Five-year neurocognitive and health outcomes after the neonatal arterial switch operation

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Objectives: We sought to assess the 5-year neurocognition and health of an interprovincial inception cohort undergoing the arterial switch operation for transposition of the great arteries.

Methods: Sixty-nine consecutive neonates had operations from 1996–2003 with full-flow cardiopulmonary bypass and selective deep hypothermic circulatory arrest. Outcomes were recorded at 58 ± 9 months of age. Univariate and multivariate analyses were used to identify outcome predictors, including surgical subtype and preoperative, operative, and postoperative variables.

Results: There was 1 (1.5%) operative death. Two children were lost to follow-up, and 1 was excluded because of postdischarge meningitis. Outcomes are reported for 65 survivors. Two (3%) children have cerebral palsy, and 7 (11%) have language disorders, 4 of whom also meet the criteria for autism spectrum disorder. Two of the 4 children with autism have an affected older sibling. Of the 61 children without autism, scores approach those of peers, with a full-scale intelligence quotient of 97 ± 16 , a verbal intelligence quotient of 97 ± 18 , a performance intelligence quotient of 96 ± 15 , and a visual–motor integration score of 95 ± 16 . Mother's education, birth gestation or weight, and postoperative plasma lactate values account for 21% to 32% of the variance of these scores. Septostomy adds 7% to the variance of visual–motor integration scores.

Conclusions: Most preschool children do well after surgical correction for transposition of the great arteries, including complex forms. Potentially modifiable variables include high preoperative plasma lactate levels and septostomy. A minority of children were given diagnoses of language disorders, including autism, in which familial factors likely contribute to outcome.

Supplemental material is available online.

Neurodevelopmental outcome after surgical intervention for congenital heart disease is multifactorial, influenced by intrinsic characteristics of individual patients, and related to intraoperative and perioperative management and course.^{1,2}

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Long-term follow-up of children who underwent the arterial switch operation (ASO) for correction of transposition of the great arteries (TGA) reveals small but important differences from general population normative data in cognitive function, motor skills, academic achievement, language ability, and behavior.^{3–10} Some deficits become apparent only at school age, when the child is required to perform more complex cognitive, social, and linguistic skills that contribute to the development of peer relationships and literacy.^{11,12} Results of a study at our institution demonstrated improved early motor outcomes in a cohort of children who had undergone the ASO compared with children from earlier surgical eras at other institutions.¹³ In this article we describe the neurocognitive and health outcomes at 5 years of age for a subset of that cohort who underwent surgical intervention between 1996 and 2003.

MATERIALS AND METHODS

This interprovincial inception cohort outcomes study enrolled 69 consecutive neonates undergoing the ASO for repair of TGA from September 1996 through May 2003 at Stollery Children's Hospital, Edmonton, Alberta, Canada. Based on the complexity of their cardiac anomalies, children were divided into 3 groups: group A, simple TGA with intact ventricular septum ($n = 38$); group B, TGA with ventricular septal defect (VSD; $n = 20$); and group C, complex TGA ($n = 11$). Additional anatomic diagnoses in group C included double-outlet right ventricle, single coronary artery, interrupted aortic arch, aortic coarctation or hypoplastic aortic arch, pulmonary artery anomaly, and left ventricle outflow tract obstruction or aortic stenosis. Two cardiac surgeons did the repairs. Operative procedures included

Abbreviations and Acronyms

ASO	= arterial switch operation
CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
FSIQ	= full-scale intelligence quotient
LD	= language disorder
PIQ	= performance intelligence quotient
TGA	= transposition of the great arteries
VIQ	= verbal intelligence quotient
VMI	= Visual–Motor Integration—fourth edition
VSD	= ventricular septal defect

predominantly full-flow ($150 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) cardiopulmonary bypass (CPB), with a target hematocrit value of greater than 0.25%, moderate hypothermia with selective use of deep hypothermic circulatory arrest (DHCA), and a modified pH-stat strategy used for cooling. The venous cannulation strategy varied throughout this period based on surgeon preference, with either a single venous cannula or bicaval cannulation used for simple TGA. Complex transpositions were repaired with bicaval cannulation. Intraoperative lactate measurements were not consistently done.

