Cognitive outcomes and health-related quality of life in adults two decades after the arterial switch operation for transposition of the great arteries

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ABSTRACT

Objective: The study objective was to evaluate the cognitive and psychosocial outcomes of young adults who underwent an arterial switch operation for transposition of the great arteries.

Methods: Sixty-seven adults with transposition of the great arteries (aged 22.9 ± 3.3 years) and 43 healthy subjects matched in age, gender, and educational level participated. Global cognitive functioning, psychologic state, and health-related quality of life were evaluated using validated tools. We analyzed patient-related and procedure-related risk factors associated with cognitive and psychosocial outcomes.

Results: Some 69% of patients had an intelligence quotient greater than 85 (normal range, 85-115). Mean full-scale, verbal, and performance intelligence quotients were lower in patients (94.9 ± 15.3 , 96.8 ± 16.2 , 93.7 ± 14.6 , respectively) than in healthy subjects (103.4 ± 12.3 , $P = .003$; 102.5 ± 11.5 , $P = .033$; 103.8 ± 14.3 , $P < .001$, respectively). Cognitive difficulties (intelligence quotient ≤ -1 standard deviation) and impairments (intelligence quotient ≤ -2 standard deviations) were more frequent in patients than in the general population (31% vs 16%, $P = .001$; 6% vs 2%, $P = .030$). Patients with cognitive difficulties had lower educational level ($P < .001$) and more grade retention at school ($P = .007$). Patients reported an overall satisfactory health-related quality of life; however, those with cognitive or psychologic difficulties reported poorer quality of life. Predictors of worse outcomes included lower parental socioeconomic and educational status, older age at surgery, and longer hospitalization stay.

Conclusions: Despite satisfactory outcomes in most adults with transposition of the great arteries, a substantial proportion has cognitive or psychologic difficulties that may reduce their academic success and quality of life. Further studies are needed to better understand the long-term outcome of this population to provide prevention, surveillance, and care strategies. (J Thorac Cardiovasc Surg 2017;154:1028-35)

Significant difference between the *TGA group and the general population, and the †TGA group and control group.

Central Message

Adults with TGA have an increased risk of cognitive disorders likely to reduce their academic success and quality of life.

Perspective

Our study provides an original description of the cognitive and psychosocial outcomes of adults 2 decades after a neonatal ASO for TGA. This is an essential step to develop prevention strategies and adapted treatments, such as cognitive remediation or psychologic support, for patients who would need it.

See Editorial Commentary page 1036.

See Editorial page 1026.

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Abbreviations and Acronyms

ACHD	= adults with congenital heart disease
ASO	= arterial switch operation
CHD	= congenital heart disease
DHCA	= deep hypothermic circulatory arrest
FIQ	= full-scale intelligence quotient
HADS	= Hospital Anxiety and Depression Scale
HADS-A	= Hospital Anxiety and Depression Scale anxiety subscale
HADS-D	= Hospital Anxiety and Depression Scale depression subscale
HRQOL	= health-related quality of life
IQ	= intelligence quotient
PIQ	= performance intelligence quotient
SD	= standard deviation
SEES	= socioeconomic and educational status
SF-36	= 36-item Short-Form Health Survey
TGA	= transposition of the great arteries
VIQ	= verbal intelligence quotient
VSD	= ventricular septal defect

Scanning this QR code will take you to a supplemental video for the article.

With the dramatic improvement in medical and surgical care of complex congenital heart disease (CHD), attention shifted from mortality and cardiac morbidity to long-term neuropsychologic and psychosocial outcomes. Studies showed that children and adolescents with CHD are at increased risk of neurodevelopmental and psychologic disorders, which may be related to biological and environmental factors.¹ Since the advent of neonatal repair of complex cardiac lesions, approximately 85% of patients survive into adulthood, giving rise to a new large patient population called “adults with congenital heart disease”² (ACHD). However, few studies have evaluated the cognitive and psychosocial outcomes of adults with complex CHD.^{3,4} The evaluation of the outcomes of young ACHDs seems particularly important because this developmental period is characterized by brain, cognitive, and behavioral changes that could determine social and professional adaptation. Indeed, early adulthood is the time when the last stages of brain development, particularly of prefrontal structures, occur. This crucial phase, marked by new academic, financial, and familial challenges, is a time of high vulnerability during which some psychiatric disorders manifest.⁵

