children

MDPI

Review

Dextro-Transposition of Great Arteries and Neurodevelopmental Outcomes: A Review of the Literature

Kalliopi Kordopati-Zilou [1,*], Theodoros Sergentanis [2], Panagiota Pervanidou [3], Danai Sofianou-Petraki [4], Konstantinos Panoulis [1], Nikolaos Vlahos [1] and Makarios Eleftheriades [1]

[1] "Maternal-Fetal Medicine" MSc, 2nd Department of Obstetrics and Gynecology, Aretaieio Hospital, School of Medicine, National and Kapodistrian University of Athens, 11528 Athens, Greece; kpanoulis@med.uoa.gr (K.P.); nikosvlahos@med.uoa.gr (N.V.); melefth@med.uoa.gr (M.E.)
[2] Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, 11528 Athens, Greece; tsergent@med.uoa.gr
[3] Laboratory of Developmental Psychophysiology and Stress Research, Unit of Developmental and Behavioral Pediatrics, First Department of Pediatrics, "Aghia Sophia" Children's Hospital, School of Medicine, National and Kapodistrian University of Athens, 11527 Athens, Greece; ppervanid@med.uoa.gr
[4] First Department of Pediatrics, "Aghia Sophia" Children's Hospital, School of Medicine, National and Kapodistrian University of Athens, 11527 Athens, Greece; danaisofianoupetraki@gmail.com
* Correspondence: kellykor@med.uoa.gr

Abstract: Background: Arterial switch operation (ASO) is the gold-standard surgical approach for dextro-transposition of the great arteries (D-TGA). It is performed during the neonatal period and has almost diminished the previously high mortality rate (from 90% if left untreated to <0.5%). Despite the impressively high survival rates, the surgical procedure itself—along with the chronic post-operative complications and the perinatal impaired cerebral oxygen delivery—introduces multiple and cumulative risk factors for neurodevelopmental impairment. Method: This study is a review of English articles, using PUBMED and applying the following search terms, "transposition of the great arteries", "neurodevelopment", "autism", "cerebral palsy", and "attention-deficit hyperactivity disorder". Data were extracted by two authors. Results: Even though general IQ is mainly found within the normal range, D-TGA children and adolescents display reduced performance in the assignments of executive functions, fine motor functions, attention, working memory, visual–spatial skills, and higher-order language skills. Moreover, D-TGA survivors may eventually struggle with inferior academic achievements and psychiatric disorders such as depression, anxiety, and ADHD. Conclusions: The existing literature concerning the neurodevelopment of D-TGA patients suggests impairment occurring during their lifespan. These findings underline the importance of close developmental surveillance so that D-TGA patients can better reach their full potential.

Keywords: dextro-transposition of great arteries; arterial switch operation; neurodevelopment; neurodevelopmental disorders

Citation: Kordopati-Zilou, K.; Sergentanis, T.; Pervanidou, P.; Sofianou-Petraki, D.; Panoulis, K.; Vlahos, N.; Eleftheriades, M. Dextro-Transposition of Great Arteries and Neurodevelopmental Outcomes: A Review of the Literature. *Children* **2022**, *9*, 502. https://doi.org/10.3390/children9040502

Academic Editor: Carl E. Stafstrom

Received: 7 January 2022
Accepted: 29 March 2022
Published: 2 April 2022

1. Rationale

Congenital heart defects (CHD) are the most frequent congenital anomalies, affecting millions of newborns every year. The incidence of severe CHD that require intensive medical/surgical intervention is nearly 2.5–3/1.000 live births [1]. Among this group, dextro-transposition of the great arteries (D-TGA) accounts for approximately 3% [2]. The gold-standard surgical approach of D-TGA is the arterial switch operation (ASO), which has decreased the mortality rate from 90% for unoperated patients to <0.5% for patients who undergo corrective surgery [3]. However, considerable adverse consequences arise, encompassing repercussions outside the cardiovascular system. Critical CHDs, such as TGA, have been related to neurodevelopmental (ND) impairments in the affected children, who experience varying degrees of morbidities within most ND domains that can be established during childhood and which persist throughout adult life [4–9].

A great effort has been made to clarify the nature of ND impairments in CHD patients. Academic underachievement, non-typical or delayed development, and behavioral adversities are morbidities found in this population [8]. Moreover, it is suggested that CHD children are at greater risk of social-cognitive and social-communication deficits as well as autism spectrum disorder [10,11]. There is a variety of factors that accumulate from the prenatal period until adulthood that have been associated with adverse ND outcomes of CHD survivors, including TGA population. Firstly, intraoperative conditions that lead to cerebral perfusion abnormalities have been suggested as the primary mechanism of ND development [12–14]. Growing evidence supports that anatomical and functional ND impairments are also present before surgery [7,15–19]. Specifically, MRI findings have indicated mild ischemic lesions, in the form of white matter injury similar to periventricular leukomalacia, on CHD neonates pre-operatively [18,20,21]. These findings have led to the last hypothesis that abnormal brain development and adverse ND outcomes derive from events in utero. Even though CHD fetuses present "brain-sparing" autoregulation, they may have lower cerebroplacental ratio (CPR) and middle cerebral artery (MCA) pulsatility index (PI) [22–25], which means impaired oxygen distribution to the brain, and progressively smaller gestational age- and fetal-weight-adjusted total brain volume throughout the third trimester [26].

2. Objectives

CHD group is typically reviewed as an entity, and in most cases, results are presented as a whole for this heterogeneous group of cardiac defects. Therefore, limited data exist regarding the impact of each CHD on ND. This review aims to examine the association of TGA on adverse ND outcomes.

A growing number of studies attempt to assess the performance of TGA survivors in each ND domain. Different validated scales are used mainly according to the region that the study is performed and the ND domain assessed. Furthermore, each study focuses on a specific age population. The heterogenous information concerning ND development of TGA survivors is not accurately stated. Thus, this review was performed in order to gather and summarize all the existing data and clarify which ND domains are found impaired and the manifestations within different age groups. In order to achieve that, we addressed the following questions, according to PICO: (1) What are the TGA survivors' neurodevelopmental impairments in different age groups? (2) Which validated neurodevelopmental (ND) scales are used? (3) Is there a discrepancy in the performance among TGA survivors and healthy peers? (4) Which particular domains are affected and what is the severity of the effect?

3. Materials and Methods

3.1. Eligibility Criteria

Population: D-TGA survivors of any age, with or without ventricular septal defect (VSD) or complex TGA, who were operated (ASO) in the neonatal period with deep hypothermia either with predominantly low-flow cardiopulmonary bypass (LFCPB) or with predominantly total circulatory arrest (TCA).

Intervention: Neurodevelopment of D-TGA survivors is evaluated by a variety of scales according to the neurodevelopmental domain assessed, age at time of the study, language, and region. Only studies using validated scales were enrolled in this review.

Outcomes: In order to be included, studies have to evaluate infants, children, or adolescents that had survived ASO, with a developmental scale appropriate for age, origin, and the developmental domains that needed to be assessed. These scales are interpreted by comparing the performance of patients to healthy peers. A study was excluded if it compared the scores of TGA patients to another group of CHD patients. Furthermore, trials that used other methods of ND evaluation, such as imaging tools or physical examination tests, were also excluded. We applied English as the language to include a study in the review.

3.2. Information Sources and Search Strategy

PUBMED was searched electronically on March 2021 utilizing a synthesis of relevant keywords and word variants for "transposition of the great arteries", "neurodevelopment", "autism", "cerebral palsy", and "attention deficit hyperactivity disorder". Reference lists of associated reviews and articles were searched by hand for additional reports.

3.3. Selection Process

Firstly, two authors independently searched the database and reviewed titles and abstracts. Subsequently, the two researchers screened full texts in order to define whether a study meets the inclusion criteria established by the PICO approach. In case of disagreement during the process, consensus was reached by discussion.

3.4. Data Collection Process

Two reviewers studied the papers independently and summarized the data on extraction forms designed a priori regarding study characteristics, design, and outcome. A consensus was reached among the reviewers by discussion whenever inconsistencies were raised.

3.5. Data Items

Any measure for each developmental domain (executive function, cognition, and adaptive function, speech-language and motor function, or neuropsychiatric domain) was eligible for inclusion. The scales used in each study should have evidence of validity. No restrictions were imposed according to the time of follow-up. In studies presenting outcomes for various CHDs, TGA measurements were isolated. In studies reporting multiple results, measurements were listed according to the ND domain assessed.

3.6. Effect Measures

Values were reported as mean SD for continuous variables. Data were reported as numbers and percentages of children affected for categorical variables and outcomes.

4. Results

The literature search provided 99 relative citations. Of these citations, 47 were excluded due to irrelevant titles or abstracts. No duplicates were discovered. Full manuscripts of 52 studies were retrieved. In the review, 24 studies were included according to the eligibility criteria. Of the 28 excluded studies, some used imaging tools or examination tests to evaluate neurodevelopment of TGA patients and others correlated the results among different CHD groups and not the mean population. Unpublished relevant studies were not retrieved (Figure A1).

