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Original Article

Cognitive Functions in Children with D-Transposition of Great Arteries who underwent Senning Procedure: A Pilot Single Center Study

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Abstract:
Background: Dextro-transposition of the great arteries (D-TGA) is one of the common cyanotic congenital heart diseases, where aorta and pulmonary arteries arise from the right and left ventricle respectively. In 1958, Senning atrial switch operation was introduced for D-TGA. Long-term hemodynamic circulatory complications in D-TGA may present from cyanosis, preoperative hypoxia, post-operative techniques, which may impact neurocognitive development.
Aim of work: to assess cognitive function in children with D-TGA who underwent Senning atrial switch.
Subjects and Methods: This study included 29 children who were diagnosed as D-TGA and underwent Senning atrial switch procedure compared to 29 normal matched controls. Cognitive function was assessed using the Wechsler Intelligence Scale for Children (WISC IV).
Results: Those with D-TGA had lower total IQ than control group (mean ± SD was 75.44 ± 15.57 and 84.6± 9.2 respectively) (p= 0.005) and lower performance test scores (mean ± SD was 27.5 ± 11.1 and 37.7± 8.2 respectively) (p< 0.001). Ten (34.5%) patients had mild mental retardation (mean ± SD IQ score= 60.3± 5.02) and one (3.4%) had moderate mental retardation (IQ score= 48). The performance subtest scores; picture arrangement, block design and coding were statistically lower among those with D-TGA than the control group (p = 0.002, p=0.008 and p<0.001 respectively). Total verbal scores and verbal subtests scores of the cases was not different than the control group (p = 0.444).
Conclusion: This study highlights the significant cognitive challenges faced by children with D-TGA, particularly in non-verbal domains. While verbal abilities remained intact, total IQ and performance scores were significantly impaired in comparison to control group. The effect of Senning operative intervention on the cognitive functions, is not clear. These findings highlight the need for routine cognitive monitoring, tailored educational support, multidisciplinary care approach, as well as parental and caregiver education for D-TGA children.

Keywords: Dextro-transposition of the great arteries; D-TGA; Senning procedure; neurocognitive functions; Wechsler Intelligence Scale for Children IV
Abbreviations: D-TGA: dextro-transposition of the great arteries; IQ: intelligence quotient; MR: mental retardation; RVEDD: right ventricle end diastolic dimeter; TAPSE: tricuspid annular plane systolic excursion; WISC: Wechsler intelligence scale for children

Introduction

Dextro-transposition of the great arteries (D-TGA) is a cyanotic congenital heart disease which results in ventriculoarterial discordance and resultant parallel circulation of the systemic and pulmonary circuits. It is the second most common cyanotic congenital heart defect presenting in neonates, accounting for 5–7% of congenital cardiac malformations (*1*). Being cyanosed and critically ill, the neonate with D-TGA needs to be operated early in life. Atrial switch operation or Senning operation is a palliative surgery that was first performed in 1958 as a management for D-TGA before improvements in cardiopulmonary bypass that made arterial switch operation more feasible**.** Senning procedure directs the venous return to the contra-lateral atrioventricular valve and contra-lateral ventricle, using an atrial baffle derived from the septal tissue of the patient (*2*). The arterial switch operation is the current standard corrective procedure for patients with D-TGA without major pulmonary valve stenosis (*3*). Due to preoperative hypoxia and risk of cardiopulmonary bypass neurodevelopmental impairment is a common comorbidity associated with complex congenital heart diseases like TGA (*4*). Wechsler tests were first

described during the World War I in England to assess intelligence quotient (IQ) score. Since then, Wechsler test developed until it reached the version of Wechsler IV in 2003. Wechsler intelligence scale for children (WISC-IV) provides comprehensive evaluation of the global cognitive functions (*5*). We aimed to assess cognitive function in children with D-TGA who underwent Senning procedure.

Subjects and Methods

This study is a case-control study designed to assess the cognitive function in patients of D-TGA after Senning operation. The study was conducted at Cairo University Specialized Pediatric Hospital (CUSPH) over a 22-month period from 11/2021 to 8/2023. The Cairo University Higher Research Committee reviewed and approved the study protocol. The study was approved by the Research Ethical Committee of Faculty of Medicine, Cairo University (approval code: MS-248-2020), according to relevant guidelines and regulations. The study complied to the requirements of Revised Helsinki Declaration of Bioethics (2013) (*6*).

