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ORIGINAL ARTICLE

Neurological consequences and short–term outcome of children with diagnosis of cyanotic congenital heart diseases at a Tertiary Care Cardiac Setup of Pakistan: A single center study.

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ABSTRACT… Objective: To determine the neurological consequences and short–term outcome of children with diagnosis of cyanotic congenital heart diseases (CHDs) at a tertiary care cardiac setup of Pakistan. **Study Design:** Single Center Observational Cohort study. **Setting:** Department of Pediatric Cardiology, National Institute of Cardiovascular Disease (NICVD), Karachi, Pakistan. **Period:** November 2021 to October 2022. **Material & Methods:** A total of 80 children of both genders, aged between 1 month to 12 years with known cyanotic CHD as per 2D transthoracic echocardiography were admitted in Pediatric Cardiology Department of NICVD, Karachi and were considered. At the time of enrollment, demographic characteristics along with presenting complaints were noted. Necessary baseline laboratory and radiological investigations were ordered and clinical neurological examination was done. Children were discharged and short term outcomes were labeled after 3 months follow up. **Results:** In a total of 80 children with cyanotic CHDs, most common underlying diagnosis was tetralogy of fallot, found in 41 (51.3%) children. The CT brain revealed ischemic infarct, brain abscess and gross oedema as the most frequent observations revealed in 47 (58.8%), 40 (50.0%) and 37 (46.3%) children. Surgical management of underlying neurological abnormality was advised in 23 (28.8%) children. After 3 months follow-up, complete recovery was observed among 43 (53.8%) children. CT findings at the time of enrollment as haemorrhagic infarct ($p<0.001$), brain abscess ($p=0.001$) and atrophic changes ($p=0.032$) were significantly associated with incomplete recovery. Surgery as a mode of treatment for the underlying neurological disease was associated with good recovery outcomes ($p<0.001$). **Conclusion:** Most common underlying diagnosis among children with cyanotic CHDs was tetralogy of fallot. CT findings at the time of enrollment as haemorrhagic infarct, brain abscess and atrophic changes, as well as hypotonia, down going plantars and developmental delay at the time of presentation were significantly linked with incomplete recovery.

Key words: Brain Abscess, Congenital Heart Disease, Cyanotic, Echocardiography, Haemorrhagic Infarct.

INTRODUCTION

The incidence of congenital heart disease (CHD) is estimated to be around 8/1000 live-births.[1,2] More than 50% of CHD survivors are thought to have some kinds of neurological deficits.[3,4] It has also been reported that increase in the complexity of CHD might result in the rise of neurodevelopmental impairments.[5]

The "central nervous system (CNS)" injury in the pediatric age groups with CHDs is linked to many patient related factors as well as peri-operative care while peri-operative cerebral ischemia has been labeled to be the most common etiology behind CNS injury among children having CHDs.[6] Children who need cardiac interventions in the young age are at increased risk of developing neurodevelopmental disorders.[7] Furthermore, children with CHDs undergoing surgeries are at increased risk of developing neurodevelopmental disorders as revealed by studies analyzing short-term as well as mid-term outcomes.[8-10]

However, data from developing countries in general and from Pakistan in particular is unavailable while our country is thought to have

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limitations in resource management and required levels of expertise at mass levels for handling CHDs.[11,12] The objective of the study was to determine the neurological consequences and short–term outcome of children with diagnosis of cyanotic congenital heart diseases at a tertiary care cardiac setup of Pakistan. In these regards, this is the first study from Pakistan and the findings of this study are thought to provide description of presentation, underlying diagnosis and baseline laboratory investigations along with short-term outcomes among children with cyanotic CHDs.

MATERIAL & METHODS

This single center observational cohort study was conducted at the Department of Pediatric Cardiology, National Institute of Cardiovascular Disease (NICVD), Karachi Pakistan from November 2021 to October 2022. Approval from Institutional Ethical Committee (2022/1018) was obtained. Written and informed consents were acquired from parents or legal guardians of all study participants.

Inclusion criteria were children of both genders, aged between 1 month to 12 years with known cyanotic CHD as per 2D transthoracic echocardiography were admitted in Pediatric Cardiology Department of NICVD, Karachi and were considered for this study. Newborn babies with pre-term birth or those having recognizable chromosomal abnormalities or syndromes were excluded. Children with past history of cardiac surgery or those who could not be evaluated for neurodevelopmental issues were also not included. Parents or legal guardians who did not want to be part of this study were also excluded. Children who left against medical advice were also not included in the study analysis. During the study period, a total of 80 children fulfilling the inclusion/exclusion were admitted and analyzed in this study.