Developmental outcome data were presented in a table by age group according to Erikson's Stages of Psychosocial Development [27]: infants (birth to ≤18 months), preschool (19 months–<5 years), school age (5–11 years), adolescents (12–18 years), and young adults (19–40 years) (Table A1).

- **Infants (birth to ≤18 months)**

McGrath et al. was the first one to publish outcomes concerning neurodevelopment in infants with D-TGA that survived surgery [28]. The evaluated population belonged to the Boston Circulatory Arrest Study (BCAS). The aforementioned trial is a longitudinal prospective study that followed up 171 D-TGA patients who underwent ASO, from infancy to adolescence. Thus, it has offered the population base for many studies concerning D-TGA survivors. In the McGarth et al. study, 135 patients were estimated with Bayley Scale of Infant Development (BSID) and Fagan Test of Infant Intelligence at one year of age. Twelve (9%) children had Mental Developmental Index (MDI) scores ≤ 84, 28 (21%) children had Psychomotor Developmental Index (PDI) scores ≤ 84, and 23 (23%) children had novelty preference scores < 53% [28].

Park et al. followed up with 10 infants at 11–13 months of age using BSID II. Five infants of the studied population were diagnosed with mild and one with severe mental development delay. Furthermore, three infants were found with mild and one with severe psychomotor development delay [29]. The small sample size should be noted.

Andropoulos et al. included 20 patients that returned for 12 months of neurodevelopmental follow-up [30]. The results illustrated that cognitive, language, and motor score means were 0.3 SD, 0.67 SD, and 0.5 SD above reference population norms, respectively. Performance on adaptive-behavioral parameters of the Bayley Scales III, that were retrieved from the parental questionnaire, was 0.1–0.5 SD below norms for all scores, except from the practical one [30].

On the contrary, Lim et al. when evaluating 24 D-TGA survivors at the age of 18 months with BSID III, did not detect any different scores between the study group and mean population [31].

- Early childhood and pre-school (19 months–<5 years)

From the studies selected for this review, the oldest entry belongs to Mendoza et al. [32]. In this study, 24 patients at the age of 1 to 5 years old were assessed with the Bayley Scales of Infant Development, for children up to 2 years, the Stanford-Binet Intelligence Scale and Denver Developmental Screening Test, for patients older than 2 years. The neurodevelopmental follow-up exhibited normal scores ($\geq$84 or <1 SD below the mean) in 18 (75%) of the patients. Only three patients were estimated as dubious, with scores ranging from 68 to 83 (between 1 and 2 SDs below the mean). Additionally, three had scores below 68 (>2 SDs below the mean) and were considered to have abnormal neurodevelopment.

Similarly, all included studies concerning this age group [33–36], except Bellinger et al. [37], demonstrated that the mean IQ of D-TGA survivors was within the normal range. As far as visual–motor integration is concerned, Bellinger et al. and Ellerbeck et al., contrary to Hövels-Gürich et al. and Neufeld et al., suggested that it differed significantly between the patients and the mean population of the same age [33,34,36,37]. In the Bellinger et al. study, expressive language, motor function, and oromotor control were significantly affected [37]. Contrariwise, three other studies in this age group indicated that complete developmental scores did not vary from those of healthy peers [33,35,36].

- School age (5–11 years)

The studies reviewed for this specific age group concluded in the same outcome. General IQ of school-age children with TGA is not found decreased compared to the mean population of the same age. Hövels-Gürich et al. presented midterm results of cognitive and motor development in children at a mean age of 5.4 years and 10.5 years after neonatal ASO performed between 1986 and 1992 with combined DHCA and low-flow CP, respectively [38,39]. They indicated reductions in vocabulary, fine and gross motor functions, and acquired abilities.

In the same way, Calderon et al. conducted two different studies with children of school age in order to assess executive functions (cognitive and response inhibition, verbal and spatial working memory, and planning) [40,41]. It became evident that D-TGA survivors carried significant impairments in inhibition and cognitive flexibility despite normal working memory.

Karl et al. identified an increased risk of parent-reported psychosocial maladjustment in children with D-TGA, as well as teacher-reported various speech and expressive language problems and minor behavioral problems [42].

Bellinger et al., at eight years assessment of the BCAS, identified that mean scores of most ND scales were within the normal range [43]. However, neurodevelopmental status was found impaired in many aspects, including academic achievement, working memory, hypothesis-generating, sustained attention, fine motor function, visual–spatial skills, testing, and higher-order language skills.

- Adolescents (12–18 years)

Eight of the 24 studies included in this review focused on the neurodevelopmental outcomes during adolescence [44–51]. The main domains of interest appeared to be psychosocial functioning and cognition of D-TGA survivors. Specifically, three of the studies illustrated that these adolescents are at greater risk of developing symptoms within the clinical range of attention-deficit/hyperactivity disorder (ADHD) during their lifespan, although the difference to the mean population was not always statistically significant [45,50,51]. In addition, inconsistent results were reported when using parent- and self-reports tools for psychiatric symptoms' assessment [45,46]. Demaso et al. revealed that depressive, anxiety, and post-traumatic stress symptoms were more frequent within the D-TGA group, whereas Heinrichs et al. suggested significantly reduced psychosocial distress level, as more than two-thirds of the patients estimated their condition within the normal range.

Regarding cognition, deficits in overall memory abilities were illustrated [44,47,49]. General intelligence of TGA adolescents was not found impaired compared to population norms [46,49]. Regarding academic attainments, Muñoz-López et al., contrary to Bellinger et al., reported that they were within the normal range [44,49]. Focusing on executive function, greater odds of impairment were outlined in letter fluency [48,49].

- Young adults (19–40 years)

While searching for studies dealing with neurodevelopment in young adulthood, only one emerged [52]. Kasmi et al. explored neurocognitive and psychiatric outcomes in D-TGA patients corrected by ASO, using a variety of tests for both domains. Adults with D-TGA displayed significantly poorer performances in tasks assessing memory, visual–spatial skills, executive functions, and attention (all $p < 0.05$). Furthermore, patients presented increased prevalence of depression ($p = 0.008$) and anxiety disorders ($p = 0.025$) throughout their lifetime.

5. Discussion

The findings of this review regarding the first age group suggest that D-TGA infants who survived ASO do not consistently present neurodevelopmental impairment. We have demonstrated that most studies regarding this age group reveal both Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) to fall within the normal range [28,30,31]. Only one of the four studies identified lower MDI and PDI scores, but no statistical significance was mentioned [29]. The small size of the cohort in most cases should be noted since it confines the strength of the results [29–31]. Homogeneity in the assessment scale was observed only in this particular age group. All studies evaluated patients with the Bayley Scale of Infant Development.

The authors attempted to associate specific parameters to lower ND scores. Andropoulos et al. suggested that risk factors include preoperative MRI brain injury, preoperative and intraoperative cerebral oxygen saturation, total bypass time, and total midazolam dose [30]. Park et al. exploited proton magnetic resonance spectroscopy to measure the cerebral metabolism of TGA infants and attempted to correlate the abnormal findings to ND outcomes [29]. Lim et al. highlighted the negative impact of surgery beyond two weeks of age on brain growth and language development in infants with TGA [31]. Lastly, McGrath et al. tried to evaluate whether test scores of CHD patients in infancy are predictive of ND status at school age. They suggested that the association between test scores at one and eight years is modest and many children who are at risk of poor late outcomes will not be identified based on 1-year test scores [28].

Following the next age group, general IQ scores of pre-school D-TGA survivors were also mainly found within the normal limits. In this age group, we came across a great paradox. The study of Bellinger et al., which included the 158 children of the Boston Circulatory Arrest Trial, concluded significant impairments in the neurodevelopment of D-TGA survivors [37]. At the same time, most of the remaining studies did not meet statistical

significance for the same neurodevelopmental domains [33–35]. The consensus was only met between Ellerbeck et al. and Bellinger et al. concerning language and visual–motor integration [34,37]. Neufeld et al. showed that the rate of autism in the group of pre-school children was unexpectedly high, roughly 10 times higher than current prevalence estimates of 6 per 1000 [36].

As far as risk factors are taken into account for the specific age group, familial predisposition should be taken into consideration [34,36]. Patients with low neurodevelopmental scores were prone to abnormalities on CT scans of the brain, head circumference less than the fifth percentile, and emergency switch operation or emergency balloon atrial septostomy [32]. Neonatal ASO with combined circulatory arrest and LFCPB was associated with neurological morbidities but not with decreased general IQ. Other potential modifiable variables constitute high plasma lactate levels preoperatively [36].