The main objective of this study was to evaluate the cognitive and psychosocial outcomes of young adults who underwent a neonatal arterial switch operation (ASO) to correct transposition of the great arteries (TGA). We also explored the association among cognitive and psychologic difficulties, health-related quality of life (HRQOL), and academic course. Our last objective was to identify potential clinical and sociodemographic risk factors associated with the cognitive and psychologic outcomes of patients.

MATERIALS AND METHODS**Participants**

Adults (aged ≥ 18 years) born with TGA between 1984 and 1995 were identified by reviewing the medical databases of 2 hospitals: Necker Children's Hospital and Marie Lannelongue Hospital, Ile-de-France. Inclusion criteria were a diagnosis of TGA, with intact ventricular septum or ventricular septal defect (VSD), corrected by ASO before 2 months of age (Video 1). Exclusion criteria were a diagnosis of TGA with hypoplastic aortic arch or left ventricular outflow tract obstruction, birth weight less than 2.5 kg, known genetic anomalies, associated severe extracardiac anomalies, severe sensory impairments (eg, vision or hearing), a history of neurologic lesion (eg, traumatic brain injury, brain tumor), and primary language other than French.

The group of patients was compared with a control group of healthy adults, matched on age, gender, and educational level and recruited from the same geographic location (Ile-de-France). We recruited control individuals from diverse social and educational environments (universities, training centers, hospital's employees, and by asking patients' close friends). This study was approved by the Institutional Review Board of Paris-Sud University Medical Center. Written informed consent was obtained from all participants.

MATERIALS

Participants underwent a comprehensive 2-hour cognitive and psychosocial evaluation based on validated scales administered in a fixed order. Intellectual ability was assessed by a trained neuropsychologist (L.K.) using the Wechsler Adult Intelligence Scale, Third Edition,⁶ the most commonly used standardized scale to measure intelligence quotient (IQ) in adults. It provides scores for verbal IQ (VIQ: verbal reasoning and comprehension), performance IQ (PIQ: processing speed and visual-motor proficiency), and full-scale IQ (FIQ: general intellectual efficiency). These subscales provide normative scores by age with a mean of 100 and a standard deviation (SD) of 15. Cognitive difficulties were measured by scores 1 SD or more below the expected mean (ie, ≤ 85), whereas scores 2 SD or more below the expected mean (ie, ≤ 70) expressed cognitive impairments. The incidence of IQ scores 85 or less or 70 or less in the general population is 16% or 2%, respectively.⁶

Participants also completed the Hospital Anxiety and Depression Scale⁷ (HADS) in the French version⁸ and the 36-item Short-Form Health Survey⁹ (SF-36) in the French version,¹⁰ which both have an acceptable internal consistency. The HADS assesses the presence and the severity of current depression and anxiety symptomatology. It is divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D), both containing 7 items. Each item is rated on a scale from 0 to 3 to evaluate semiquantitatively the intensity of current symptoms. For each of the 2 subscales, the range of possible scores varies from 0 to 21 points (with higher scores indicating worse outcomes). A score of 8 to 10 suggests a potential anxiety or depressive disorder. A score of 11 to 21 is indicative of more severe anxiety or depressive disorder.

The SF-36 allows a generic measure of HRQOL across 8 physical and emotional domains. It provides 2 summary scales: physical (Physical Component Summary) and psychosocial HRQOL (Mental Component Summary), both calculated from the 8 subscales using algorithms.¹¹

VIDEO 1. Neonatal ASO in a 5-day-old neonate with simple TGA and abnormal coronary anatomy and coronary intramural course. With permission of Dr Belli, Paris, France. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30638-4/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30638-4/addons).

