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Original Article

Cognitive Assessment in children with Congenital Heart Diseases after Cardiac Surgeries

Amir Fawzy Kamal[1]*, Fatma Al Zahraa Mostafa[1], Walaa Fakher[2], Ahmed Soltan[3], Mohamed Mohamed Abdelraoof[4]

[1] Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo, Egypt
[2] Department of Psychiatry, Faculty of Medicine, Cairo University, Cairo, Egypt
[3] Department of Pediatrics, Department of Pediatrics, Beheira Children's Specialized Hospital, Ministry of Health, Beheira, Egypt
[4] Department of Cardiac Surgery, Faculty of Medicine, Cairo University, Cairo, Egypt
* Correspondence: amirfawzy12314@gmail.com
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Abstract:
Background: Children with congenital heart defects (CHD) now live longer due to advances in surgical and catheter techniques. Their neurodevelopment, including intellectual functioning, has become a major area of concern, attracting both clinical and research interest**.**
Objectives: To assess the cognitive functions in children with CHD after cardiac surgeries and to compare between cyanotic and acyanotic heart disease regarding cognitive functions**.**
Patients and methods: This cross-sectional study included sixty patients with CHD, 30 patients with cyanotic heart disease and 30 patients with acyanotic heart disease, who underwent cardiac surgeries and were examined by Stanford Binet IQ test 5th edition. They were recruited from the post cardiac intervention clinic at Pediatric Hospitals of Cairo University.
Results: The mean ± SD age of the children with cyanotic and acyanotic heart diseases was 5±2 and 4 ±1 years respectively (p= 0.345). The IQ was higher among the children with cyanotic compared to those acyanotic heart diseases with mean ± SD (range) of 85.4 ± 12 and 99.9 ± 13 respectively (p= 0.0001). IQ was not influenced by age at operation (p= 0. 171), type of operation (p= 0. 381), sex (p= 0.323), or oxygen saturation (p= 0.308). Mean ±SD IQ of those with cyanotic CHD who underwent closed and open heart surgeries was 88±11 and 84±13 respectively (p= 0.381), and in acyanotic group was 104±14 and 98±13 respectively (p= 0.323).
Conclusion: Children with congenital heart defects may have cognitive dysfunction. Children with cyanotic CHD have significantly lower IQ values than those with acyanotic CHD. No significant differences in IQ were found between patients who underwent closed and open heart surgery.

Level of Evidence of Study: IV (*1*)**.**
Keywords: Congenital heart defects; IQ Assessment; Cardiac Surgery; closed and open heart surgery; Stanford Binet 5th edition
Abbreviations: CHD: congenital heart defects; IQ: intelligence quotient;

Introduction

Children with congenital heart defects (CHD) now live longer due to advances in surgical and catheter techniques. Their neurodevelopment, including intellectual functioning, has become a major area of concern, attracting both clinical and research interest (*2–4*). Severity of the heart disease in children with CHD has been suggested as an important predictor for intellectual functioning: the more severe the heart disease, the higher the risk for lower intellectual functioning and poorer academic performance (*5*). There is growing evidence that brain development in children with CHD can differ from normal brain development. This mis-development may even start prenatally due to impaired cerebral blood flow. Postnatally, infants and older children with CHD may have preoperative and postoperative white matter abnormalities, which may relate to worse neurocognitive outcome in children with CHD. Surgery seems to impact neurocognitive outcome in CHD as well. Considering the vulnerability of their brain, neurocognitive functions may be worse in children with CHD than those in healthy control children without CHD (*6*).