When estimating the results of school-aged children, someone expects to find consistency with the results of pre-school children, as many studies were conducted longitudinal in the same sample. Specifically, Hövels-Gürich, Bellinger, and Calderon examined the same group of children throughout their lifespan [38–41,43]. Bellinger's results did not meet an agreement as he issued impaired general intelligence at four years of age and normal average IQ in the same children at eight years [35,40]. Calderon et al., focusing on executive function, displayed adverse scores in cognitive inhibition and cognitive flexibility, that persisted from ages 5 to 7, as well as frustration planning a strategy to achieve a goal, i.e., anticipating the correct number of actions to reproduce a visual model [40,41]. Executive function impairments seemed to have an early onset during the pre-school years. A significant proportion also struggled to determine the emotional and cognitive states of others (Theory of Mind deficits). Hövels-Gürich et al. demonstrated accordance among their results at 5.4 and 10.5 years [38,39]. Both studies concluded with findings of poorer motor functions, language skills, and acquired abilities within D-TGA patients. The rate of adverse outcomes at school age (55%) was twice the rate at age 5 (26%), a fact that supports the presumption that these children may straggle more as they grow older in particular abilities.

To our knowledge, adolescents with D-TGA constitute the most evaluated age group since we retrieved eight manuscripts concerning neurodevelopmental impairments that emerge during adolescence. Generally, lower than anticipated scores were found in academic achievements, visuo-spatial skills, memory, psychosocial, and executive functions. Two studies also identified a higher rate of internalizing (i.e., anxiety, somatic complaints, depressive symptoms) and externalizing problems on both parent and self-report measures [44,45].

Psychosocial and ADHD sequelae are a matter of great concern in CHD population in general. Even though no statistical significance was consistently met, it appears that TGA survivors should be closely monitored as they found themselves at risk of these conditions. Taking into consideration the BCAS, 16-year-olds with TGA were more prone than the control group (35% versus 20%) to a lifetime psychiatric diagnosis when assessed with the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS) [44]. As for ADHD, it was suggested that adverse psychosocial status in adolescence was highly predicted by attention deficits at age 8 years [50]. Therefore, specially designed studies that focus on the treatment of childhood ADHD are needed in an effort to promote adolescents' well-being. Demaso et al. proposed primary care clinicians and cardiologists consider psychotropic medication as a treatment option, given the high rates correlated to D-TGA, the efficacy of stimulants, and the reported tolerability of these medications in children with CHD [45].

Efforts to identify prognostic factors of ND impairments have also been identified in these age group studies. Specifically, while extracting the results from Muñoz-López et al., we came across the attempt to correlate the degree of memory impairment to the degree of hippocampal atrophy [49]. Although cyanosis occurred in all of the children, only a small proportion had detectable hippocampal pathology. No other structure can fully compensate

for hippocampal injury, even as early as neonatal life, and its unique role in serving episodic long-term memory is to be investigated. Moreover, according to Heinrichs et al. 32% of the D-TGA presented with moderate or severe structural brain abnormalities in magnetic resonance imaging [46]. Periventricular leukomalacia was demonstrated in >50% and the severity of the impairment was linked to the grade of neurologic morbidity. The last one was significantly correlated with decreased intelligence, orthography, and analytical thinking.

The majority of the studies established explicit neuropsychological weaknesses in children with TGA and recommended the utilization of tailored programs of interventions. Academic problems, along with long-term neuropsychological sequelae, might be mitigated over a D-TGA patient's lifetime by the incorporation of these programs. Continuous surveillance of D-TGA survivors, as well as further research on neurobiological and psychological mechanisms of impairment, are needed to help fill gaps in our knowledge.

Our study should be perceived along with its limitations. Most of them are induced by a possible selection bias. The studies included in this review present heterogeneity among cohort characteristics, assessment tools, age of TGA patients, and rate of follow-up. Furthermore, a discrepancy is found among the types of studies themselves, including cohort, case-control, and observational. We should underline the restricted strength of the observational studies. Moreover, many studies' outdated operative/perioperative strategies constitute a confounding factor so that current cohorts of TGA survivors could benefit from advanced surgical and medical intervention.

6. Conclusions

The existing literature suggests neurodevelopmental impairment of D-TGA patients occurring during their lifespan. New advanced technologies may eliminate operative risks and achieve a better understanding of the underlying mechanisms. These data emphasize the importance of close developmental surveillance starting early in life in order to best help D-TGA patients to reach their full potential.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

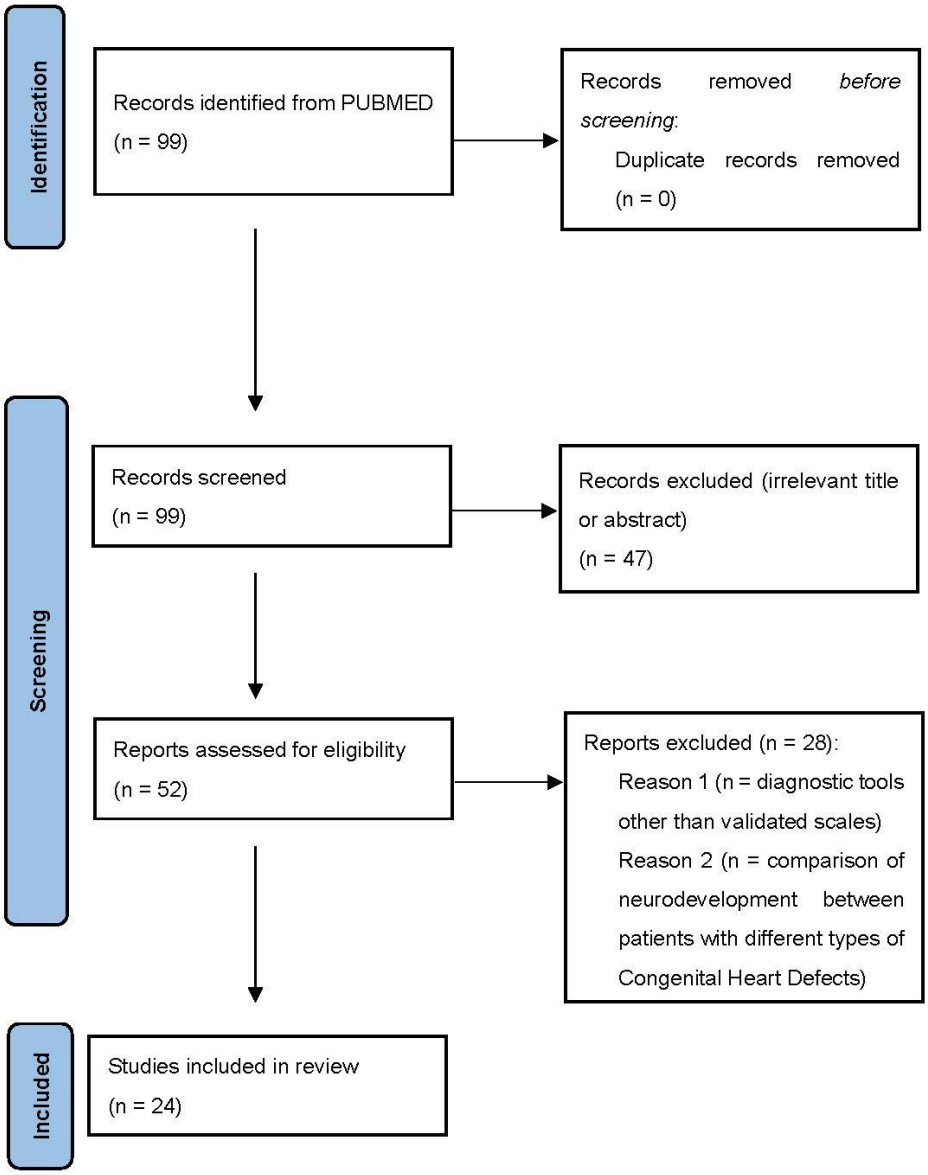

Figure A1. Diagram for the review examining the neurodevelopmental outcomes of D-TGA survivors.

Table A1. The table displays—for each included study—the citation, incident cases, mean age and characteristics of the population, definition/features of TGA patients, definition/features of the assessment methods of neurodevelopment, and outcomes. Studies are sorted by the age of the population included.