Participants

The study included 29 children with D-TGA who underwent Senning procedure. They were recruited from the post-operative cardiology clinic. Their ages were older than six years of age at the time of study to be able to comprehend the WISC-IV tests. Patients who had known hypoxic-ischemic insult or neurological deficit/ pathology like epilepsy prior to or after the surgical intervention were also excluded from the study. A control group was selected from the General Pediatrics Clinic, Cairo University Children Hospitals. The control group comprised 29 children matched with the study group regarding age and sex. Children in both groups attended school.

Methods

All patients underwent detailed history taking and clinical examination. The data collected from each patient included demographic data: age, sex, height and weight (with corresponding Z score), operative data (age at the time of Senning operation, preoperative Rashkind procedure), and basic cardiac examination which included NYHA classification for heart failure.

All patients underwent 12-lead ECG, and echocardiographic examination in a supine or left lateral position using General Electric Vivid 5 or 7 series system (General Electric Health Care company, USA) with 3S probe (multifrequency transducer). To indicate the start of the cardiac cycle, the ECG wire was attached to the ultrasound device. The following data were collected: measurement of tricuspid annular plane systolic excursion (TAPSE), right ventricle end diastolic diameter (RVEDD) and their corresponding Z- scores. Venous baffle leak or obstruction was also assessed (*7*).

Both case and control groups were evaluated using WISC-IV in the psychiatric outpatient clinic in Cairo University Children Hospitals. This evaluation assessed two main domains: verbal and performance tests. The time needed to accomplish the test is about 1 hour for each child. The scores from the subtests were collected to calculate the total IQ score for each child. The total IQ score ranges from below 20 (profound mental retardation) up to ≤130 (extremely high intelligence). Average IQ score range was 80-109, borderline IQ was 70-79, mild mental retardation (MR) range was 52-69, moderate MR range was 36-51, severe MR 21-35 (*8*).

The WISC-IV included validated verbal and performance function subtests in Arabic (*9*). The verbal function tests tested: a) Comprehension: items that required the child to describe what to do in specific situations. This assessed common sense, practical judgment, and the capacity to comprehend and adjust to social situations, b) Arithmetic: problems were given orally and were solved without paper and pencil. This test measured concentration and systematic problem-solving abilities, c) Similarities: the child was asked to explain the similarities between two provided items. This measured the child's capacity for comparison analysis, d) Vocabulary: words of increasing difficulty were presented orally and visually. The child was required to define the words. A score of 0-2 was given based on sophistication of definition. It measured the verbal knowledge and concept formation, and e) Digit span: which consisted of two parts, digits forward and digits backward. The child is required to repeat three to nine digits forward and two to nine digits backward. It measured short-term memory, attention, and concentration.

The performance function tests tested: a) Picture completion: several pictures, each having a missing part, were shown to the child. The child should be able to identify the missing part. This was used to measure the ability to observe details and recognize specific features of the environment, b) Picture arrangement: a partially filled grid was presented to the child who was asked to select the item that properly completes the matrix. The test measured fluid reasoning, c) Block design: the examiner's design or the design on the cards was matched by the child's

arrangement of the blocks. Each item received a speed score in addition to an accuracy score. This evaluated fluid intellect, spatial problem-solving skills, and manipulative talents, e) Coding: The child is given a key with symbols matched to common shapes (ages 6-7 years) or numerals 1–7 (ages 8 years and up). The child has 120 seconds to locate the appropriate symbol beneath each of the 90 numerals or shapes in a grid. This assesses motor coordination, visual-motor speed, and complexity, f) Object assembly: The child chose items that complement one another based on a fundamental idea from each of two or three rows of objects. This test assessed perceptual organization and flexible reasoning (*10*).

Statistical Analysis

Data were analyzed using IBM, SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). The mean and standard deviation (SD) of continuous numerical variables were displayed. The unpaired t-test was used to compare differences across groups. Fisher's exact test was used to compare the differences between the categorical variables, which were displayed as ratios, numbers, and percentages. Charts and graphs were prepared using SPSS programs. P-values less than 0.05 were considered statistically significant.