Neurocognitive deficits can occur in intelligence, but also in more specific functions, such as attention and executive functions. Executive functions cover a variety of higher cognitive

functions, such as inhibition and cognitive flexibility. Attention deficit/hyperactivity disorder, with impaired inhibition as a key feature, is more prevalent in children with CHD. These executive functions especially depend on the developing pre frontal cortex, which continues to mature until young adulthood (*7*). Neurocognitive deficits at school starting age may affect as many as 50% of children who underwent cardiac surgery for complex CHD due to relative hypoxemia and systemic inflammatory response occurring during such surgeries. Impaired neurodevelopment was associated with increase of glial fibrillary acidic protein (GFAP) plasma levels during cardiopulmonary bypass for CHD surgery, which is a marker of neurologic insult during cardiac surgery in infants (*8*).

The aim of this study was to assess the cognitive functions in children with congenital heart diseases after cardiac surgeries and to compare between cyanotic and acyanotic heart disease regarding cognitive functions.

Subjects and Methods

This was a cross-sectional study included sixty children with CHD who underwent cardiac surgery. They were recruited from the Post-Cardiac Intervention Clinic at Pediatric hospitals of Cairo University. The study was approved by the Ethics Committee of Cairo University. Written informed consent was obtained from the care givers.

Participants

The included 60 children with CHD were divided into 2 groups: 30 patients with cyanotic heart disease and 30 patients with acyanotic heart disease, they had underwent un-eventful cardiac surgeries for at least 6 months prior to inclusion in the study. Children with genetic syndromes affecting mental status, known cases of neurometabolic and neurodegenerative disorders were excluded from the study. Patients with acquired brain insults as perinatal asphyxia, history of intracranial hemorrhage and central nervous system infection were also excluded.

Methods

All included children were subjected to detailed history taking and clinical examination. The type of surgery was named as open or closed. Open heart surgery was coined to surgery that directly accessed the heart through opening the chest, while closed surgery refers to surgery that was outside cardiac muscle (*9*).

They all underwent O_2 saturation assessment by pulse oximeter (SP025, Hans Dinslage GMbH, Germany), chext Xray, echocardiography that assessed post-operative cardiac structure and function. They underwent trans-thoracic two dimensional (2D), (M mode) and Doppler echocardiogram were performed using GE vivid 5 (General Electric Medical System, Horten, Norway with a 3.5-MHz multifrequency transducer) ultrasonic machine phased array sector scanner.

Linear measurements of left ventricle (LV) cavity were obtained: Left ventricular dimensions were measured from M-mode; LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), walls (interventricular septum (IVS) and posterior wall (PW) and calculation of fractional shortening (FS%) as an indicator of LV systolic function. LV systolic function were done according to the recommendations of the American Society of Echocardiography. FS value < 28% was considered lower than normal with impaired LV systolic function (*10*).

They all underwent psychometric assessment by Stanford Binet IQ test 5th edition with its subtests to measure their cognitive functions. Where IQ>145 is labeled very gifted or highly advanced, IQ 130-144: Gifted or very advanced, IQ 120-129: superior, IQ 110-119: high average, IQ 90-109: average, IQ 80-89: low average, IQ 70-79: border line impaired or delayed, IQ55-69: mildly impaired or delayed and IQ < 54: moderately impaired or delayed (*11*).

Statistical Analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences, IBM, USA) version 25. Data were summarized using mean, standard deviation, range and median in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non- parametric Mann-Whitney test. For comparing categorical data, Chi square (x^2) test was performed. Correlations between quantitative variables were done using Spearman correlation coefficient. P-values less than 0.05 were considered as statistically significant.

Results

The mean ±SD (range) age of the children with cyanotic CHD and acyanotic CHD was 5±2 (2-8) and 4±1 (2-9) years respectively (p= 0.345). (Table 1). Among the cyanotic and acyanotic CHD 15 (50%) and 18 (60%) were males (p= 0.604). They were comparable in weight and height percentiles (p=1) and (p=0.63) respectively. The underlying diagnosis of CHD and intervention is presented in Table 2. IQ among cyanotic group participants was 85.4±12 (range 65-113) compared to mean IQ of acyanotic group participants 99.9±1 (average 78±126); and this difference was statistically significant (p<0.001). There was no correlation between IQ and duration of disease or type of surgery. (Tables 4 and 5).