Prospectively collected predictor variables included patient and family demographics (sex, socioeconomic status,¹⁴ maternal education, and year of operation), factors related to preoperative health status (antenatal diagnosis, use of balloon septostomy, ventilation time, age at operation, gestational age, and birth weight), preoperative and early and late postoperative measures of illness severity (highest dopamine level used, highest plasma lactate value, and lowest base deficit), operative variables (CPB time, lowest flow for >10 minutes on bypass, crossclamp time, DHCA time [if used], lowest temperature in degrees Celsius, and repeat CPB, if needed), and overall duration of ventilation, hospital days, presence of convulsions, or need for cardiopulmonary resuscitation, extracorporeal membrane oxygenation, or reintervention (see Table E1). The cohort was assessed at 6 to 10 months of age, 18 to 24 months of age (as previously reported¹³), and 4 to 6 years (range, 47.8–76.3 months) of age.

Outcome Assessment

Neurocognitive, neurologic, and health status outcomes were assessed at 58 ± 9 months of age by multidisciplinary neurodevelopmental teams at one of 5 centers in Western Canada: Calgary and Edmonton, Alberta; Regina and Saskatoon, Saskatchewan; and Winnipeg, Manitoba. History of hospitalizations, illnesses, medication use, and growth parameters, as well as family socioeconomic status¹⁴ and maternal education (years of schooling), were recorded (Table 1). Physicians experienced in neurodevelopmental follow-up examined each child, as previously described.^{10,13} Motor or sensory impairment was diagnosed if a child had cerebral palsy, visual impairment (corrected visual acuity in the better eye <20/60), or sensorineural hearing loss (responses >25 dB hearing level at any frequency from 250–4000 Hz). Hearing was evaluated by certified audiologists. Experienced pediatric psychologists or psychometrists assessed cognitive ability and visual–motor skills by using current age-appropriate standardized measures, including the Weschler Preschool and Primary Scales of Intelligence—third edition¹⁵ and the Beery–Buktenica Developmental Test of Visual–Motor Integration—fourth edition (VMI; Table 2).¹⁶ Variables included the United States normed full-scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), and VMI, each expressed as a standard score with a mean of 100 and standard deviation of 15.

Speech and language concerns were identified by means of a 2-stage process. Children were assessed during cognitive evaluations, with further assessments completed by certified speech–language pathologists when

concerns were identified. Speech disorders (articulation and phonologic), language delay (slower rate of language development but with typical sequence),¹⁷ or language disorder (LD; deviation from typical rate and sequence of acquisition of specific language skill)¹⁷ were diagnosed by speech–language pathologists based on clinical judgment informed by the results of standardized tests (Table 3 and see Table E2).

Children with LD were referred for further diagnostic assessment. Autism spectrum (hereafter autism) diagnoses were established based on structured clinical interview and behavioral observation (including the Autism Diagnostic Observation Schedule),^{18,19} with clinical best diagnostic estimate based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.²⁰

Ethics board approval was obtained from each site, and all parents or guardians provided written informed consent. The funding agency has had no role in the data interpretation.

Statistics

One-way analysis of variance with Tamhane's post-hoc multiple comparisons, *t* tests, χ^2 analysis, and Fisher's exact tests (all 2 sided) were used to compare groups; the Bonferroni correction was applied. Psychologic test results are given for the total group and for those without and with LD. In addition, predictions of outcome were determined separately for children without and with autism.

To screen for variables associated with psychologic scores, we used linear regression analysis. Multiple regression models consisted of variables found significant at a *P* value of .10 or less in the univariate analysis after screening for multicollinearity.

To screen for variables associated with autism, we used univariate logistic regression models. The final multiple logistic regression consisted of variables found significant at a *P* value of less than .10 in the univariate analysis after screening for multicollinearity.