Results

This case-control study was conducted on 29 children with D-TGA who underwent Senning procedure between 2006 and 2023 and a matched control group regarding age, sex, and number. The cases comprised 21 males (72.4%) and eight females (27.6%). The mean ± SD age of the cases was 10.59 ± 2.92 years (range= 7 -16 years). Their mean ± SD height z-score was –1.35±1.6 (range= –5.10 - +2.70). Their mean ± SD weight Z-score was –1.14±1.96 (range= -1.6 to +3.3). The means ± SD of age, sex, height Z score and weight Z score matched with the control group (p=0.965, p=1, p=0.161, and p=0.072) respectively. They all underwent successful Senning operation. Their age at the time of Senning operation ranged between 9 – 78 months, (mean ± SD= 22.72±15.08 months), of them 25 (86.2 %) underwent pre-operative atrial balloon septostomy (the Rashkind procedure) (*11*), and 4 (13.8 %) did not undergo a pre-Senning procedure. The mean ± oxygen saturation of the cases before the Senning procedure was 79 ±4 %. All studied cases had normal neurological examination findings. Of those with D-TGA, 25 (86.2%) were NYHA class I (asymptomatic), and 4 (13.8%) were NYHA class II (they had dyspnea on moderate or prolonged exercise), all were on anti-heart failure medications. They all showed normal sinus rhythm on ECG during the serial follow up visits, and 3 (10%) had postoperative atrio-ventricular block, which required trans catheter permanent pacemaker placement, with no recorded complications related to pacemaker insertion. Echocardiography revealed no significant baffle leak or obstruction, and markedly reduced RV systolic function (TAPSE z-score of -7.04 ± 1.78) and significantly dilated RV (RVEDD z-score of +10.89 ± 2.23) in the those with D-TGA. (Table 2).

Table 1. Demographic data of studied groups

		D-TGA Group			Control Group			P value
		Number		%	Number		%	
Sex	Males	21		72.4	21		72.4	1
	Females	8		27.6	8		27.6	
		Mean	SD	Range	Mean	SD	Range	
Age(years)		10.59	2.92	7.00 – 16	10.55	3.00	6 to16	0.965
Height z score		– 1.35	1.60	– 5.10 – 2.7	–0.67	1.50	– 3.10 – 2.7	0.161
Weight z score		– 1.14	1.96	– 1.60 – 3.3	–0.68	1.37	– 3.5 – 1.96	0.072

D-TGA: dextro-transposition of great arteries; IQ: intelligent quotient; MR: mental retardation.

Table 2. Z-scores of TAPSE and RVEDD in those with D-TGA

	Mean ± SD	Range	Median
TAPSE Z-score	– 7.04 ±1.78	– 9.80 - -3.54	– 7.61
RVEDD Z- score	+10.89 ±2.23	+6.53 - +14.36	+11.28

D-TGA: dextro-transposition of great arteries; RVEDD: Right Ventricle End diastolic dimeter; TAPSE: tricuspid annular plane systolic excursion

The total IQ score of the cases was statistically lower than the control group (p=0.005). Only 13 (44.8%) had average IQ test score (range = 80-105; mean ± SD= 90.7± 8.6), 5 (17.2%) had

borderline IQ (range = 70-77; mean ± S =73 ± 2.6), 10 (34.5%) had mild mental retardation (range = 52-69; mean ± SD= 60.3±5.02), and one (3.4%) had moderate mental retardation (IQ score = 48). (Table 3 and Figure 1).

Table 3. IQ, verbal and performance subtests scores among studied cases and control group

	D-TGA group (Number= 29)		Control Group (Number= 29)		P value
	Mean	± SD	Mean	± SD	
Total IQ score	75.44	15.57	84.62	9.28	0.005
Total verbal score	38.34	11.91	40.38	7.69	0.444
Total performance score	27.55	11.09	37.72	8.17	<0.001
	Number	%	Number	%	
Average IQ score	13	44.8	22	75.8	0.0001
Borderline IQ	5	17.2	5	17.2	
Mild MR	10	34.4	2	6.89	
Moderate MR	1	3.4	0	0	

IQ: intelligence quotient; MR: mental retardation.

The total verbal tests scores among those with D-TGA was not different than among the control group (p = 0.444). Analysis of verbal subtests (comprehension, arithmetic, digital span, similarities, and vocabulary) showed no difference between the cases and control group (p= 0.783, p= 0.144, p= 0.208, p= 0.340, and p= 0.767 respectively). (Table 4). The scores of performance tests were found to be lower among those with D-TGA than the control group (p= <0.001). The cases had lower scores than the control group in picture arrangement, block design and coding tests (p =0.002, p= 0.008, and p= <0.001 respectively) but not in the picture completion and object assembly (p= 0.238 and p= 0.051 respectively). (Table 5).