Table 1. Operative and post-operative data of the studied participants

		Cyanotic group (n=30)		Acyanotic group (n=30)		P value
Age at operation (month)	Mean ±SD	4±2		3±1		0.381
	Range	1-7		2-8		
Age at study (years)	Mean ±SD	5±2		4±1		0.345
	Range	2-8		2-9		
Pre-operative O_2 saturation %	Mean ±SD	82±4		99±2		0.001
Postoperative O_2 saturation %	Mean ±SD	97±2		98±3		0.76
Hospital stay in days	Mean ±SD					
		Number	%	Number	%	
Type of operation	Closed surgery	11	36.7	8	26.7	0.58
	Open surgery	19	63.3	22	73.3	
Postoperative O_2 saturation %	75-85	0	0	0	0	0.056
	85-90	4	13.3	0	0	
	90-100	26	86.7	30	100	

Table 2. Diagnoses of the congenital heart defect among the studied cohort

	Number	%	Surgical Intervention		IQ range
Diagnosis of Cyanotic CHD			Open	Closed	
TOF	13	43.3	Total repair, RVOT reconstruction, VSD closure, homograft		65 - 113
TGA	14	46.7	Senning , Arterial switch		69 - 106
Single ventricle, pulmonary atresia	2	6.7		Fontan , Glenn	80 - 100
DORV, pulmonary atresia	1	3.3		Glenn	91
Diagnosis of Acyanotic CHD					
ASD	4	13.3	Complete closure , Patch closure, surgical closure		79 - 94
VSD	12	40	VSD closure, Patch closure	Pulmonary artery banding before closure	89 - 126
PDA	1	3.3		Ligation by surgery	123
ASD,VSD	3	10	Closure of Both	Pulmonary artery banding before closure	78 - 102
VSD, ASD, PDA	2	6.7		Pulmonary artery banding, PDA ligation	98-102
VSD, PH	1	3.3	VSD closure		85
VSD, PS	1	3.3	VSD closure, pulmonary valvotomy		83
PAPVR	1	3.3	Total repair		112
TAPVR	2	6.7	Total repair		94 - 116
COA	1	3.3	Coarctectomy		97
Complete AV canal	2	6.7	Total repair		78 - 114

ASD: Atrial Septal Defect; AV: atrio-ventricular; COA: coarctation of Aorta; DORV: Double outlet right ventricle; PAPVR: partial anomalous pulmonary venous return; PDA: patent ductus arteriosus; PH: pulmonary hypertension; PS: pulmonary stenosis; RVOT: right ventricular outflow tract; TAPVR: total anomalous pulmonary venous return; TGA: transposition of great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect.

Table 3. IQ of the studied participants

	Cyanotic Group (n=30)		Acyanotic Group (n=30)		P value
Mean ±SD	85.4±12		99.9±13		0.0001*
Range	(65-113)		(78-126)		
	Number	%	Number	%	0.004**
Very gifted or highly advanced	0	0	0	0	
Gifted or very advanced	0	0	0	0	
Superior	0	0	2	6.7	
High average	1	3.3	7	23.3	
Average	9	30	15	50	
Below average	9	30	3	10	
Border line impaired or delayed	8	26.7	3	10	
Mildly impaired or delayed	3	10	0	0	
Moderately impaired or delayed	0	0	0	0	

* T- test is statistically significant at level of confidence of 95%.
**Exact Fisher's test is statistically significant at level of confidence of 95%.