They have a mean (SD) of 50 (10), a higher score suggesting a better HRQOL. Finally, we collected preoperative, intraoperative, postoperative, and sociodemographic variables (Table 1).

Statistical Analysis

Results are expressed as mean $\pm$ SD or percentages. Cognitive and psychosocial outcomes of patients were compared with outcomes of healthy subjects and with normative values of general population, when available. Comparisons between the TGA group and the control group on numeric variables were performed using independent-sample *t* tests. Standardized scores were compared with normative values from the general population, using 1-sample *t* tests. Chi-square tests were used for comparisons of categorical variables between groups. Binomial tests were used for comparisons of frequencies observed in the TGA group with those expected in the general population.

In the TGA group, we evaluated the association among cognitive or psychologic difficulties, HRQOL, and academic course. Chi-square tests were used to assess the association between 2 categorical variables, and independent-sample *t* tests were used to assess the association between categorical and numeric variables.

Finally, we used linear regression analyses to identify risk factors for cognitive and psychosocial outcomes in adults with TGA among the predictors listed in Table 1. We performed multiple imputations¹² using the fully conditional specification method (ie, the Markov Chain Monte Carlo method)¹³ and carried out 5 imputations to replace missing values of independent variables (ie, predictors) when a variable had less than 25% of missing values. Regression analyses were performed from complete data (or “combined results”) corresponding to the mean score between observed data and data obtained from the 5 imputations conducted. Predictors associated with outcomes at a level of *P* less than .20 were considered for stepwise backward regression. Statistical analysis was performed using the Statistical Package for Social Sciences version 22 (IBM, Bois-Colombes, France).

RESULTS

Among 154 patients meeting eligibility criteria and living in Ile-de-France, 55 (36%) were unreachable. Of the remaining 99 patients, 16 refused to participate and 16 accepted but never presented for evaluation (68% of participation rate). Participants did not differ from nonparticipants on gender (*P* = .137), birth weight (*P* = .730), VSD prevalence (*P* = .883), Rashkind procedure use (*P* = .881), deep hypothermic circulatory

TABLE 1. Clinical characteristics of the transposition of the great arteries group

Variables	Percentage (frequency),* mean $\pm$ SD (n)* or quartiles (n)*
Preoperative	
Prenatal diagnosis	23.7% (14/59)
VSD	34.8% (23/66)
Gestational age (wk)	39.4 $\pm$ 1.5 (59)
C-section delivery	15.8% (9/57)
Birth weight (kg)	3.3 $\pm$ 0.4 (60)
Head circumference (cm)	34.3 $\pm$ 1.1 (45)†
Apgar score at 5 min	9.5 $\pm$ 0.9 (52)
Rashkind procedure	66.7% (42/63)
Intraoperative	
Age at surgery (d)	Q1 = 5, median = 7, Q3 = 10 (66)
Duration of aortic clamping time (min)	76.4 $\pm$ 12.8 (63)
Duration of CPB (min)	157.3 $\pm$ 35.3 (51)
Use of DHCA‡	9.5% (6/63)
Duration of DHCA‡ (min)	4.2 $\pm$ 3.6 (6)
Postoperative	
Length of stay in ICU (d)	8.5 $\pm$ 4.9 (61)
Cerebral seizures during ICU stay	2.2% (1/44)†
Total length of hospitalization (d)	26.4 $\pm$ 8.1 (55)
Medical history after ASO	
Delayed psychomotor development in childhood	10.7% (6/56)
Subsequent percutaneous intervention	6.5% (4/62)
Subsequent surgical intervention	18.8% (12/64)
Sociodemographic and family characteristics	
Gender, male	59.7% (40/67)
Age at assessment, y	22.9 $\pm$ 3.3 (67)
Parental educational level§	1.4 $\pm$ 1.0 (67)
Parental socioeconomic status	1.7 $\pm$ 0.8 (67)