Regression model results are reported as effect sizes (for psychologic scores) and odds ratios (for autism), along with confidence intervals and *P* values. Stepwise multiple regressions were used to explore the change in the percentage of variation in outcomes explained by each additional predictor to a significance level of .05.²¹ Statistical analyses were performed with SAS version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS**Description of Cohort**

Of the 69 neonates, outcomes are reported for 65 children. One child with a complex lesion of the interrupted aortic arch, right ventricular outflow tract obstruction, and coronary artery anomalies died on postoperative day 22 after cardiopulmonary resuscitation and redo surgical intervention for right ventricular outflow tract obstruction. A second child was excluded because of problems unrelated to surgical treatment; this child had postdischarge bacterial meningitis with cerebral vasculitis and infarction, mild left lower extremity spastic monoplegia, low intelligence scores, and right profound sensorineural hearing loss. Preschool outcome information is not available for 2 children with operations within this time period; both were free of motor and sensory disability at 18 months of age.

Table E1 shows the background characteristics of the 65 five-year-old children after the neonatal ASO in relation to type of operation. Fewer neonates undergoing the ASO and VSD repair required any DHCA. Those undergoing complex repairs were more likely to require repeat CPB and longer crossclamp times.

TABLE 1. Five-year health, growth, and development after the neonatal arterial switch operation in relation to the complexity of cardiac anomaly (n = 65)

	Total (n = 65)	ASO (n = 36)	ASO/VSD (n = 19)	Complex (n = 10)	χ^2	P value*
Height <5th percentile	2 (3%)	0 (0%)	2 (11%)	0 (0%)	4.996	.082
Weight <5th percentile	3 (6%)	1 (3%)	1 (5%)	1 (10%)	0.953	.621
Microcephaly	2 (3%)	1 (3%)	1 (5%)	0 (0%)	0.663	.729
Specialists regularly seen: >2	10 (15%)	7 (70%)	2 (20%)	1 (10%)	1.023	.600
Current medication for chronic lung disease	6 (9%)	4 (11%)	1 (5%)	1 (10%)	0.516	.773
Current medication for heart disease	4 (6%)	1 (3%)	2 (11%)	1 (10%)	1.596	.450
Visual impairment (<20/60)	1 (2%)	0 (0%)	0 (0%)	1 (10%)†	5.586	.061
Strabismus	5 (8%)	1 (3%)	1 (5%)	3 (30%)	8.391	.015
Cerebral palsy	2 (3%)	1 (3%)‡	0 (0%)	1 (10%)§	2.221	.329
Sensorineural hearing loss	2 (3%)	2 (6%)	0 (0%)	0 (0%)	1.662	.436
Bilateral	1 (2%)	1 (3%)	0 (0%)	0 (0%)		
Unilateral	1 (2%)	1 (3%)¶	0 (0%)	0 (0%)		
Epilepsy	2 (3%)	1 (3%)#	1 (5%)*	0 (0%)	0.633	.729
Language/speech abnormality††	17 (26%)	12 (33%)	3 (16%)	2 (20%)	2.214	.331
Speech sound disorder	3 (5%)	3 (8%)	0 (0%)	0 (0%)		
Language disorder	7 (11%)	5 (14%)	2 (11%)	0 (0%)		
Language delay as expected for mental development	7 (11%)	4 (11%)	1 (5%)	2 (20%)		

Note: After the Bonferroni correction, *P* values of .004 or less remain significant. Also, all children were receiving an appropriate oral diet for age with no additional supplements; 6 children had oral supplements at less than 6 months of age. No child required supplemental oxygen. ASO, Isolated arterial switch operation; ASO/VSD, ASO with ventricular septal defect repair. * χ^2 Analysis. †Ocular albinism. ‡Mild left spastic hemiplegia, ambulatory without aids, preoperative right middle cerebral artery infarction. §Spastic ambulatory cerebral palsy, ambulatory without aids, preoperative dural sinus thrombosis. ||Bilateral mild-to-moderate high-frequency sensorineural hearing loss. ¶Right unilateral profound sensorineural hearing loss. #Focal seizures, normal magnetic resonance imaging results, language disorder, autism, spectrum disorder. **Atypical absence epilepsy, receiving antiepileptics, normal magnetic resonance imaging results, language disorder. ††Language and speech were screened during the psychologic assessment: 40 children were considered to have normal language and speech, 8 others were referred to a speech–language pathologist with normal results, and 17 others were assessed as having an abnormality by 1 or more speech–language pathologists.