Table 4. Correlation between IQ with age at operation and duration after operation

		IQ		
		Cyanotic group (n=30)	Acyanotic group (n=30)	Total (n=60)
Age at operation	r	-0.103	-0.183	-0.179
	P-value	0.587	0.332	0.171
Duration after operation	r	-0.053	0.048	-0.133
	P-value	0.78	0.0802	0.311

Table 5. Relation between IQ and type of surgery among the children with congenital heart defects

IQ	Cyanotic group (n=30)					Acyanotic group (n=30)				
	Closed (n=11)		Open (n=19)		P-value	Closed (n=11)		Open (n=19)		P value
Mean ±SD	88±11		84±13		0.381	104±14		98±13		0.323
	Number	%	Number	%		Number	%	Number	%	
Very gifted or highly advanced	0	0	0	0		0	0	0	0	
Gifted or very advanced	0	0	0	0		0	0	0	0	
Superior	0		0	0		2(25)		0	0	
High average	0	0	1	5.3	0.293	0	0	7	31.8	0.045
Average	6	54.5	3	15.8		5	62.5	10	45.5	
Below average	2	18.2	7	36.8		1	12.5	2	9.1	
Border line impaired or delayed	2	18.2	6	31.6		0	0	3	13.6	
Mildly impaired or delayed	1	9.1	2	10.5		0	0	0	0	
Moderately impaired or delayed	0	0	0	0		0	0	0	0	

Discussion

Cognitive functions were measured by IQ of the study participants, showed that most of study participants had average IQ, yet those with cyanotic CHD had statistically lower IQ ($p<0.001$). IQ score was higher with higher oxygen saturation among both acyanotic and cyanotic, although this difference was insignificant ($p= 0.308$). The early life hypoxia prior to the surgical intervention maybe responsible for the long standing IQ decline among those with cyanotic CHD, which was suggested to be the cause of preoperative focal white matter lesions detected among 21- 40% of infants with cyanotic CHD (*12*, *13*). Infants with CHD were reported to have smaller brain measures in the frontal lobe, parietal lobe, cerebellum, and brainstem, with the frontal lobe and brainstem displaying the greatest alterations. A smaller brain size in the frontal and

parietal lobes correlated with delayed white matter microstructure reflected by diffusion imaging.

Others justified lower cognitive functions that may be associated with cyanotic CHD, to cerebral accident due to polycythemia and microcytosis, particularly during blue spells (cyanosis) or when blood viscosity is increased (*14*). In addition, in a study among adolescents with history of corrective congenital heart defects, it was found that adolescents with cyanotic CHD had brain volume reductions, more than adolescents with an acyanotic CHD, who also showed a significant volume reduction compared with control subjects. This finding broadens the knowledge of how cardiac disease severity affects brain development and injury (*15*).

The lower IQ might reflect the effect of a combination of developmental vulnerability and regional differences in cerebral circulation in children with cyanotic CHD. Hence, it may result in neurodevelopmental delays and lower intellectual functions. Thus the severity of the cyanotic CHD maybe an important predictor for intellectual functioning; i.e : the more severe the heart defect, the higher the risk for lower intellectual functioning and poorer academic performance (*16*). We did not asses the IQ before the operative intervention, and the children did not undergo brain imaging pre-operatively, hence we are not aware if the early life hypoxia was responsible for the lower IQ. We did not perform brain imaging for our studied cohort as it was beyond the scope of the current study, yet it seems important to evaluate if there is an underlying brain organic lesion associated with this lower IQ.

We did not asses the IQ before the operative intervention, hence we do not know if the surgical intervention was responsible for the lower IQ among those with cyanotic CHD. There was no correlation between the age at operation, type of operation or duration of disease and the lower IQ among those with cyanotic CHD. Cardiac surgery is known to be associated with hospital stay that is often longer than acyanotic group. This may be attributed to more prevalence of complex open-heart surgery among them with more complications that requires longer postoperative recovery, that may have risks of postoperative complications, thus intensive postoperative care is needed (*17*).

The mean IQ did not differ among those who underwent closed or open cardiac surgery among those with acyanotic CHD (p=0.323), yet the ANOVA demonstrated that the upper IQ among those with open cardiac surgery was high average while that among the closed was average IQ. Yet, it seems that in other centers the open cardiac surgery incites systemic inflammatory response to the invasive procedure that causes post-operative cognitive function delay in 43% of patients (*15*, *18*).