At the time of enrollment, demographic characteristics along with presenting complaints were noted. Necessary baseline investigations like complete blood count analysis along with inflammatory markers were ordered from the institutional laboratory. Neurological examination of all the children was done as per the standard examination techniques laid down in Macleod's clinical examination textbook. Presence of any computed tomography (CT) brain abnormalities were noted as per the observation of a consultant radiologist with a post fellow-ship experience above 5 years. Management in terms of surgical intervention or conservative management were done. Indication for surgery were the presence of any of these:[13] i) abscess in occipital lobe, ii) gas in abscess, iii) fungus in abscess, iv) size of abscess more than 2.5 cm. Standard management protocols were observed for all children. Children were discharged as per departmental discharge criteria. Children were advised follow up after every month and short term outcomes in terms of presence of any residual neurological deficit or complete recovery (as per clinical neurological examination) were labeled after 3 months follow up. Children were advised cardiac surgery for the correction of cyanotic CHD if no residual neurological deficit was present. Children using anti-epileptic drugs with good control of fits were also advised cardiac surgery. A special proforma was made to record study data.

Data analysis was performed utilizing "Statistical Package for Social Sciences (SPSS)", version 26.0. Qualitative data was represented as frequencies and percentages whereas quantitative variables were highlighted as mean and standard deviation (SD). Data was stratified according to the short-term neurological outcome (complete recovery or not complete recovery). Qualitative variables were compared using chi-square test while comparison of quantitative data was made using independent sample t-test. P value < 0.05 was taken as of statistical significance.

RESULTS

In a total of 80 children with cyanotic CHDs, 43 (53.8%) were male representing a male to female ratio of 1.2:2. The mean age was 2.62 ± 1.8 years ranging between 1 month to 12 years whereas 29 (36.3%) children were aged above 2 years. Most frequent indications for CT brain were fever and weakness of any part of the body noted in 62 (77.5%) and 52 (65.0%) respectively. Most common underlying diagnosis was tetralogy

of fallot, found in 41 (51.3%) children. Table-I is showing baseline characteristics of children with cyanotic CHDs.

Baseline Characteristics		Frequency (%)
Gender	Male	43 (53.8%)
	Female	37 (46.3%)
Age	<6 months	26 (32.5%)
	6 months to 2 years	25 (31.3%)
	>2 years	29 (36.3%)
Indications for CT Brain	Fever	62 (77.5%)
	Fits	41 (51.3%)
	Vomiting	36 (45.0%)
	Headache	44 (55.0%)
	Loss of consciousness	31 (38.8%)
	Respiratory irregularities	30 (37.5%)
	Cranial nerve involvement	32 (40.0%)
	Weakness of any part of the body	52 (65.0%)
Underlying Diagnosis	Tetralogy of Fallot (TOF)	41 (51.3%)
	Cyanotic CHD with decreased pulmonary blood flow other than TOF	25 (31.3%)
	Cyanotic CHD with increased pulmonary blood flow	14 (17.5%)

Table-I. Baseline characteristics of children with cyanotic CHD

Most frequent laboratory abnormality were iron deficiency anemia and polycythemia noted in 40 (50.0%) children each. Figure-1 is representing frequency of important laboratory findings among children with cyanotic CHDs.

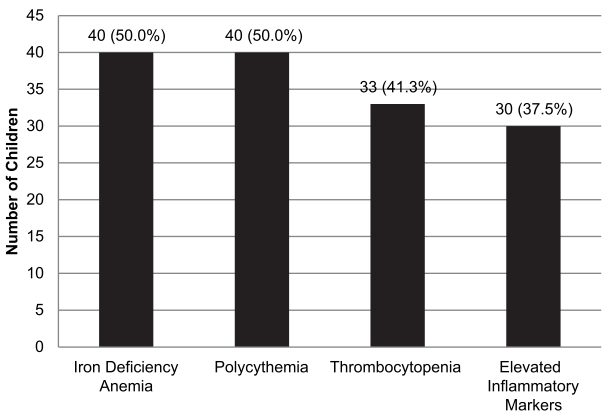

Figure-1. Important laboratory findings among children with cyanotic CHD

The CT brain revealed ischemic infarct, brain abscess and gross oedema as the most frequent observations revealed in 47 (58.8%), 40 (50.0%) and 37 (46.3%) children. Involvement of frontal lobe was found to be the most frequent cerebral involvement noted in 39 (48.8%). Anterior cerebral artery was the most common artery involved found in 39 (48.8%) children. Table-II is showing frequency of CT brain and neurological examination findings among children with cyanotic CHDs.