SD, Standard deviation; VSD, ventricular septal defect; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; ICU, intensive care unit; ASO, arterial switch operation. *Clinical data were missing for some patients (overall rate of missing values = 8.9%). †Variables with >25% of missing values were not considered for regression analysis. ‡The use of DHCA in both institutions during the study period was limited to the intracardiac part of the procedure (atrial septal defect or VSD closure) and not to the extracardiac part (harvest and reimplantation of the coronary arteries, LeCompte maneuver). §Level of the highest degree reached, from 0 to 3 (0 = no high school diploma; 1 = high school diploma; 2 = college undergraduate; 3 = from college graduate to doctoral degree). ||Socioeconomic status calculated on the basis of the French average income depending on socio-professional category (source: National Institute of Statistics and Economic Studies), from 0 (very low socioeconomic level, long-term unemployment, homemaker) to 3 (high socioeconomic level: executive manager, higher intellectual profession).

arrest (DHCA) use (*P* = .392), aortic clamp duration (*P* = .119), or bypass duration (*P* = .270). Nevertheless, compared with nonparticipants, participants had an earlier mean age at surgery (9.4 $\pm$ 9.7 days vs 12.4 $\pm$ 11.3 days, *P* = .018), shorter duration of circulatory arrest (4.2 $\pm$ 3.6 minutes vs 29.9 $\pm$ 9.5 minutes, *P* < .001), and earlier age at assessment (22.9 $\pm$ 3.4 years vs 25.7 $\pm$ 3.1 years, *P* < .001). Finally, compared with patients not lost to follow-up but who refused or never presented for

TABLE 2. Sociodemographic, academic, and professional characteristics by group

Variables	Groups, percentage (frequency) or mean $\pm$ SD		P value
	TGA group (n = 67)	Control group (n = 43)	
Gender, male	59.7% (40/67)	55.8% (24/43)	.687
Age (18-31 y)	22.9 $\pm$ 3.3	23.8 $\pm$ 2.8	.164
Educational level			
No. of years of education*	13.6 $\pm$ 2.1	14.1 $\pm$ 2	.177
Diploma degree†	1.4 $\pm$ 0.9	1.5 $\pm$ 0.8	.414
Rates of grade retention at school	56.7% (38/67)	48.8% (21/43)	.419
Unemployment rates among nonstudents	23.3% (7/30)	14.3% (3/21)	.108
Socioeconomic status of nonstudents‡	1.7 $\pm$ 0.7	1.7 $\pm$ 0.8	.818
Parental educational level†	1.4 $\pm$ 1.0	1.4 $\pm$ 1.2	.639
Parental socioeconomic status‡	1.7 $\pm$ 0.8	1.6 $\pm$ 0.7	.622

SD, Standard deviation; TGA, transposition of the great arteries. *Number of years of education starting from the first grade of elementary school (12 years of education corresponding to the high school diploma). †Level of the highest degree reached, from 0 to 3 (0 = no high school diploma; 1 = high school diploma; 2 = college undergraduate; 3 = from college graduate to doctoral degree). ‡Socioeconomic status calculated on the basis of the French average income depending on socio-professional category, from 0 (very low socioeconomic level, long-term unemployment) to 3 (high socioeconomic level: executive manager).

evaluation, participants had a higher educational level (13.6 ± 2.1 years of education vs 12.3 ± 1.8 years of education, $P = .014$) for an equivalent age at assessment ($P = .586$).

A total of 67 adults (aged 18-31 years) who underwent an ASO for TGA were included. The clinical characteristics of the TGA group are presented in Table 1. The control group consisted of 43 healthy subjects matched to the patients in age, gender, and educational level. Sociodemographic data by group are presented in Table 2.

Cognitive Outcomes

Mean IQ scores are presented in Table 3. Sixty-nine percent of patients had an FIQ greater than 85 (normal range, 85-115). Mean FIQ and PIQ were significantly lower in patients than the expected population's mean of 100 ($P = .008$ and $P < .001$, respectively). Moreover, mean FIQ, VIQ, and PIQ were significantly lower in patients (94.9 ± 15.3 , 96.8 ± 16.2 , and 93.7 ± 14.6 , respectively) compared with healthy subjects (103.4 ± 12.3 , $P = .003$; 102.5 ± 11.5 , $P = .033$; and 103.8 ± 14.3 , $P < .001$, respectively).