There was no significant difference in IQ between cyanotic and acyanotic group based on their age at undergoing corrective cardiac surgery (p= 0.171). Both underwent surgery within the earliest 6 months of life and none was beyond the first year of life at operation. Delay in surgical correction beyond 1 year of age, in children with CHD, has deleterious effects over cognitive outcomes of these patients, due to having longer period of preoperative chronic cerebral hypoxia. This cognitive outcome correlates with patients` scholar degrees, in older patients (*6*). The varying durations of cyanosis, numbers of surgical procedures, and types of medical management may imply a predisposition to that outcome (*19*).

It should be mentioned that one limitation of the current study is that there was no available data about the study sample IQ preoperatively, thus it cannot be determined if the neuro-intellectual delay is either due to the severity of the congenital heart defect, and/ or aggravated, by the invasiveness of the major cardiac surgery. Secondly, no available data about the other factors that could have contributed to the etiology of these neurological abnormalities; as one potential cause is abnormal cerebrovascular blood flow dynamics in utero, that may cause lower oxygen content due to intra-cardiac mixing and cardio pulmonary bypass microembolization affection in IQ which can assessed post operatively.

Children with cyanotic CHD need educational and vocational support to help them lead a healthy productive life. IQ, hearing and visual assessment are mandatory, as children with CHD are known to be prone to cognitive dysfunction and deafness.

Conclusion

Children with congenital heart defects may have cognitive dysfunction. Children with cyanotic CHD have significantly lower IQ values than those with acyanotic CHD. No significant differences in IQ were found between patients who underwent closed and open heart surgery.

Author Contributions:

All authors shared in design, data curation analysis and drafting of the work. All authors approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