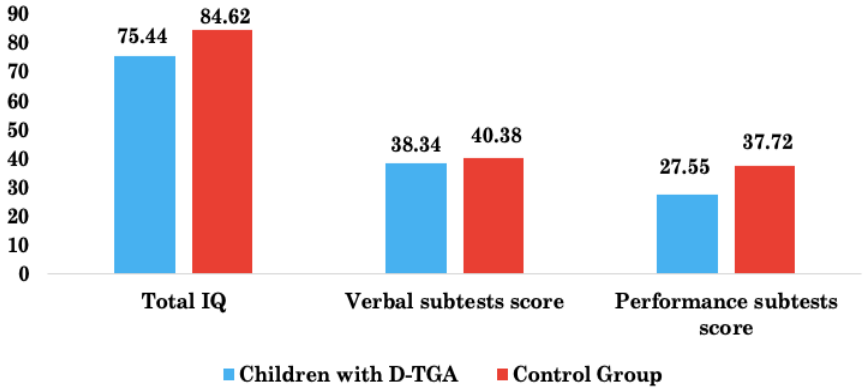

Figure 1. Total IQ scores of cases and control groups

Table 4. The verbal subtests scores in the studied groups

		Number	Mean	SD	P value
Verbal total score	D-TGA group	29	38.34	11.91	0.444
	Control group	29	40.38	7.69	
Comprehension	D-TGA group	29	7.28	3.06	0.783
	Control group	29	7.03	1.97	
Arithmetic	D-TGA group	29	7.69	3.13	0.144
	Control group	29	8.38	2.54	
Digital span	D-TGA group	29	6.72	2.28	0.208
	Control group	29	7.21	1.72	
Similarities	D-TGA group	29	8.79	3.27	0.340
	Control group	29	9.62	2.43	
Vocabulary	D-TGA group	29	7.86	3.90	0.767
	Control group	29	8.14	4.64	

D-TGA: dextro-transposition of great arteries

The total IQ, verbal and performance tests were not influenced by the age at operation (p= 0.229, p=0.233 and p=0.264 respectively), sex (p=0.49) or the Rashkind procedure (p= 0.972,

p=0.962 and p=0.985 respectively). There was no statistical difference between those in class I and class II NYHA in the total IQ, verbal tests, and performance tests (p= 0.434, p=0.555 and p=0.360 respectively). (Table 6).

Table 5. The performance subtests scores in the studied groups

		Number	Mean	SD	P value
Performance total score	D-TGA group	29	27.55	11.09	<0.001
	Control group	29	37.72	8.17	
Picture arrangement	D-TGA group	29	3.83	2.35	0.002
	Control group	29	5.83	2.22	
Picture completion	D-TGA group	29	7.48	3.42	0.238
	Control group	29	8.59	3.57	
Block design	D-TGA group	29	6.00	2.76	0.008
	Control group	29	7.79	2.16	
Object assembly	D-TGA group	29	3.79	2.41	0.051
	Control group	29	5.31	2.12	
Coding	D-TGA group	29	6.48	2.87	<0.001
	Control group	29	10.14	3.20	

D-TGA: dextro-transposition of great arteries

Table 6. Correlation between NYHA classifications and cognitive functions in the D-TGA cohort

	NYHA I		NYHA II		P value
	Mean	SD	Mean	SD	
Verbal tests	38.88	12.36	35.00	9.20	0.555
Performance tests	28.32	11.08	22.75	11.38	0.360
IQ total	67.20	22.34	57.75	19.91	0.434