Surgical management of underlying neurological abnormality was advised in 23 (28.8%) children for the resolution of underlying neurological abnormality while remaining 57 (71.3%) children were managed conservatively (medical management). After 3 months follow-up, complete recovery was observed among 43 (53.8%) children and they were advised to undergo cardiac surgery while remaining 37 (46.3%) children were still having some kinds of neurological deficit. CT findings at the time of enrollment as haemorrhagic infarct ($p<0.001$), brain abscess ($p=0.001$) and atrophic changes ($p=0.032$) were significantly associated with incomplete recovery at the final outcome reported at 3 months follow up. Furthermore, Hypotonia ($p=0.002$), down going plantars ($p=0.002$) and developmental delay ($p=0.022$) at the time of presentation were significantly linked with incomplete recovery. Surgery as a mode of treatment for the underlying neurological disease among children with cyanotic CHDs was significantly associated with good recovery outcomes at 3-months follow up ($p<0.001$). No mortality reported in the current set of children with cyanotic CHDs. Table-III is showing comparison of short-term outcome (after 3-months follow up) with respect to study variables.

DISCUSSION

Structural brain abnormalities are more common in children born with CHD when compared to the general population.[14-17] Though preoperative neurological abnormalities have been described in literature, their exploration have been limited to the newborn period.[18,19]

Findings			Frequency (%)
CT Brain Findings		Gross Oedema	37 (46.3%)
		Ischemic Infarct	47 (58.8%)
		Haemorrhagic Infarct	19 (23.8%)
		Brain Abscess	40 (50.0%)
		Atrophic Changes	29 (36.3%)
		Any underlying congenital brain malformation	17 (21.3%)
CT Brain Findings	Cerebral Involvement	Frontal lobe	39 (48.8%)
		Temporal lobe	33 (41.3%)
		Parietal lobe	30 (37.5%)
		Occipital lobe	16 (20.0%)
	Artery Involvement	Anterior cerebral artery	39 (48.8%)
		Middle cerebral artery	36 (45.0%)
		Posterior cerebral artery	16 (20.0%)
Clinical Neurological Examination Findings	Tone	Hypertonia	43 (53.8%)
		Hypotonia	9 (11.3%)
		Indeterminate	28 (35.0%)
	Plantars	Up going	42 (52.5%)
		Down going	9 (11.3%)
		Indeterminate	29 (36.3%)
	Sensory changes	Intact	37 (46.3%)
		Deficit	16 (20.0%)
		Indeterminate	27 (33.8%)
	Reflexes	Exaggerated	41 (51.3%)
		Diminished	18 (22.5%)
		Indeterminate	21 (26.3%)
	Syndromic		16 (20.0%)
	Developmental delay		10 (12.5%)
	Systemic involvement		15 (18.8%)

Table-II. Frequency of important CT brain and neurological examination findings

The present study is perhaps the first one from Pakistan revealing presenting features, radiological findings and short term neurological outcomes among children with cyanotic CHDs. In this study, the commonest underlying diagnosis was TOF, found in 51.3% children with cyanotic CHDs. A retrospective study from India found TOF to be the most common cyanotic CHD type observed in 44.8% cases.[20] The same study also reported that neurological abnormalities were clearly more common in cyanotic CHD cases in comparison to acyanotic CHD cases (86.2% vs. 22.8%).[20] In the present study, hypotonia (p=0.002), down going plantars (p=0.002) and developmental delay (p=0.022) at the time of presentation were significantly linked with incomplete recovery at 3-months follow up. Some other researchers have shown that presence of neuromotor abnormalities (labeled through clinical examination) before hospital discharge were more closely linked with adverse outcomes than abnormal neuroimaging findings.[21,22] The more subjective nature of neurologic examinations compared to neuroimaging defects should not deter clinicians from performing thorough neurologic evaluations prior to discharge. Dent and colleagues studied infants with complex CHDs and revealed that 14% had post-operative neuromotor abnormalities and 73% developed new or worsened ischemic lesions.[23] Studies have shown that children with CHD are at increased risk of mortality and morbidity following non-cardiac surgery so these children should be considered at to have relatively higher risk of developing complications.[24,25]