References

1. S. Tenny, M. Varacallo, *Evidence Based Medicine.* (StatPearls Publishing; Treasure Island (FL), 2020; https://www.ncbi.nlm.nih.gov/books/NBK470182/).
2. J. M. Wotherspoon, K. J. Eagleson, L. Gilmore, B. Auld, A. Hirst, S. Johnson, C. Stocker, H. Heussler, R. N. Justo, Neurodevelopmental and health-related quality-of-life outcomes in adolescence after surgery for congenital heart disease in infancy. *Dev. Med. Child Neurol.* **62**, 214–220 (2020).
3. N. Derridj, R. Guedj, J. Calderon, L. Houyel, N. Lelong, N. Bertille, F. Goffinet, D. Bonnet, B. Khoshnood, Long-Term Neurodevelopmental Outcomes of Children with Congenital Heart Defects. *J. Pediatr.* **237**, 109-114.e5 (2021).
4. D. Huisenga, S. La Bastide-Van Gemert, A. Van Bergen, J. Sweeney, M. Hadders-Algra, Developmental outcomes after early surgery for complex congenital heart disease: a systematic review and meta-analysis. *Dev. Med. Child Neurol.* **63**, 29–46 (2021).
5. R. Spillmann, S. Polentarutti, M. Ehrler, O. Kretschmar, F. M. Wehrle, B. Latal, Congenital heart disease in school-aged children: Cognition, education, and participation in leisure activities. *Pediatr. Res.* **94**, 1523–1529 (2023).
6. D. Ilardi, J. H. Sanz, A. R. Cassidy, R. Sananes, C. K. Rollins, C. Ullman Shade, G. Carroll, D. C. Bellinger, Neurodevelopmental evaluation for school-age children with congenital heart disease: recommendations from the cardiac neurodevelopmental outcome collaborative. *Cardiol. Young* **30**, 1623–1636 (2020).
7. S. H. Lau-Jensen, B. Asschenfeldt, L. Evald, V. E. Hjortdal, Hyperactivity and Inattention in Young Patients Born With an Atrial Septal or Ventricular Septal Defect. *Front. Pediatr.* **9**, 786638 (2021).
8. M. Vergine, L. Vedovelli, M. Simonato, V. Tonazzo, A. Correani, E. Cainelli, D. Gregori, M. A. Padalino, P. Cogo, Perioperative Glial Fibrillary Acidic Protein Is Associated with Long-Term Neurodevelopment Outcome of Infants with Congenital Heart Disease. *Children* **8**, 655 (2021).
9. G. N. Jabur, J. Donnelly, A. F. Merry, S. J. Mitchell, A prospective observational study of emboli exposure in open versus closed chamber cardiac surgery. *Perfusion* **37**, 715–721 (2022).
10. M. Kotb, F. A. Z. Mostafa, A. Badr, A. Hegazy, M. Eid, N. Sabry, R. Shamma, Structural and Functional Cardiac Changes in Children with Wilson Disease. *Pediatr. Sci. J.* **2**, 72–81 (2022).
11. K. G. Stephenson, A. Levine, N. C. C. Russell, J. Horack, E. M. Butter, Measuring intelligence in Autism and ADHD : Measurement invariance of the -BINET 5TH EDITION and impact of subtest scatter on abbreviated IQ accuracy. *Autism Res.* **16**, 2350–2363 (2023).
12. D. J. Licht, M. Jacobwitz, J. M. Lynch, T. Ko, T. Boorady, M. Devarajan, K. N. Heye, K. Mensah-Brown, J. J. Newland, A. Schmidt, P. Schwab, M. Winters, S. C. Nicolson, L. M. Montenegro, S. Fuller, C. Mascio, J. W. Gaynor, A. G. Yodh, J. Gebb, A. Vossough, G. H. Choi, M. E. Putt, Impaired Maternal-Fetal Environment and Risk for Preoperative Focal White Matter Injury in Neonates With Complex Congenital Heart Disease. *J. Am. Heart Assoc.* **12**, e025516 (2023).
13. S. P. Miller, P. S. McQuillen, Neurology of congenital heart disease: insight from brain imaging. *Arch. Dis. Child. - Fetal Neonatal Ed.* **92**, F435–F437 (2007).
14. M. Kehrer, G. Blumenstock, S. Ehehalt, R. Goelz, C. Poets, M. Schöning, Development of Cerebral Blood Flow Volume in Preterm Neonates during the First Two Weeks of Life. *Pediatr. Res.* **58**, 927–930 (2005).
15. A. Fudickar, S. Peters, C. Stapelfeldt, G. Serocki, J. Leiendecker, P. Meybohm, M. Steinfath, B. Bein, Postoperative cognitive deficit after cardiopulmonary bypass with preserved cerebral oxygenation: a prospective observational pilot study. *BMC Anesthesiol.* **11**, 7 (2011).

16. C. Ortinau, J. Beca, J. Lambeth, B. Ferdman, D. Alexopoulos, J. S. Shimony, M. Wallendorf, J. Neil, T. Inder, Regional alterations in cerebral growth exist preoperatively in infants with congenital heart disease. *J. Thorac. Cardiovasc. Surg.* **143**, 1264-1270.e2 (2012).
17. X. Miao, J. Liu, M. Zhao, Y. Cui, Z. Feng, J. Zhao, C. Long, S. Li, F. Yan, X. Wang, S. Hu, The influence of cardiopulmonary bypass priming without FFP on postoperative coagulation and recovery in pediatric patients with cyanotic congenital heart disease. *Eur. J. Pediatr.* **173**, 1437–1443 (2014).
18. A. E. Van Harten, T. W. L. Scheeren, A. R. Absalom, A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. *Anaesthesia* **67**, 280–293 (2012).
19. A. Dimitropoulos, P. S. McQuillen, V. Sethi, A. Moosa, V. Chau, D. Xu, R. Brant, A. Azakie, A. Campbell, A. J. Barkovich, K. J. Poskitt, S. P. Miller, Brain injury and development in newborns with critical congenital heart disease. *Neurology* **81**, 241–248 (2013).