%), brain magnetic resonance imaging (MRI) (8/26, 31%), and scalp electroencephalography (EEG) (3/26, 12%). Brain MRI was performed preoperatively in (5/26, 19%) and postoperatively in (3/26, 12%). One patient had both pre- and post-operative MRI. Preoperatively, 3/5 MRI studies were normal and 2/5 demonstrated abnormalities. All postoperative brain MRI studies demonstrated abnormalities. Preoperative and postoperative MRI abnormalities included white matter injury in 2/8 (25%), multifocal micro-hemorrhage in 1/8 (12.5%), focal encephalomalacia in 2/8 (25%), and cavernous malformation in 1/8 (12.5%). Among these findings, preoperative abnormalities included white matter injury and cavernous malformation. Both patients with focal encephalomalacia on brain MRI had documented gross motor delay. One of the two patients with white matter injury had documented gross and fine motor delay. Given that only eight patients underwent brain MRI, the presence of an abnormal MRI was not used for univariate logistic regression analysis.

Acute symptomatic seizures were documented both clinically and on EEG in 2/26 (7.7%) patients, of whom one patient (1/26; 3.8%) was diagnosed with epilepsy. This patient also had focal encephalomalacia on brain MRI. The presence of symptomatic seizures was not associated with developmental delay.

Discussion

All 26 patients in our retrospective review survived through the end of the study period despite high mortality risk in 85% of the neonates, as recognized by the Society of Thoracic Surgeons. With respect to neurologic morbidity, 58% had documented developmental delay, 25% had cerebral white matter injury, 25% had focal encephalomalacia on MRI, and 4% had epilepsy at a mean follow-up of 3 years from the perioperative period. Such findings support the neurodevelopmental challenges that patients with transposition of the great artery experience and also highlight the importance of current surgical and intensive care practices. In this study, we sought to retrospectively review our experience to evaluate trends in neurodevelopmental sequelae and subsequently compare our findings to those reported previously.[6-8,12]

Those with transposition of the great arteries are an ideal cohort to study among those with congenital heart disease due to their low incidence of extra-cardiac anomalies and associated syndromes and relatively less severe neurodevelopmental differences.[32,41] Although testing was limited to chromosomal microarrays in this study, no contributory genetic conditions were identified, supporting the notion that most transposition of the great arteries is secondary to complex, sporadic polygenic inheritance.[27]

Patient and cardiac characteristics

Pregnancy complications and neonatal factors such as the APGAR score, birth weight, and head circumference were not associated with developmental outcomes. Assessment of perioperative factors and developmental outcomes revealed a statistically significant relationship between those who required a balloon atrial septostomy and subsequent developmental delay, without significant differences in average SpO_2 prior to balloon atrial septostomy and the arterial switch. The relationship between balloon atrial septostomy and neurologic differences, whether related to acquired brain injury or developmental outcomes, has not been consistently established. The findings from this study suggest a more complex relationship; however, due to the small sample size, multivariate analysis was not feasible.

Timing of the arterial switch has been another topic of interest, with lower language scores correlating with older age at surgery.[22] In our study, most patients had their arterial switch operation in the first 2 weeks of life; these patients were classified into the early repair group as per Lim et al.[22] The IVS/DORV group was compared with the VSD group approximately 1 week later. Regardless, the timing of the arterial switch operation in our study was not associated with developmental outcomes.

Perioperative factors related to the duration of cardiopulmonary bypass and cross-clamp time have been positively correlated with developmental delay, notably within motor domains.[42] Findings from this study were the opposite. Reasons for a statistically significant relationship between shorter durations in both variables and developmental outcomes are challenging to pinpoint, but the primary hypothesis is a notable variation in the cardiothoracic surgical technique at our center. Although ideal cardiopulmonary bypass and cross-clamp durations have not been established, faster surgeries may prove disadvantageous in ways longer durations have, negatively impacting cerebral hemodynamics and consequently long-term neurodevelopmental outcomes.