In the TGA group, the frequency of scores 1 SD or greater or 2 SD or greater below the expected mean (ie, ≤ 85 or ≤ 70 ; expected frequency 16% or 2%) was 31% and 6% for FIQ, respectively, and 28% and 4% for both VIQ and PIQ, respectively (Figure 1). Thus, compared with expected frequencies in the general population, the proportion of

TABLE 3. Cognitive and psychosocial outcomes in adults with operated transposition of the great arteries compared with control group

Variables	Groups, mean $\pm$ SD		P value*
	TGA (n = 67)	Control (n = 43)	
WAIS-III			
FIQ	94.9 $\pm$ 15.3	103.4 $\pm$ 12.3	.003
VIQ	96.8 $\pm$ 16.2	102.5 $\pm$ 11.5	.033
PIQ	93.7 $\pm$ 14.6	103.8 $\pm$ 14.3	<.001
HADS			
HADS-D†	3.2 $\pm$ 2.3	3.4 $\pm$ 2.7	.631
HADS-A†	7.1 $\pm$ 3.7	6.7 $\pm$ 3.7	.589
SF-36			
PCS	52.1 $\pm$ 7.5	55.4 $\pm$ 5.9	.012
MCS	47.2 $\pm$ 10.3	44.5 $\pm$ 11.5	.201

SD, Standard deviation; TGA, transposition of the great arteries; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition; FIQ, full-scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; HADS, Hospital Anxiety and Depression Scale; HADS-D, Hospital Anxiety and Depression Scale depression subscale; HADS-A, Hospital Anxiety and Depression Scale anxiety subscale; SF-36, 36-item Short-Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary. *P values are determined by independent samples *t* tests comparing the TGA group with the control group.

†Data from the HADS were missing for 3 patients with TGA.

patients with scores of 85 or less was significantly higher for FIQ ($P = .001$), VIQ ($P = .005$), and PIQ ($P = .005$), whereas the proportion of patients with scores of 70 or less was significantly higher for FIQ only ($P = .030$).

Psychosocial Outcomes

Mean scores of depression and anxiety symptomatology are presented in Table 3. Mean scores in HADS-D and in HADS-A were not significantly different between the TGA and control groups. Furthermore, the proportion of patients with possible depression (HADS-D ≥ 8 ; 3.1%) or anxiety disorder (HADS-A ≥ 8 ; 39.1%) was not different from that of healthy participants (7%, $P = .39$ and 34.9%, $P = .66$, respectively). Finally, the frequency of disorders (HADS-D or HADS-A ≥ 11) was not different between groups: No patient and 1 healthy subject (2.3%) showed high depressive symptomatology ($P = .40$), and 18.8% of patients versus 18.6% of healthy subjects presented high anxiety symptomatology ($P = .99$).

Overall, patients reported satisfying HRQOL, as expressed by mean scores in the physical domain (SF-36 Physical Component Summary) and psychosocial domain (SF-36 Mental Component Summary) falling within the normal range of 40 to 60 (Table 3). Among 67 patients, 61 (91%) had a score greater than 40 (expressing normal or high level of HRQOL) in the physical domain and 53 (79%) had a score greater than 40 in the psychosocial domain. However, compared with healthy subjects, patients reported poorer HRQOL in the physical domain (55.4 ± 5.9 vs 52.1 ± 7.5 , respectively, $P = .012$).

FIGURE 1. *Significant difference between frequencies observed in the TGA group and expected frequencies in the general population. †Significant difference between frequencies observed in the TGA group and those observed in the control group. IQ, Intelligence quotient; SD, standard deviation; TGA, transposition of the great arteries.