Study	Incident Cases	Age	Populations' Characteristics	Definition/Features of TGA Patients	Definition/Assessment Method of Neurodevelopmental Outcomes	Outcomes
McGrath (2004) [28]	135	1 year	The Boston Circulatory Arrest Study	Eligibility criteria: D-TGA with IVS or VSD, repair by 3 months of age and coronary artery anatomy suitable for the ASO. Exclusion criteria: birth weight <2.5 kg, known syndrome of congenital anomalies, associated extra cardiac anomaly of greater than minor severity, previous cardiac surgery, and associated cardiovascular anomalies that require surgical procedures.	1 year assessment: 1. Bayle Scale of Infant Development (PDI: Psychomotor Development Index, MDI: Mental Developmental Index) 2. Fagan test of Infant Intelligence	-12 (9%) children with MDI scores $\leq$ 84; -28 (21%) children with PDI scores $\leq$ 84; -23 (23%) children with novelty preference scores < 53%
Park (2006) [29]	10	1 year	Full-term newborns with TGA-IVS	Eligibility criteria: post conceptional mean age 40 weeks, mean body weight 3.2 kg, mean height 51.1 cm, mean head circumference 34.1 cm, mean blood oxygen saturation 47.5%, atrial septostomy and prostaglandin E1 infusion. Exclusion criteria: prematurity (<38 weeks), associated anomalies, abnormal brain MRI, neurologic complications before or after surgery, prolonged preoperative hypoxemia, non cardiac complications, poor general condition, and any other major post operative complications.	Bayle Scale of Infant Development II	-5 children with mild and 1 children with severe mental development delay; -3 had mild and 1 had severe psychomotor development delay
Andropoulos (2012) [30]	20	12 months	Neonates with D-TGA underdoing ASO	Eligibility criteria: <30 days of age. Exclusion criteria: Gestational age <35 weeks at birth, weight < 2 kg, recognizable dysmorphic syndrome, pre-operative cardiac arrest for greater than 3 min.	Bayle Scale of Infant and Toddler Development Third Edition, parental questionnaires.	-All scores fall within the normal range -Cognitive Score mean: 0.3 SD above reference population norms; -Language Score median: 0.67 SD below norms; -Motor Score mean 0.5 SD below norms; -Adaptive-behavioral parameters of the Bayley Scales III derived from parental questionnaire: 0.1–0.5 SD below population norms, except Practical Score
Lim (2019) [31]	24	18 months	TGA patients operated between 2013 and 2017	The median gestational age at birth was 39 (35–41) weeks, and the mean birth-weight was 3.4 $\pm$ 0.5 kg. 11 of 45 patients (24%) had VSDs. Patients were divided into those undergoing surgery during the first 2 weeks of life (32/45) versus those being repaired later (13/45). Exclusion criteria: double-outlet right ventricle and outflow tract or aortic arch obstruction, clinical features of a genetic syndrome or genetic testing confirming a syndrome.	Bayle Scale of Infant and Toddler Development Third Edition	Normal range scores for all patients

Table A1. *Cont.*

Study	Incident Cases	Age	Populations' Characteristics	Definition/Features of TGA Patients	Definition/Assessment Method of Neurodevelopmental Outcomes	Outcomes
Bellinger (1999) [37]	158	4 years	The Boston Circulatory Arrest Trial	Eligibility criteria: D-TGA with IVS or VSD, repair by 3 months of age and coronary artery anatomy suitable for the ASO. Exclusion criteria: birth weight < 2.5 kg, known syndrome of congenital anomalies, associated extra cardiac anomaly of greater than minor severity, previous cardiac surgery, and associated cardiovascular anomalies that require surgical procedures.	Wechsler Preschool and Primary Scale of Intelligence–Revised, Peabody Developmental Motor Scales, Grooved Pegboar, Language: Test for Auditory Comprehension of Language, Receptive One-Word Picture Vocabulary Test, Expressive One-Word Picture Vocabulary Test, Grammatic Closure subtest of the Illinois Test of Psycholinguistic Abilities, Speech: Oral and Speech Motor Control test, Mayo Tests for Apraxia of Speech and Oral Apraxia-Children's Battery, Goldman-Fristoe Test of Articulation	Results for general intelligence (IQ), expressive language, visual–motor integration, motor function, and oromotor control in the full cohort were significantly below population means ($p < 0.001$)
Hovels-Gurich (2001) [33]	33	3–4.6 years	D-TGA patients who underwent ASO between January 1994 and December 1995	72.8% with simple TGA, 12.1% with an unimportant VSD, 12.1% with VSD closed during the ASO, and 3% had a coarctation of the aorta corrected at a later date.	Vienna Developmental Test, consists of a complete developmental score including 6 subscores consisting of 14 subscales in total	-Complete developmental score: normal in 87.9% and reduced below the SD in 6.5% of 31 patients; -Motor score: normal in 98.7%, visual perception and visual motor integration: in 89.5%, learning and memory: in 96.7%, cognitive score, language, and socioemotional score in 100% of the tested patients; -All standardized developmental test results did not differ statistically from published age-matched normal children
Mendoza (1991) [32]	24	5 years	TGA patients who underwent ASO within the first year of life	Mean GA of infants 39.8 weeks, mean birth weight 3.480 g, weight/length/head circumference within normal for GA at birth, 27 simple TGA, 6 TGA with VSD.	Bayle Scale of Infant Development for patients up to 2 years of age, Stanford-Binet Intelligence Scale, and Denver Developmental Screening Test for those >2 years old	-18 (75%) with normal scores (≥84 or <1 SD below the mean); -3 with scores from 68 to 83 (between 1 and 2 SDs below the mean); -3 with scores below 68 (>2 SDs below the mean), considered to be abnormal neurodevelopmentally
Hovels-Gurich (1997) [39]	77	5.4 years	D-TGA patients who underwent ASO between March 1986 and February 1982	Mean birth weight 3.49 kg, 71.4% with simple TGA, 9.5% with an unimportant VSD, 3.9% with VSD closed during the ASO, and 5.2% had a coarctation of the aorta corrected at a later date.	Kiphard and Schilling Body Coordination Test (motor quotient, MQ), Kaufman Assessment Battery for Children (IQ, language), Denver Developmental Screening Test, parts of the Frostig Developmental Test of Visual Perception	-General Intelligence was not different in patients compared with normal children (p= 0.11); -Motor function (p = 0.01), vocabulary (p = 0.04), and acquired abilities (p = 0.005) were poorer

Table A1. *Cont.*

Study	Incident Cases	Age	Populations' Characteristics	Definition/Features of TGA Patients	Definition/Assessment Method of Neurodevelopmental Outcomes	Outcomes
Brosig (2007) [35]	13	6 years	D-TGA patients who underwent ASO	Eligibility criteria: Preschool age (3–6 years), English speaking. Exclusion criteria: major congenital anomalies, medical condition/treatments that impact development, prematurity, low birth weight, complex TGA.	McCarthy Scales of Children's Abilities, Woodcock Johnson III Tests of Achievement, Developmental Test of Visual–motor Integration, Receptive One-Word Vocabulary Test, Expressive One-Word Vocabulary Test, and Child Behavior Checklist.	IQ score = 110.5 SD (p = 0.77), Motor scale = 50 SD (p = 0.038), Picture vocabulary test = 104 SD (p = 0.0025), Attention problems = 50 SD (p = 0.49), Externalizing problems = 42.5 SD (p = 0.026), Total behavior problems = 42 SD (p = 0.042),No statistical significance
Neufeld (2008) [36]	65	6 years	Neonates who underwent ASO for repair of TGA from Sept 1996 to May 2003.	Based on the complexity of cardiac anomalies children were divided into three groups. Group A:TGA-IVS, Group B:TGA-VSD, Group C: Complex TGA.	Wechsler Intelligence, Scale for Children-Third Edition (WISC-III), Beery-Buktenica Developmental Test of Visual–Motor-Integration Fourth Edition, Autism Diagnostic Observation Schedule.	-2 children with cerebral palsy; -7 with language disorders, 4 of whom met the criteria for autism spectrum disorders; -61 children without autism with scores approaching those of peers (FSIQ mean = 96 SD, VMI = 95 SD)
Calderon (2014) [41]	45	5–7 years	TGA requiring ASO under cardiopulmonary bypass (CPB)	Exclusion criteria: requirements for deep hypothermic circulatory arrest, birth-weight less than 2500 g, presence of genetic syndromes, complex associated cardiovascular anomalies or extra-cardiac pathologies, additional surgical procedures.	Columbia Mental Maturity Scale, Comprehension subtest from the NEPSY, digit span, spatial span, the hand game, hearts and flowers incongruent and mixed conditions, day and night, animal Stroop test, dimensional change card sorting test	-Children with TGA did not significantly differ from comparison children in age and non-verbal IQ at all time points; -Receptive language scores ("comprehension of instructions" NEPSY subtest) and verbal short-term memory scores (Digit Span Forwards) were significantly lower; -Visuospatial short-term memory scores did not significantly differ between the groups; -Persistent impairments in cognitive inhibition and cognitive flexibility from ages 5 to 7
Calderon (2010) [40]	21	7.4 years	TGA with IVS or VSD who underwent ASO between January 2001 and April 2002, using continuous full-flow cardiopulmonary bypass	Eligibility criteria: French as a first language, geographic location (region of Paris). Exclusion criteria: birthweight less than 2.5 kg, presence of genetic syndromes (including 22q11 deletion), associated extracardiac anomaly, associated cardiovascular anomalies requiring aortic arch reconstruction, use of deep hypothermic circulatory arrest or additional open surgical procedures.	Columbia Mental Maturity Scale, animal Stroop test, statue subtest from the NEPSY, Tower of London, digit span, Corsi block-tapping task, false belief tasks (first and second order)	-General IQ was within the normal range in both the TGA group and the comparison group (mean IQ 113 (SD 9.3) and 118 (SD 10.1)); -Performance on all executive functions and on ToM (first and second level) was significantly lower in the TGA group (p values of 0.02, 0.01, and 0.004 respectively)