Study Variables			Complete Recovery		P-Value
			Yes (n=43)	No (n=37)	
Gender		Male	23 (53.5%)	20 (54.1%)	0.960
		Female	20 (46.5%)	17 (45.9%)	
Age		<6 months	9 (20.9%)	17 (45.9%)	0.058
		6 months to 2 years	16 (37.2%)	9 (24.3%)	
		>2 years	18 (41.9%)	11 (29.7%)	
Underlying Diagnosis		Tetralogy of Fallot (TOF)	26 (60.5%)	15 (40.5%)	0.076
		Cyanotic CHD with decreased pulmonary blood flow other than TOF	13 (30.2%)	12 (32.4%)	
		Cyanotic CHD with increased pulmonary blood flow	4 (9.3%)	10 (27.0%)	
CT Brain Findings		Gross Oedema	16 (37.2%)	21 (56.8%)	0.080
		Ischemic Infarct	29 (67.4%)	18 (48.6%)	0.089
		Haemorrhagic Infarct	3 (7.0%)	16 (43.2%)	<0.001
		Brain Abscess	29 (67.4%)	11 (29.7%)	0.001
		Atrophic Changes	11 (25.6%)	18 (48.6%)	0.032
		Any underlying congenital brain malformation	12 (27.9%)	5 (13.5%)	0.117
CT Brain Findings	Cerebral Involvement	Frontal lobe	21 (48.8%)	18 (48.6%)	0.987
		Temporal lobe	20 (46.5%)	13 (35.1%)	0.303
		Parietal lobe	20 (46.5%)	10 (27.0%)	0.073
		Occipital lobe	6 (14.0%)	10 (27.0%)	0.145
	Artery Involvement	Anterior cerebral artery	21 (48.8%)	18 (48.6%)	0.987
		Middle cerebral artery	21 (48.8%)	15 (40.5%)	0.457
		Posterior cerebral artery	6 (14.0%)	10 (27.0%)	0.145
Clinical Neurological Examination Findings	Tone	Hypertonia	28 (65.1%)	15 (40.5%)	0.002
		Hypotonia	-	9 (24.3%)	
		Indeterminate	15 (34.9%)	13 (35.1%)	
	Plantars	Up going	27 (72.8%)	15 (40.5%)	0.002
		Down going	-	9 (24.3%)	
		Indeterminate	16 (37.2%)	13 (35.1%)	
	Sensory changes	Intact	24 (55.8%)	13 (35.1%)	0.077
		Deficit	5 (11.6%)	11 (29.7%)	
		Indeterminate	14 (32.6%)	13 (35.1%)	
	Reflexes	Exaggerated	25 (58.1%)	16 (43.2%)	0.137
		Diminished	6 (14.0%)	12 (32.4%)	
		Indeterminate	12 (27.9%)	9 (24.3%)	
	Syndromic		5 (11.6%)	11 (29.7%)	0.044
	Developmental delay		2 (4.7%)	8 (21.6%)	0.022
	Systemic involvement		10 (23.3%)	5 (13.5%)	0.266
Management / Treatment	Surgery		20 (46.5%)	3 (8.1%)	<0.001
	Medical management		23 (53.5%)	34 (91.9%)	

Table-III. Comparison of short-term outcome (after 3-months follow up) with respect to study variables

Being a single center study on a relatively small sample size were some of the limitations of this study. We only noted short-term outcomes (at 3 months follow up) and were unable to follow these children for longer durations. Many of these children were advised cardiac surgery after they got recovered from the neurological deficit but we could not report CHD related outcomes in the current set of cyanotic CHD children.

CONCLUSION

Most common underlying diagnosis among children with cyanotic CHDs was tetralogy of fallot. The CT brain revealed ischemic infarct, brain abscess and gross oedema as the most frequent observations. CT findings at the time of enrollment as haemorrhagic infarct, brain abscess and atrophic changes were significantly associated with incomplete recovery. Hypotonia, down going plantars and developmental delay at the time of presentation were significantly linked with incomplete recovery. Surgery as a mode of treatment for the underlying neurological disease among children with cyanotic CHDs was significantly associated with good recovery outcomes at 3-months follow up.

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3	Fazal ur Rehman	Literature review, Methodology.	
4	Veena Kumari	Data collection.	
5	Ammara Rashid	Literature review, Methodology.	
6	Mujeeb Ur Rehman	Drafting, References.	
7	Abdul Sattar Shaikh	Proof reading.	