Relations Between Cognitive or Psychologic Difficulties With Health-Related Quality of Life and Academic Course in the Transposition of the Great Arteries Group

Cognitive difficulties (FIQ ≤ 85) and anxiety disorder (HADS-A ≥ 11) were significantly associated with poorer HRQOL. Patients presenting with an FIQ of 85 or less reported lower physical HRQOL (48.8 ± 7.4) compared with patients with an FIQ greater than 85 (53.6 ± 7.2 , $P = .013$). Moreover, patients with HADS-A of 11 or greater reported lower psychosocial HRQOL (41.1 ± 9.6) compared with patients with HADS-A less than 11 (48.9 ± 9.8 , $P = .015$).

Finally, cognitive difficulties were associated with lower educational level (years of education: 12.4 ± 2.2 vs 14.3 ± 1.7 , $P < .001$) and higher proportion of grade retention at school (81% vs 46%, $P = .007$).

Multivariate Risk Factors Analysis for Cognitive and Psychosocial Outcomes

Predictors of cognitive and psychosocial parameters are presented in Table 4. Among predictors associated with outcomes in univariate linear regression analysis, few remained significantly associated with outcomes in multivariate analysis. Risk factors for lower IQ were lower parental socioeconomic and educational status (SEES) and older age at surgery. Predictors of higher anxiety

symptomatology were older age at surgery and longer total length of hospitalization. Predictors of higher depressive symptomatology were intact ventricular septum and absence of Rashkind procedure before ASO. Finally, among significant HRQOL predictors in univariate analysis (parental SEES, Apgar score, length of stay in intensive care unit), no variable remained significantly associated with HRQOL in multivariate analysis.

DISCUSSION

The aims of this study were to evaluate the (1) cognitive and psychosocial outcomes of adults with TGA corrected by ASO, (2) possible impact of cognitive and psychologic difficulties on academic course and HRQOL, and (3) potential risk factors of cognitive or psychologic outcomes.

Our cohort of adults with TGA displayed FIQ and PIQ scores significantly reduced compared with the normal values and the control group's scores. Our findings suggest that the cognitive morbidities commonly reported in children and adolescents with complex CHD¹⁴ persist into adulthood in individuals with TGA after the ASO. Of note, the proportion of patients with cognitive difficulties (IQ ≤ 85 ; 31%) or cognitive impairments (IQ ≤ 70 ; 8%) was significantly higher than the expected frequency in the general population. These results are in line with previous findings in adolescents with cyanotic CHD¹⁵⁻¹⁷

TABLE 4. Multivariate risk factors analysis in the transposition of the great arteries group

Predictors	Outcome variables		
	Global cognitive functioning (FIQ)	Anxiety symptoms (HADS-A)	Depressive symptoms (HADS-D)
	β Estimate ± SE (P value)		
Gender	X		
Parental SEES*	8.3 ± 2.0 (<.001)	X	
Prenatal diagnosis		X	
VSD			−1.2 ± 0.6 (.048)
Birth weight		X	
Rashkind procedure			−1.2 ± 0.6 (.043)
Age at surgery	−0.4 ± 0.2 (.015)	0.1 ± 0.04 (.022)	
Length of stay in ICU			X
Total length of hospitalization		0.1 ± 0.06 (.044)	
Delayed psychomotor development in childhood	X		

FIQ, Full-scale intelligence quotient (a higher score indicates a better outcome); HADS-A, Hospital Anxiety and Depression Scale anxiety subscale (a higher score indicates a worse outcome); HADS-D, Hospital Anxiety and Depression Scale depression subscale; SE, standard error; X, variables correlated in univariate linear regression but not correlated in multivariate analysis; SEES, socioeconomic and educational status; VSD, ventricular septal defect; ICU, intensive care unit. *Mean score between levels of parental degrees, from 0 (no high school diploma) to 3 (from college graduate to doctoral degree), and their socioeconomic status, from 0 (very low socioeconomic level) to 3 (high socioeconomic level).