Neurodevelopmental differences

Those with transposition of the great arteries have a relatively lower prevalence of neurodevelopmental differences than those with other types of congenital heart disease.[32,43] However, the risk for neurologic abnormalities begins in the preoperative period pertaining to muscle tone, movement patterns, state regulation, and feeding. In the study by Newburger et al.,[44] definite preoperative neurologic abnormalities were recognized in 36% of the 152 patients with transposition of the great arteries. Additionally, in this study, preoperative EEG was dysmature for postmenstrual age in 37% of 134 patients.[44] EEG background dysmaturity is reflective of brain maturity and function and has been correlated with poor neurodevelopmental outcomes at 12 and 24 months.[45] The peri- and postoperative periods superimpose additional risk neurodevelopmental differences due to altered cerebral blood flow and hemodynamics. Although preoperative neurologic assessments were not available in our study and confounding factors such as comorbid conditions or sedative medications were not documented at the time of evaluation, 42% of patients had documented abnormal neurologic exams by the time of their discharge.

In the long run, neurodevelopmental differences take time to manifest, coinciding with the natural developmental complexity achieved over time. A previous review of 24 different studies grouped results by age.[46] Between 19 months through 5 years of life, deficits in expressive language, visual–motor integration, motor function, and oro-motor control are observed, and patients have an increased risk for autism spectrum disorder and cerebral palsy compared with the general population.[47-52] Although standardized developmental assessments were lacking in this study and no patient was diagnosed with autism spectrum disorder or cerebral palsy, patients had documented delays in oro-motor, speech/language, and motor domains by a mean follow-up of three years, consistent with developmental differences identified in this age range.

Neuroimaging

Neuroimaging studies can be an important diagnostic tool for understanding neurodevelopmental outcomes. Imaging differences in patients with transposition of the great arteries include diminished brain growth, white matter injury, diminished white matter connectivity and maturation, intracranial hemorrhage (including micro-hemorrhage), and ischemic infarctions.[14,53-58] Among the types of injury seen in this population, white matter injury is the most recognized, with a prevalence between 14–38%, while ischemic infarctions have a prevalence between 5–29%.[59,60] The etiology of structural differences is multifactorial and cumulative from the effects of cerebral immaturity, reduced oxygen and substrate delivery, hemodynamic instability, intraoperative factors, and delayed arterial switch operations, all of which increase vulnerability to acquired brain injury and neurodevelopmental differences.[7,41,53,54,56,61-69] Due to the small number of MR images obtained in this study, no associations could be established.

Electroencephalography

The Boston Circulatory Arrest Study[44,70,71] evaluated neonates with transposition of the great arteries who underwent arterial switch operations in the first three months of life between 1988 and 1992. This is a hallmark dataset in this population, from which we learned that electrographic seizures occurred three times more than clinical seizures (20% *vs*. 6.5%) through 36 hours following surgery. Subsequent studies have supported this discrepancy and helped identify risk factors for seizures, including complex heart defects associated with > 2 cardiac interventions, concurrent ventricular septal defects, deep hypothermic cardiac arrest, delayed sternal closure,

perioperative extracorporeal membrane oxygenation, and comorbidities such as prematurity, low birth weight, intellectual disability, genetic diagnoses, and acquired brain injury.[72-77]

Risk factors for a diagnosis of remote symptomatic seizures or epilepsy in those with congenital heart defects are multifactorial from genetic conditions, altered white matter connectivity, imbalance between excitatory and inhibitory neurons, and acquired brain injury.[70,71,76-78] Importantly, the risk of epilepsy is elevated in those with congenital heart defects, even when extracardiac anomalies, intellectual disability, low birth weight, and prematurity are excluded from the analysis.[72-75]

In our cohort, acute symptomatic seizures were identified in 2/26 (7.7%) patients, among whom one patient (3.8%) was ultimately diagnosed with epilepsy. Scalp encephalography was performed at the discretion of the clinician only with clinical concern; due to the elevated risk of electrographic seizures, the actual incidence of seizures in our cohort was most likely underestimated. In 2011, the American Clinical Neurophysiology Society established the utility of continuous video EEG for neonates at risk for seizures, among which those with congenital heart defects requiring early surgery with cardiopulmonary bypass were included.[79] Continuous video EEG should therefore be considered in the perioperative period for those at high risk for seizures even without clinical evidence of seizure activity. Moreover, neonatal seizures are not only associated with brain injury but also with poor neurodevelopmental outcomes,[43,52,70-82] warranting investigation in high-risk patients. The severity of the seizure burden and the impact of treated versus untreated seizures on outcomes have yet to be established in this population. Owing to the small number of EEG studies included in this study, no associations could be established.