Table A1. *Cont.*

Study	Incident Cases	Age	Populations' Characteristics	Definition/Features of TGA Patients	Definition/Assessment Method of Neurodevelopmental Outcomes	Outcomes
Bellinger (2003) [43]	155	8 years	The Boston Circulatory Arrest Study	Eligibility criteria: D-TGA with IVS or VSD, repair by 3 months of age and coronary artery anatomy suitable for the ASO. Exclusion criteria: birth weight < 2.5kg, known syndrome of congenital anomalies, associated extra cardiac anomaly of greater than minor severity, previous cardiac surgery, and associated cardiovascular anomalies that require surgical procedures.	General Intelligence: Wechsler Intelligence, Scale for Children-Third Edition (WISC-III), Academic achievement: Wechsler Individual Achievement Test (WIAT), Adaptive Fucntioning scales of the Teacher Report Form, parent completed Child Behaviour Checklist/4-18, Neuropsychologic status: Wide Range Assessment of Memory and Learning (screener), Wisconsin Card Sorting Test, Developmental Test of Visual–Motor Integration, Third Revision, Trail-Making Test-Intermediate Version, Rey-Osterrieth Complex Figure (copy condition), Grooved Pegboard, Formulated Sentences subtest of the Clinical Evaluation of Language Fundamentals—Third Edition, Controlled Oral Word Association Test, Verbal Fluency subtest of the McCarthy Scales, Test of Variables of Attention, version 6.0.8, Speech: Mayo Test for Apraxia of Speech and Oral Apraxia-Children's Battery, Oral and Speech Motor Control Test, Goldman-Fristoe Test of Articulation, Auditory Closure subtest of the Illinois Test of Psycholinguistic Ability, Test of Auditory Analysis	-Mean scores on most outcomes were within normal limits; -Academic achievement, fine motor function, visual–spatial skills, working memory, hypothesis generating and testing, sustained attention, and higher-order language skills were lower than expected
Ellerbeck (1998) [34]	57	8.2 years	The Baltimore-Washington Infant Study	Patients with D-TGA with or without VSD, patent foramen ovale, atrial septum defect or pulmonic stenosis with two ventricles and two atrioventricular valves, registered into Baltimore-Washington Infant Study.	Stanford–Binet Intelligence Scale (IQ), Early Developmental Profile of the Woodcock-Johnson Psychoeducational Battery-Revised, Developmental Test of Visual Motor Integration (VMI), Achenbach Child Behavior Checklist	-Mean IQ: no significant difference between D-TGA and control group ($p = 0.14$); -VMI: significant difference ($p < 0.001$);-Letter-word identification test ($p = 0.005$);-Child Behavior Checklist ($p = 0.004$)

Table A1. *Cont.*

Study	Incident Cases	Age	Populations' Characteristics	Definition/Features of TGA Patients	Definition/Assessment Method of Neurodevelopmental Outcomes	Outcomes
Karl (2004) [42]	74	109 months	D-TGA–IVS patients who underwent ASO between 1988 and 1994 at a median age of 9 days	Eligibility criteria: Mean gestational age was 39.6 weeks, mean weight at the time of ASO 3.42 kg. Exclusion criteria: complex forms of TGA.	Achenbach Child Behavior Checklist, Teacher Report Form, Movement Assessment Battery for Children, Wechsler Preschool and Primary Scale of Intelligence (WPPSI) or Wechsler Intelligence Scale for Children Third Edition (WISC III), neurologic evaluation	-Full-scale IQ scores (WPPSI, WISC III) where higher in control subjects ($p = 0.0007$) with both groups having scores greater than the population based test means; -Patients had higher motor impairment scores ($p = 0.0004$); -Parents assigned higher total social behavioral competence scores to control subjects; -Teachers suggested that patients were more likely to have speech and expressive language problems as well as minor behavioral problems
Hovels-Gurich (2002) [38]	60	10.5 years	D-TGA patients who underwent ASO between March 1986 and February 1982	Mean birth weight 3.49 kg, 71.4% with simple TGA, 9.5% with an unimportant VSD, 3.9% with VSD closed during the ASO, and 5.2% had a coarctation of the aorta corrected at a later date.	Kiphard and Schilling Body Coordination Test (motor quotient, MQ), Kaufman Assessment Battery for Children (IQ, language), oral and speech motor control test, Mayo tests of speech and oral apraxia, Illinois test of psycholinguistic abilities, test of auditory analysis skills	-Neurologic and speech impairments were evidently more frequent (27% and 40%, respectively) than in the general population; -Intelligence was not different ($p = 0.29$); -Motor function, acquired abilities, and language were significantly reduced ($p = 0.04$ for each)
Munoz-Lopez (2017) [49]	40	8–16 years	TGA patients who underwent ASO	Inclusion/exclusion criteria: (1) 8–16 years of age at the start of the study; (2) no overt neurological impairment or diagnosis of motor or epileptic disorder, nor learning, or cognitive difficulties; (3) free of genetic syndromes; (4) native English speakers residing in the UK. Of the final sample of 40 patients, 10 had VSD and 30 had IVS.	Children's Memory Scale (CMS), Rivermead Behavioral Memory Test (RBMT-II), Child Behavior Checklist, Wechsler Intelligence Scale for Children–Version IV (WISC-IV), Wechsler Individual Achievement Test-II (WIAT-II), Delis-Kaplan Executive Function System	-Same level as the normal population on the measures of intelligence, academic attainments, and verbal fluency (with one exception: processing speed); -Lower than control population at processing speed ($p = 0.001$), letter fluency ($p = 0.005$), general memory (MQ) ($p = 0.025$), visual delayed memory ($p = 0.01$), verbal immediate memory ($p = 0.024$), verbal delayed memory ($p = 0.01$), delayed recognition ($p = 0.04$), and episodic memory ($p < 0.001$)

Table A1. *Cont.*

Study	Incident Cases	Age	Populations' Characteristics	Definition/Features of TGA Patients	Definition/Assessment Method of Neurodevelopmental Outcomes	Outcomes
Holst (2020) [51]	46	13 years		Inclusion criteria: surgically corrected TGA in Denmark, 10–16 years, Danish-speaking parents. Exclusion criteria: presence of syndromes, genetic, or neurological abnormalities or other chronic diseases.	Attention-Deficit/Hyperactivity Disorder-Rating Scale (parent and school teacher), Pediatric Quality of Life (PedsQLTM) version 4.0	Children with TGA presented a markedly higher inattention symptom load and almost twice as many children with TGA (15%) were in the clinical range of attention-deficit/hyperactivity disorder symptoms compared to the controls, although the difference was not statistically significant
Cassidy (2015) [48]	139	14–16 years	The Boston Circulatory Arrest Study	Eligibility criteria: D-TGA with IVS or VSD, repair by 3 months of age and coronary artery anatomy suitable for the ASO with either DHCA or LFBP. Exclusion criteria: birth weight < 2.5 kg, known syndrome of congenital anomalies, associated extra cardiac anomaly of greater than minor severity, previous cardiac surgery and associated cardiovascular anomalies that require surgical procedures.	Delis-Kaplan Executive Function System (D-KEFS), questionnaire data from the Behavior Rating Inventory of Executive Function (BRIEF)	Greater odds of impairment in the domain of letter fluency ($p < 0.001$), Cat. switch correct ($p = 0.002$), TCC ($p = 0.001$), design fluency test/ empty dots ($p = 0.004$), sorting test ($p < 0.001$)
Cassidy (2017) [47]	139	14–16 years	The Boston Circulatory Arrest Study	Eligibility criteria: D-TGA with IVS or VSD, repair by 3 months of age and coronary artery anatomy suitable for the ASO with either DHCA or LFBP. Exclusion criteria: birth weight < 2.5 kg, known syndrome of congenital anomalies, associated extra cardiac anomaly of greater than minor severity, previous cardiac surgery, and associated cardiovascular anomalies that require surgical procedures.	Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version (K-SADS-PL), Children's Memory Scale	-Immediate and delayed visual–spatial memory deficits; -Immediate and delayed verbal memory was relatively preserved; -Although overall verbal learning and memory abilities were significantly lower than expected population means, the weaknesses were modest in magnitude
Belliinger (2011) [44]	139	16 years	The Boston Circulatory Arrest Study	Eligibility criteria: D-TGA with IVS or VSD, repair by 3 months of age and coronary artery anatomy suitable for the ASO. Exclusion criteria: birth weight < 2.5kg, known syndrome of congenital anomalies, associated extra cardiac anomaly of greater than minor severity, previous cardiac surgery, and associated cardiovascular anomalies that require surgical procedures.	Wechsler Individual Achievement Test Second Edition, General Memory Index of the Children's Memory Scale, Delis-Kaplan Executive Function System, Test of Visual-Perceptual Skills, Rey-Osterreith Complex Figure, Connors attention-deficit/hyper activity disorder scale, Adult Autism Spectrum Quotient, Reading the Mind in the Eyes Test-Revised	-Higher than expected proportion of patients with scores >1SD or >2SD below normative values in academic skills, memory and visuo-spatial skills -Lower than expected scores on academic skills, visuo- spatial skills, memory, executive functions, and social cognition; -By parent reports, about 1 in 5 had attention or executive impairments in daily life