and provide evidence that a substantial proportion of patients with TGA continue to display impaired global cognitive functioning in adulthood. IQ scores are important markers of cognitive function; however, they may not reflect the specific neuropsychologic individual strengths and weaknesses. Future assessments should examine specific cognitive domains (eg, attention, memory, executive functions) in adults with TGA to provide an in-depth developmental course for these abilities. This consideration is important for evaluation of the whole ACHD population because specific cognitive impairments are increasingly documented into adolescence⁴ but remain rarely investigated in adulthood.³

Furthermore, in adults with TGA, cognitive difficulties were associated with lower HRQOL, lower educational level, and higher proportion of grade retention at school, highlighting the potential impact of such deficits on daily life functioning and academic achievement. This impediment to academic success could have, in turn, negative effects on socio-professional adaptive skills of these patients. In our study, the unemployment rate among nonstudent adults was slightly higher in patients (23%) than in healthy subjects (14%). Several studies reported lower educational levels^{18,19} and higher rates of unemployment in ACHDs.^{19,20} This increased risk deserves particular attention because education and employment are crucial factors of financial stability and well-being.

In patients and healthy subjects, we observed few cases of current depressive disorders (0%-2%) but high frequencies of anxiety symptoms (35%-39%). The high prevalence of anxiety symptomatology in these young adults could be explained by the fact that early adulthood is a stressful period marked by changes and new challenges. During this period,

ACHDs may face additional difficulties (eg, scar-related discomfort, treatment decision-making, life-expectancy concerns) that could expose them to a greater risk.

Depression and anxiety are known to play an important role in quality of life and health outcomes.²¹ In our cohort, the presence of anxiety disorder was associated with poorer psychosocial HRQOL, suggesting that anxiety might have negative effects on social, academic, or occupational functioning of the patients concerned. Nevertheless, the relationship between anxiety disorder and HRQOL is not necessarily causal but may reflect the fact that these variables are influenced by common factors. Given their potential adverse effects and as mentioned in the guidelines for the care of ACHDs,² psychologic disorders should be systematically screened in this population to provide appropriate treatment.

Similar to some findings in adolescents with TGA,²² our study showed that most adults with TGA reported HRQOL within or superior to normal ranges. Several hypotheses could explain these results. The use of normalization strategies (ie, coping strategies that enable individuals and families to maintain typical or “normal” life patterns despite the chronic illness) or a strong sense of coherence (ie, sense of confidence based on the understanding of life events, the feeling to be able to manage them, and that they have a meaning) seem frequently observed in this population^{23,24} and could contribute to favorable outcomes. However, compared with healthy subjects, patients reported lower satisfaction in the physical HRQOL domain. This confirms previous data²⁵ and highlights the need to develop therapeutic programs aimed at improving the quality of life, such as physical training and specific educational programs for particular challenges of ACHDs.²⁶

With regard to risk factors associated with outcomes, we found that most surgical management variables we considered (including DHCA use or bypass and aortic clamp duration) were not associated with cognitive or psychologic scores. In children with CHD, surgical factors seem to be less relevant than patient-specific and preoperative factors and postoperative events in predicting neurodevelopmental outcomes.²⁷ It is possible that the impact of intraoperative factors on outcomes may be even less manifest in adulthood, when 2 or 3 decades have passed since surgery. Longitudinal studies in adults may be necessary to confirm this. In our study, lower SEES was significantly associated with lower IQ. The influence of parental SEES on children's cognitive development is a well-known phenomenon²⁸ also observed in patients with CHD.^{27,29} In our cohort, older age at the ASO was significantly associated with lower IQ. The negative effect of older age at surgery on neurocognitive development is frequently observed in patients with CHD³⁰ and could be interpreted by the fact that later correction of cyanotic CHD extends the period of hemodynamic instability during which the risk of hypoxia is high.³¹ In our study, predictors of higher anxiety symptomatology were variables related to the patients' care (older age at surgery, longer total length of hospitalization) that had already been identified as psychosocial predictors in children and adolescents with CHD.³² If later correction of cyanotic CHD could be associated with an increased risk of hypoxia, a longer length of hospitalization may be indicative of a less stable condition and more complications (hypotension, hypoxia, seizures) in the perioperative period. Surprisingly, we found that the presence of a VSD and the use of the Rashkind procedure before the ASO were associated with lower depressive symptomatology in adults with TGA. The presence of a VSD and the use of the Rashkind procedure both allow the mix of oxygenated and deoxygenated blood and therefore are generally associated with fewer risks of hemodynamic decompensation during the neonatal period. This, in turn, could have a favorable impact on specific long-term psychiatric outcomes. However, this remains speculative. These results should be interpreted with caution and deserve to be verified in larger groups to ascertain their clinical significance not only for the individual but also for the broader population with TGA.