Strengths and limitations

The strengths of our study were utilizing fixed criteria for cardiovascular diagnoses and risk factors based on the Congenital Heart Surgery database of the Society of Thoracic Surgeons and standardized interventions for those with transposition of the great arteries. Although neurologic consultations were not routine for patients with congenital heart defects at our hospital, standard evaluation by inpatient therapy teams allowed for early neurodevelopmental assessment and recognition of those at risk. Limitations of our study included a small sample size and the single-center retrospective study design. Unfortunately, as a retrospective observation of a fixed period of time, we did not have the opportunity to include additional patients operated on to increase the total number, and consequently, the sample size remained relatively small. Additionally, neurologic consultations were limited, and a paucity of neurologic diagnostic studies were performed. Lastly, the absence of validated developmental screening tools and discrepancies in documentation detailing neurodevelopmental differences impacted our understanding of the breadth of neurodevelopmental outcomes.

Key points and future directions

Approximately 85% of patients with congenital heart disorders progress from childhood into adulthood.[6] The mortality following neonatal heart surgery has decreased[3,4] secondary to improvements introduced in the prenatal period[30-31] through the postoperative period.[83,84] These include advances in general anesthesia, cardiopulmonary bypass, myocardial protection,[5,6,9,17,32-34,85-89] intraoperative technique,[90,91] and intensive care management to maintain stable homeostasis to target organs, including the brain.[30,92-94] Such changes have resulted in better outcomes with arterial switch procedures for transposition of the great arteries[5,94,95]; however, the incidence of long-term neurologic impairments in this population is not negligible.[5,6,8-12,14,32]

In our experience, the variability in clinical documentation, limited number of neurologic diagnostic studies, and lack of consistent developmental surveillance in this study made it difficult to properly illustrate neurodevelopmental differences and evaluate associations with neurodevelopmental outcomes. However, the absence of early or late mortality at a mean follow-up of 3 years from the perioperative period is promising. The differences in our study from those reported in the literature support the idea that neurodevelopmental differences in those with transposition of the great arteries are multifactorial and cumulative, emphasizing the importance of maintaining stable homeostasis, optimizing intraoperative techniques, and employing multimodal forms of neuromonitoring for adequate neurologic protection and early recognition of neurologic injury in this vulnerable population. These observations have been confirmed by more recent reports of the perioperative management of neonates with transposition of the great arteries, with prenatal and postnatal investigations, somehow duplicating our findings.[96-103] Recognition of neurodevelopmental challenges encourages the implementation of a multidisciplinary approach between cardiologists, neurologists, pediatricians, neuropsychologists, and therapists for developmental surveillance. This would be useful both through the inpatient course and after discharge for early recognition of neurodevelopmental differences to optimize therapy services and developmental trajectories in this population.

Pertaining to the future direction, single-center studies have thus far mostly contributed to the knowledge we have on neurodevelopmental outcomes in congenital heart patients. Although population-based and multi-center studies would strengthen the data, the practicality of such studies would be difficult with variable institutional practices. Clinical registries with both cardiac and neurologic data could help standardize relevant variables, allowing for improved analysis. In turn, this could be beneficial for consensus statements pertaining to cardiac, neurologic, and developmental evaluation.

Conclusion

Arterial switch operations for transposition of the great arteries can be performed with satisfactory clinical and neurologic outcomes assessed in early childhood, even in high-risk neonates based on the Society of Thoracic Surgeons risk factors. Despite study limitations, our findings provide further evidence that neonates with transposition of the great arteries have optimal outcomes related to mortality but would benefit from neurologic monitoring and neurodevelopmental surveillance for early detection of neurologic differences and improved neurodevelopmental outcomes.

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