Table A1. *Cont.*

Study	Incident Cases	Age	Populations' Characteristics	Definition/Features of TGA Patients	Definition/Assessment Method of Neurodevelopmental Outcomes	Outcomes
Heinrichs (2014) [46]	60	16 years	TGA neonates who underwent ASO from 1986 to 1992	74% simple TGA, 1 8% TGA-unimportant VSD, 5% TGA-important VSD. At re-evaluation, all patients, except for 2 with spastic tetraplegia and 1 with distinct scoliosis, had a normal endurance capacity as assessed by spiroergometry, and none were taking cardiac or psychiatric medication. The rate of attendance to special schools and the lack of a final school examination was 12% each.	Hamburg-Wechsler intelligence test, Leistungsprufsytem nach Horn, Mannheimer Rechtschreib test, Brief Symptom Inventory	-The average full-scale, verbal, and performance IQs were not reduced compared with the population norms; -A score greater than the expected mean for subtest 3 of the Leistungsprufsytem nach Horn had a mean percentage of 86%; -The average orthographic performance was significantly reduced in four of the six subtests; -The average Global Severity Index T score indicated a significantly reduced psychological distress level compared with the norm
DeMaso (2014) [45]	139	16 years	The Boston Circulatory Arrest Study	Eligibility criteria: D-TGA with IVS or VSD, repair by 3 months of age and coronary artery anatomy suitable for the ASO with either DHCA or LFBP. Exclusion criteria: birth weight < 2.5kg, known syndrome of congenital anomalies, associated extra cardiac anomaly of greater than minor severity, previous cardiac surgery, and associated cardiovascular anomalies that require surgical procedures.	Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version (K-SADS-PL), Children's Global Assessment Scale (CGAS), Brief Psychiatric Rating Scale for Children (BPRS-C), Children's Depression Inventory (CDI), Revised Children's Manifest Anxiety Scale (RCMAS), Child Stress Disorders Checklist (CSDC),Conners' ADHD Rating Scales, Conduct Disorder Scale (CDS)	-Higher lifetime prevalence of structured interview-derived ADHD ($p = 0.03$) -Reduced global psychosocial functioning $p < 0.001$); -Significant increases in self-reported depressive ($p = 0.01$), anxiety ($p = 0.02$), and disruptive behavior symptoms (parent $p < 0.001$ and adolescent $p = 0.03$); -Nevertheless, these youth scored in the non- clinical range on all self-report measures
Robson (2019) [50]	137	16 years	The Boston Circulatory Arrest Study	Eligibility criteria: D-TGA with IVS or VSD, repair by 3 months of age and coronary artery anatomy suitable for the ASO with either DHCA or LFBP. Exclusion criteria: birth weight < 2.5kg, known syndrome of congenital anomalies, associated extra cardiac anomaly of greater than minor severity, previous cardiac surgery, and associated cardiovascular anomalies that require surgical procedures.	Child Health Questionnaire—Parent Form-50 (CHQ-PF50), Wechsler Individual Achievement Test/Second Edition, Children's Memory Scale, Test of Visual-Perceptual Skills—Revised, Conners' Attention-Deficit/Hyperactivity Disorder (ADHD)/Diagnostic and Statistical Manual-IV Scales—Parent and Adolescent, CADS-P and CADS-A27, Behavior Rating Inventory of Executive Function—Parent and Self-Report, Reading the Mind in the Eyes Test / Autism Spectrum Quotient	High scores on the Conners' Attention-Deficit/Hyperactivity Disorder/Diagnostic and Statistical Manual-Fourth Edition Scales (parent: $r = -0.62$, $p < 0.00$, adolescent: $r = -0.43$, $p < 0.001$) and the Behavior Rating Inventory of Executive Function Global Executive Composite (parent: $r = -0.66$, $p < 0.001$, adolescent: $r = -0.39$, $p < 0.001$)

Table A1. *Cont.*

Study	Incident Cases	Age	Populations' Characteristics	Definition/Features of TGA Patients	Definition/Assessment Method of Neurodevelopmental Outcomes	Outcomes
Kasmi (2017) [52]	67	22.9	D-TGA patients born in 1984 and 1995	Eligibility criteria: age $\geq$ 18 years, D-TGA with intact ventricular septum or with ventricular septal defect, corrected by ASO during the first months of life, primary language French. Exclusion criteria: birth weight < 2.5 kg, genetic anomalies, associated extracardiac or cardiovascular anomalies requiring aortic arch reconstruction, severe sensory deficits (vision, hearing), severe neurologic comorbidities (e.g., traumatic brain injury, brain tumors).	Wechsler Adult Intelligence Scale, Third Version (WAIS-III), Wisconsin Card Sorting Test, California Verbal Learning Test, Mini-International Neuro- psychiatric Interview (MINI)	Adults with d-TGA compared to control displayed reduced performance in tasks assessing attention, visual–spatial skills, executive functions, and memory (all $p < 0.05$), had a higher life-time prevalence of depression (43% vs. 19%, $p = 0.008$) and anxiety disorders (54% vs. 33%, $p = 0.025$). Predictors of long-term outcomes included gender and parental socioeconomic and educational status (all $p < 0.05$)

D-TGA: dextro-transposition of the great arteries/TGA: transposition of the great arteries; ASO: arterial switch operation; SD: standard deviation; IVS: intact ventricular septum; VSD: ventricular septal defect; DHCA: deep hypothermic circulatory arrest; LFBP: low-flow cardiopulmonary bypass; ADHD: attention-deficit/hyperactivity disorder.