Study Limitations

To our knowledge, this study is the first to address the cognitive outcomes of patients with TGA corrected by ASO during the crucial period of early adulthood. It provides evidence of substantial rates of cognitive and psychologic difficulties in the underinvestigated population of adults with complex CHD. However, the study should be interpreted in light of several limitations. Our study was cross-sectional and enrolled patients treated from the

1980s to the mid-1990s; thus, because of the rapid evolution of medico-surgical neonatal management over the last 20 years, our results might not be generalized to neonates born with TGA today. Moreover, to minimize confounders, we limited inclusion criteria to 1 cardiac defect (TGA with or without VSD) successfully repaired with a single open surgery (ASO) and excluded other cardiac anomalies and some potential risk factors of adverse neurocognitive outcome (eg, neurologic antecedents). Therefore, our results cannot be generalized to the larger population of ACHDs or to adults with TGA presenting such comorbidities. Although participants and nonparticipants were comparable in most clinical variables, patients included in our study had an earlier age at surgery, and those who underwent DHCA during the ASO had a shorter duration of arrest compared with the nonparticipant group. Furthermore, for an equivalent age, participants had a higher educational level than patients who refused to participate or accepted but never presented for evaluation. These differences support the fact that our cohort may represent a lower-risk part of the population of patients with TGA, with fewer cognitive difficulties and higher academic achievement. Indeed, given the known association between longer DHCA durations and lower cognitive outcomes, the fact that our cohort had significantly shorter mean durations of arrest (4 vs 30 minutes in the nonevaluated group) suggests that our findings may have underestimated the adverse impact of the TGA on outcomes. Thus, our results may not be generalized to patients with TGA with more complicated operative characteristics. In addition, because patients were evaluated at the hospital and healthy subjects were evaluated outside the hospital, the psychologist who administered tests was not blinded to participants' group status. However, tests were administered and scored in accordance with a strict standardized procedure, reducing this potential bias. In our cohort, all patients were free of genetic syndrome diagnosis, as reported in medical records. Nevertheless, we did not conduct systematic genetic testing providing information on the patients' genotype and the presence of nonsyndromic genetic variations. There is growing evidence of the influence of nonsyndromic genetic variations, such as copy number variations, on the incidence of neurodevelopmental impairments in patients with CHD.^{33,34} Future research on the neurodevelopment of patients with CHD may integrate advanced genetic testing to better apprehend the potential impact of genetic polymorphisms on outcomes. Finally, because patients underwent operations in hospitals other than the recruitment institutions, some medical data serving as predictors of outcomes were missing. To conduct our regression analyses on the total cohort of patients ($n = 67$) and improve prediction precision,³⁵ we used the multiple imputations method.^{12,13} We carried out 5

imputations to replace the missing data of variables having less than 25% of missing values. It is worth noting that our cut-point of 25% may be high and susceptible to some bias; thus, more conservative approaches for handling missing data could be considered. Results from our regression analyses should be interpreted with caution and verified in larger cohorts of adults with TGA.

CONCLUSIONS

Our results suggest that despite satisfactory cognitive or psychosocial outcomes in most adults with TGA corrected by ASO, a significant proportion presents substantial cognitive or psychologic difficulties that may reduce their quality of life and academic success. Further studies targeting more specific neurocognitive and psychosocial outcomes in adults with complex CHD are necessary to provide a more comprehensive approach in prevention, surveillance, and care of this population.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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