IQ: Intelligence Quotient; NYHA: New York Heart Association classification

Discussion

With increased survival of children with D-TGA into adulthood, long-term neurodevelopmental and cognitive outcomes have become important areas of investigation. Senning operation is not commonly used in practice nowadays as more modern procedures have been developed like arterial switch techniques (*12*). However, we included only those who underwent Senning technique in our studied cohort underwent at our hospital at the time of surgery. Our studied cohort had lower IQ (p= 0.005) and lower scores in the performance subtests (p< 0.001) than the control group. The impairment in cognitive function in our studied cohort with D-TGA was not affected by the age at Senning operation (p= 0.229), sex (p= 0.49), pre-Senning atrial septostomy (p= 0.972), or NYHA class (p=0.434). Cognitive function in those with D-TGA may be influenced by multiple factors, including the period of preoperative hypoxia prior to surgery and surgical techniques which potentially result in neurodevelopmental delay during critical early years of life (*13*). We did not study the influence of surgical details or post-operative complications and hospital stay as it was beyond the scope of our current study. Yet, many factors could be responsible for this compromised cognitive function impairment, as the cyanosis early in life. Congenital heart defects are known to be associated with neurocognitive deficits that was attributed to the early deprivation from to normal oxygen levels and the stress associated with the surgery, leading to under achievement in areas such as attention, memory, executive functioning, and academic achievement (*14*).

In the performance subtests, those with D-TGA scored significantly lower in picture arrangement, block design, and coding compared to the controls (p= 0.002, p= 0.008, and p < 0.001 respectively). These tests measure fluid reasoning, spatial problem-solving, and motor coordination. This finding showed that children with D-TGA tend to mentally suffer more than those without TGA. It is important to highlight that the differences in object assembly and picture completion were not statistically significant (p= 0.051, and p=0.238 respectively), suggesting that certain aspects of perceptual reasoning may be relatively spared. On the other hand, verbal IQ scores were not significantly different between the two groups (p=0.444). This marked discrepancy between performance and verbal IQ scores indicates that verbal skills may be relatively preserved. This specific finding of affection of performance scores directs us for providing educational aids for children with D-TGA targeting improvement in non-verbal domains such as spatial reasoning and executive functions.

We are not aware if this cognitive impairment represents an improvement of the pre-existing

cognition as we did not assess the cognition of the children with D-TGA earlier in life, and we are not aware if the Senning procedure improved or worsened the cognition in these children as we did not assess the cognition among other cohorts with D-TGA who underwent other corrective surgeries.

The typical verbal function sparing while performance cognition is reported to be influenced by type of insult to the brain. Verbal skills, including language comprehension and production, are primarily controlled by areas like Broca's and Wernicke's areas in the left hemisphere (*15*). Executive functions, which are crucial for performance cognition (like planning, attention, and problem-solving), are often associated with the prefrontal cortex, which is more widespread and interconnected. Damage or dysfunction in the prefrontal cortex can impair performance cognition while leaving language functions mostly intact (*16*). Hypoxia is known to cause impairment of performance and executive functions (*13*), yet we did not perform objective imaging of the brain among our studied cohort, as it was beyond the scope of our study. Moreover, cyanosis is associated with polycythemia, which protects against tissue hypoxia.

As the early years of primary education allows the children to move to next academic year irrespective of academic achievement, we recommend the early screening of children with D-TGA as their intact verbal domains will mask their intellectual disabilities.

The lack of relationship between age at operation and cognitive scores, suggest that earlier surgery does not provide a cognitive advantage contrary to other studies that suggest that early surgical intervention may usually lead to better neurodevelopmental outcomes (*17*). Yet, the hypoxia, metabolic acidosis, stress of cardiopulmonary bypass machine, post-operative neurological sequelae should be all managed promptly and limited to save future cognitive functions of D-TGA survivors.

As a limitation of our study, the preoperative cognitive function prior to the Senning operation was not assessed to detect how much Senning operation affected the neurocognitive outcomes. Also, we did not study the cognitive functions of D-TGA patients after other arterial switch operations to test which provides the better cognitive outcome. We also did not assess hearing and vision functions in children with D-TGA to study other factors that affected their neurocognitive functions. The fact of the multifactorial etiology of cognitive neurodevelopment points to the importance of cooperation between pediatric cardiology and neuropsychiatric teams to improve cognitive functions of post Senning children. Finally familial support groups should be provided for post Senning families to provide psychological aid and to increase awareness to improve children quality of life.

Conclusion

This study highlights the significant cognitive challenges faced by children with D-TGA, particularly in non-verbal domains despite undergoing Senning operation early in life. While verbal abilities may remain intact, performance IQ, particularly in tasks requiring fluid reasoning and motor coordination, is significantly impaired. These findings highlight the need for routine cognitive monitoring, tailored educational support, interdisciplinary care approach, as well as parental and caregiver education for them. Further research is needed to explore the underlying mechanisms for neurocognitive delay and suggest different types of management depending on the severity of neurodevelopmental delay in children with D-TGA.

Author Contributions

All authors shared in the study and drafting. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

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

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