References

1. Hoffman, J.I.E.; Kaplan, S. The Incidence of Congenital Heart Disease. *J. Am. Coll. Cardiol.* **2002**, *39*, 1890–1900. [CrossRef]
2. Reller, M.D.; Strickland, M.J.; Riehle-Colarusso, T.; Mahle, W.T.; Correa, A. Prevalence of Congenital Heart Defects in Metropolitan Atlanta, 1998–2005. *J. Pediatrics* **2008**, *153*, 807–813. [CrossRef] [PubMed]
3. Hutter, P.A.; Kreb, D.L.; Mantel, S.F.; Hitchcock, J.F.; Meijboom, E.J.; Bennink, G.B.W.E. Twenty-five years' experience with the arterial switch operation. *J. Thorac. Cardiovasc. Surg.* **2002**, *124*, 790–797. [CrossRef] [PubMed]
4. Marino, B.S.; Lipkin, P.H.; Newburger, J.W.; Peacock, G.; Gerdes, M.; Gaynor, J.W.; Mussatto, K.A.; Uzark, K.; Goldberg, C.S.; Johnson, W.H., Jr.; et al. Neurodevelopmental outcomes in children with congenital heart disease: Evaluation and management a scientific statement from the american heart association. *Circulation* **2012**, *126*, 1143–1172. [CrossRef] [PubMed]
5. Ballweg, J.A.; Wernovsky, G.; Gaynor, J.W. Neurodevelopmental outcomes following congenital heart surgery. *Pediatric Cardiol.* **2007**, *28*, 126–133. Available online: https://pubmed.ncbi.nlm.nih.gov/17265108/ (accessed on 22 February 2022). [CrossRef]
6. Bellinger, D.C.; Jonas, R.A.; Rappaport, L.A.; Wypij, D.; Wernovsky, G.; Kuban, K.C.K.; Barnes, P.D.; Holmes, G.L.; Hickey, P.R.; Strand, R.D.; et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *N. Engl. J. Med.* **1995**, *332*, 549–555. Available online: https://pubmed.ncbi.nlm.nih.gov/7838188/ (accessed on 22 February 2022). [CrossRef]
7. Limperopoulos, C.; Majnemer, A.; Shevell, M.I.; Rohlicek, C.; Rosenblatt, B.; Tchervenkov, C.; Darwish, H. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J. Pediatrics* **2002**, *141*, 51–58. Available online: https://pubmed.ncbi.nlm.nih.gov/12091851/ (accessed on 23 February 2022). [CrossRef]
8. Wernovsky, G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. *Cardiol. Young* **2006**, *16* (Suppl. 1), 92–104. Available online: https://pubmed.ncbi.nlm.nih.gov/16401370/ (accessed on 25 February 2022). [CrossRef]
9. Kordopati-Zilou, K.; Sergentanis, T.; Pervanidou, P.; Sofianou-Petraki, D.; Panoulis, K.; Vlahos, N.; Eleftheriades, M. Neurodevelopmental Outcomes in Tetralogy of Fallot: A Systematic Review. *Children* **2022**, *9*, 264. [CrossRef]
10. Bellinger, D.C. Are children with congenital cardiac malformations at increased risk of deficits in social cognition? *Cardiol. Young* **2007**, *18*, 3–9. Available online: https://pubmed.ncbi.nlm.nih.gov/18093362/ (accessed on 25 February 2022). [CrossRef]
11. Bean Jaworski, J.L.; Flynn, T.; Burnham, N.; Chittams, J.L.; Sammarco, T.; Gerdes, M.; Bernbaum, J.C.; Clancy, R.R.; Solot, C.B.; Zackai, E.H.; et al. Rates of autism and potential risk factors in children with congenital heart defects. *Congenit. Heart Dis.* **2017**, *12*, 421–429. [CrossRef] [PubMed]
12. Newburger, J.W.; Jonas, R.A.; Wernovsky, G.; Wypij, D.; Hickey, P.R.; Kuban, K.; Farrell, D.M.; Holmes, G.L.; Helmers, S.L.; Constantinou, J.; et al. A Comparison of the Perioperative Neurologic Effects of Hypothermic Circulatory Arrest versus Low-Flow Cardiopulmonary Bypass in Infant Heart Surgery. *N. Engl. J. Med.* **1993**, *329*, 1057–1064. Available online: https://pubmed.ncbi.nlm.nih.gov/8371727/ (accessed on 23 February 2022). [CrossRef] [PubMed]
13. Jonas, R.A.; Wypij, D.; Roth, S.J.; Bellinger, D.C.; Visconti, K.J.; du Plessis, A.J.; Goodkin, H.; Laussen, P.C.; Farrell, D.M.; Bartlett, J.; et al. The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: Results of a randomized trial in infants. *J. Thorac. Cardiovasc. Surg.* **2003**, *126*, 1765–1774. Available online: https://pubmed.ncbi.nlm.nih.gov/14688685/ (accessed on 23 February 2022). [CrossRef] [PubMed]
14. Newburger, J.W.; Jonas, R.A.; Soul, J.; Kussman, B.D.; Bellinger, D.C.; Laussen, P.C.; Robertson, R.; Mayer, J.E.; del Nido, P.J.; Bacha, E.A.; et al. Randomized trial of hematocrit 25% versus 35% during hypothermic cardiopulmonary bypass in infant heart surgery. *J. Thorac. Cardiovasc. Surg.* **2008**, *135*, 347–354.e4. Available online: https://pubmed.ncbi.nlm.nih.gov/18242267/ (accessed on 23 February 2022). [CrossRef]
15. Limperopoulos, C.; Majnemer, A. Neurologic Status of Newborns With Congenital Heart Defects Before Open Heart Surgery. *Pediatrics* **1999**, *103*, 402–408. [CrossRef]
16. Limperopoulos, C.; Majnemer, A.; Rosenblatt, B.; Shevell, M.; Rohlicek, C.; Tchervenkov, C. Multimodality evoked potential findings in infants with congenital heart defects. *J. Child Neurol.* **1999**, *14*, 702–707. Available online: https://pubmed.ncbi.nlm.nih.gov/10593545/ (accessed on 23 February 2022). [CrossRef]
17. Limperopoulos, C.; Majnemer, A.; Rosenblatt, B.; Shevell, M.I.; Rohlicek, C.; Tchervenkov, C.; Gottesman, R. Association between electroencephalographic findings and neurologic status in infants with congenital heart defects. *J. Child Neurol.* **2001**, *16*, 471–476. Available online: https://pubmed.ncbi.nlm.nih.gov/11453441/ (accessed on 23 February 2022). [CrossRef]
18. Licht, D.J.; Wang, J.; Silvestre, D.W.; Nicolson, S.C.; Montenegro, L.M.; Wernovsky, G.; Tabbutt, S.; Durning, S.M.; Shera, D.M.; Gaynor, J.W.; et al. Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects. *J. Thorac. Cardiovasc. Surg.* **2004**, *128*, 841–849. Available online: https://pubmed.ncbi.nlm.nih.gov/15573068/ (accessed on 23 February 2022). [CrossRef]
19. te Pas, A.B.; Wezel-Meijler, G.; Bökenkamp-Gramann, R.; Walther, F.J. Preoperative cranial ultrasound findings in infants with major congenital heart disease. *Acta Paediatr.* **2005**, *94*, 1597–1603. Available online: https://pubmed.ncbi.nlm.nih.gov/16352496/ (accessed on 23 February 2022). [CrossRef]
20. Mahle, W.T.; Tavani, F.; Zimmerman, R.A.; Nicolson, S.C.; Galli, K.K.; Gaynor, J.W.; Clancy, R.R.; Montenegro, L.M.; Spray, T.L.; Chiavacci, R.M.; et al. An MRI study of neurological injury before and after congenital heart surgery. *Circulation* **2002**, *106* (Suppl. 1), I-109–I-114. [CrossRef]

21. Miller, S.P.; McQuillen, P.; Hamrick, S.; Xu, D.; Glidden, D.; Charlton, N.; Karl, T.; Azakie, A.; Ferriero, D.M.; Barkovich, A.J.; et al. Abnormal Brain Development in Newborns with Congenital Heart Disease. *N. Engl. J. Med.* **2007**, *357*, 1928–1938. Available online: https://pubmed.ncbi.nlm.nih.gov/17989385/ (accessed on 23 February 2022). [CrossRef] [PubMed]
22. Masoller, N.; Martinez, J.M.; Gomez, O.; Bennasar, M.; Crispi, F.; Sanz-Cortes, M.; Egaña-Ugrinovic, G.; Bartrons, J.; Puerto, B.; Gratacos, E. Evidence of second-trimester changes in head biometry and brain perfusion in fetuses with congenital heart disease. *Ultrasound Obstet. Gynecol.* **2014**, *44*, 182–187. Available online: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.13373 (accessed on 23 February 2022). [CrossRef] [PubMed]
23. Scherjon, S.A.; Smolders-DeHaas, H.; Kok, J.H.; Zondervan, H.A. The "brain-sparing" effect: Antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. *Am. J. Obstet. Gynecol.* **1993**, *169*, 169–175. Available online: https://pubmed.ncbi.nlm.nih.gov/8333447/ (accessed on 23 February 2022). [CrossRef]
24. Donofrio, M.T.; Bremer, Y.A.; Schieken, R.M.; Gennings, C.; Morton, L.D.; Eidem, B.W.; Cetta, F.; Falkensammer, C.B.; Huhta, J.C.; Kleinman, C.S. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: The brain sparing effect. *Pediatr. Cardiol.* **2003**, *24*, 436–443. Available online: https://pubmed.ncbi.nlm.nih.gov/14627309/ (accessed on 23 February 2022). [CrossRef] [PubMed]
25. Kaltman, J.R.; Di, H.; Tian, Z.; Rychik, J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet. Gynecol.* **2005**, *25*, 32–36. Available online: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.1785 (accessed on 23 February 2022). [CrossRef]
26. Limperopoulos, C.; Tworetzky, W.; McElhinney, D.B.; Newburger, J.W.; Brown, D.W.; Robertson, R.L., Jr.; Guizard, N.; McGrath, E.; Geva, J.; Annese, D.; et al. Brain volume and metabolism in fetuses with congenital heart disease: Evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation* **2010**, *121*, 26–33. [CrossRef]
27. Orenstein, G.A.; Lewis, L. Eriksons Stages of Psychosocial Development. [Updated 2021 November 14]. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA. 2022. Available online: https://www.ncbi.nlm.nih.gov/books/NBK556096/ (accessed on 30 March 2022).
28. McGrath, E.; Wypij, D.; Rappaport, L.A.; Newburger, J.W.; Bellinger, D.C. Prediction of IQ and achievement at age 8 years from neurodevelopmental status at age 1 year in children with D-transposition of the great arteries. *Pediatrics* **2004**, *114*, e572–e576. [CrossRef]
29. Park, C.S.; Lee, J.R.; Lim, H.G.; Kim, W.H.; Kim, Y.J. The long-term result of total repair for tetralogy of Fallot. *Eur. J. Cardio-Thorac. Surg.* **2010**, *38*, 311–317. [CrossRef]
30. Andropoulos, D.B.; Easley, R.B.; Brady, K.; McKenzie, E.D.; Heinle, J.S.; Dickerson, H.A.; Shekerdemian, L.; Meador, M.; Eisenman, C.; Hunter, J.V.; et al. Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation. *Ann. Thorac. Surg.* **2012**, *94*, 1250–1256. [CrossRef]
31. Lim, J.M.; Porayette, P.; Marini, D.; Chau, V.; Au-Young, S.H.; Saini, A.; Ly, L.G.; Blaser, S.; Shroff, M.; Branson, H.M.; et al. Associations Between Age at Arterial Switch Operation, Brain Growth, and Development in Infants With Transposition of the Great Arteries. *Circulation* **2019**, *139*, 2728–2738. [CrossRef]
32. Mendoza, J.C.; Wilkerson, S.A.; Reese, A.H. Follow-Up of Patients Who Underwent Arterial Switch Repair for Transposition of the Great Arteries. Available online: http://archpedi.jamanetwork.com/ (accessed on 26 March 2021).
33. Hövels-Gürich, H.H.; Seghaye, M.C.; Sigler, M.; Kotlarek, F.; Bartl, A.; Neuser, J.; Minkenberg, R.; Messmer, B.J.; von Bernuth, G. Neurodevelopmental outcome related to cerebral risk factors in children after neonatal arterial switch operation. *Ann. Thorac. Surg.* **2001**, *71*, 881–888. Available online: https://pubmed.ncbi.nlm.nih.gov/11269469/ (accessed on 23 February 2022). [CrossRef]
34. Ellerbeck, K.A.; Smith, M.L.; Holden, E.; McMenamin, S.C.; Badawi, M.A.; Brenner, J.I.; Kan, J.S.; Hyman, S.L. Neurodevelopmental Outcomes in Children Surviving d-Transposition of the Great Arteries. *J. Dev. Behav. Pediatr. IDBP* **1998**, *19*, 335–341. [CrossRef] [PubMed]
35. Brosig, C.L.; Mussatto, K.A.; Kuhn, E.M.; Tweddell, J.S. Neurodevelopmental Outcome in Preschool Survivors of Complex Congenital Heart Disease: Implications for Clinical Practice. *J. Pediatric Health Care* **2007**, *21*, 3–12. [CrossRef] [PubMed]
36. Neufeld, R.E.; Clark, B.G.; Robertson, C.M.; Moddemann, D.M.; Dinu, I.A.; Joffe, A.R.; Sauve, R.S.; Creighton, D.E.; Zwaigenbaum, L.; Ross, D.B.; et al. Five-year neurocognitive and health outcomes after the neonatal arterial switch operation. *J. Thorac. Cardiovasc. Surg.* **2008**, *136*, 1413–1421.e2. [CrossRef] [PubMed]
37. Bellinger, D.C.; Wypij, D.; Kuban, K.C.K.; Rappaport, L.A.; Hickey, P.R.; Wernovsky, G.; Jonas, R.A.; Newburger, J.W. Developmental and Neurological Status of Children at 4 Years of Age After Heart Surgery With Hypothermic Circulatory Arrest or Low-Flow Cardiopulmonary Bypass. *Circulation* **1999**, *100*, 526–532. Available online: http://www.circulationaha.org (accessed on 26 March 2021). [CrossRef]
38. Hövels-Gürich, H.H.; Seghaye, M.-C.; Schnitker, R.; Wiesner, M.; Huber, W.; Minkenberg, R.; Kotlarek, F.; Messmer, B.J.; von Bernuth, G. Long-term neurodevelopmental outcomes in school-aged children after neonatal arterial switch operation. *J. Thorac. Cardiovasc. Surg.* **2002**, *124*, 448–458. [CrossRef]
39. H6vels-Gfirich, H.H.; Seghaye, M.-C.; Dfibritz, S.; Messmer, B.J.; Bernuth, V. I Illll cognitive and motor development in preschool and school-aged children after neonatal arterial switch operation. *Cardiovasc Surg.* **1997**, *114*, 5785.

40. Calderon, J.; Bonnet, D.; Courtin, C.; Concordet, S.; Plumet, M.-H.; Angeard, N. Executive function and theory of mind in school-aged children after neonatal corrective cardiac surgery for transposition of the great arteries. *Dev. Med. Child Neurol.* **2010**, *52*, 1139–1144. [CrossRef]
41. Calderon, J.; Jambaqué, I.; Bonnet, D.; Angeard, N. Executive functions development in 5- to 7-year-old children with transposition of the great arteries: Longitudinal study. *Dev. Neuropsychol.* **2014**, *39*, 365–384. [CrossRef]
42. Karl, T.R.; Hall, S.; Ford, G.; Kelly, E.A.; Brizard, C.P.R.; Mee, R.B.B.; Weintraub, R.G.; Cochrane, A.D.; Glidden, D. Arterial switch with full-flow cardiopulmonary bypass and limited circulatory arrest: Neurodevelopmental outcome. *J. Thorac. Cardiovasc. Surg.* **2004**, *127*, 213–222. [CrossRef]
43. Bellinger, D.C.; Wypij, D.; Duplessis, A.J.; Rappaport, L.A.; Jonas, R.A.; Wernovsky, G.; Newburger, J.W. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial. *J. Thorac. Cardiovasc. Surg.* **2003**, *126*, 1385–1396. [CrossRef]
44. Bellinger, D.C.; Wypij, D.; Rivkin, M.J.; Demaso, D.R.; Robertson, R.L.; Dunbar-Masterson, C.; Rappaport, L.A.; Wernovsky, G.; Jonas, R.A.; Newburger, J.W. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: Neuropsychological assessment and structural brain imaging. *Circulation* **2011**, *124*, 1361–1369. [CrossRef] [PubMed]
45. DeMaso, D.R.; Labella, M.; Taylor, G.A.; Forbes, P.W.; Stopp, C.; Bellinger, D.C.; Rivkin, M.J.; Wypij, D.; Newburger, J.W. Psychiatric Disorders and Function in Adolescents with d-Transposition of the Great Arteries. *J. Pediatr.* **2014**, *165*, 760–766. [CrossRef] [PubMed]
46. Heinrichs, A.K.M.; Holschen, A.; Krings, T.; Messmer, B.J.; Schnitker, R.; Minkenberg, R.; Hövels-Gürich, H.H. Neurologic and psycho-intellectual outcome related to structural brain imaging in adolescents and young adults after neonatal arterial switch operation for transposition of the great arteries. *J. Thorac. Cardiovasc. Surg.* **2014**, *148*, 2190–2199. [CrossRef]
47. Cassidy, A.R.; Newburger, J.W.; Bellinger, D.C. Learning and Memory in Adolescents With Critical Biventricular Congenital Heart Disease. *J. Int. Neuropsychol. Soc.* **2017**, *23*, 627–639. [CrossRef]
48. Cassidy, A.R.; White, M.T.; DeMaso, D.R.; Newburger, J.W.; Bellinger, D.C. Executive Function in Children and Adolescents with Critical Cyanotic Congenital Heart Disease. *J. Int. Neuropsychol. Soc.* **2015**, *21*, 34–49. [CrossRef]
49. Muñoz-López, M.; Hoskote, A.; Chadwick, M.J.; Dzieciol, A.M.; Gadian, D.G.; Chong, K.; Banks, T.; de Haan, M.; Baldeweg, T.; Mishkin, M.; et al. Hippocampal damage and memory impairment in congenital cyanotic heart disease. *Hippocampus* **2017**, *27*, 417–424. [CrossRef]
50. Robson, V.K.; Stopp, C.; Wypij, D.; Dunbar-Masterson, C.; Bellinger, D.C.; DeMaso, D.R.; Rappaport, L.A.; Newburger, J.W. Longitudinal Associations between Neurodevelopment and Psychosocial Health Status in Patients with Repaired D-Transposition of the Great Arteries. *J. Pediatr.* **2019**, *204*, 38–45.e1. [CrossRef]
51. Holst, L.M.; Kronborg, J.B.; Jepsen, J.R.M.; Christensen, J.Ø.; Vejlstrup, N.G.; Juul, K.; Bjerre, J.V.; Bilenberg, N.; Ravn, H.B. Attention-deficit/hyperactivity disorder symptoms in children with surgically corrected Ventricular Septal Defect, Transposition of the Great Arteries, and Tetralogy of Fallot. *Cardiol. Young* **2020**, *30*, 180–187. [CrossRef]
52. Kasmi, L.; Calderon, J.; Montreuil, M.; Geronikola, N.; Lambert, V.; Belli, E.; Bonnet, D.; Kalfa, D. Neurocognitive and Psychological Outcomes in Adults with Dextro-Transposition of the Great Arteries Corrected by the Arterial Switch Operation. *Ann. Thorac. Surg.* **2018**, *105*, 830–836. [CrossRef]