Health, Growth, and Impairment Outcomes

Table 1 shows the health, growth, and impairment outcomes of these children at 5 years of age. The surgical subtype did not define outcomes. For one child, we confirm ambulatory cerebral palsy reported at 18 months.¹³ That child had complex surgical intervention but without septostomy, a normal preoperative plasma lactate value, and a dural sinus thrombosis found on preoperative imaging. At 5 years of age, another child was given a diagnosis of mild left spastic hemiplegia. This second child had balloon septostomy, preoperative right middle cerebral artery infarction on brain imaging, and an increased preoperative plasma lactate value.

Neurocognitive Outcomes

Table 2 shows the psychologic scores for the entire cohort. There were no significant differences in relation to surgical subgroups, although scores for the ASO with VSD repair group are closest to normative values.

Further analyses of the 7 (11%) of 65 children (shown in Table 1) with LD was required. Psychologic scores of children with and without LD in relation to surgical subtype are shown in Table 2. For 58 children without LD, there were no differences in relation to surgical subtype. LD were found only in the children undergoing the ASO with and without VSD, with no difference between these 2 surgical subtypes.

Comparisons between the 58 children without LD and the 7 with LD were as follows: FSIQ—98 ± 16 (no LD) versus 76 ± 23 (LD), *t* = 2.444, *P* = .046; VIQ—98 ± 17 (no LD) versus 69 ± 19 (LD), *t* = 4.329, *P* < .001; PIQ—96 ± 15 (no LD) versus 85 ± 26 (LD), *t* = 1.079, *P* = .319; and VMI—94 ± 14 (no LD) versus 85 ± 31 (LD), *t* = 6.282, *P* = .415. Similarly, the proportion of scores less than 2 standard deviations (SDs) below the mean (IQ <70) was affected by children with LD as follows: FSIQ—1 (2%; no LD) versus 3 (43%; LD), sig = .003; VIQ—6 (10%; no LD) versus 3 (43%; LD), sig = .050; PIQ—3 (5%; no LD) versus 2 (29%; LD), sig = .086; and VMI—2 (3%; no LD) versus 2 (29%; LD), sig = .054.

Subgroup With LDs

Results of further assessment of the 7 children with LDs are reported in Table 3. All 7 children had a normal examination result at 7 to 10 months of age by a neurodevelopmental pediatrician, nurse, audiologist, and physical therapist. All 7 children had a multidisciplinary assessment at age 5 years, and all had normal hearing. Six of these 7 children were available for further assessment. Four (6.1%) children received a Diagnostic and Statistical Manual of Mental Disorders, fourth edition, diagnosis of autism by an expert multidisciplinary team consisting of a neurodevelopmental pediatrician, speech–language pathologist, and psychologist.

TABLE 2. Five-year psychologic test results in relation to type of cardiac lesion after the neonatal arterial switch operation

	Total	ASO	ASO/VSD	Complex	F or t	P value
Total cohort	n = 65	n = 36	n = 19	n = 10		
FSIQ	95 (17)	94 (19)	99 (16)	93 (12)	0.676	.513
VIQ	95 (19)	92 (19)	101 (21)	94 (15)	1.126	.331
PIQ	95 (16)	95 (19)	97 (13)	90 (11)	0.559	.575
VMI	94 (16)	95 (16)	95 (17)	87 (16)	1.146	.324
Subgroup without language disorder	n = 58	n = 31	n = 17	n = 10		
FSIQ	98 (16)	97 (17)	101 (15)	92 (12)	0.959	.389
VIQ	98 (17)	96 (17)	104 (18)	94 (15)	1.579	.215
PIQ	96 (15)	97 (19)	97 (13)	90 (11)	1.022	.367
VMI	94 (14)	97 (12)	97 (14)	87 (16)	2.353	.105
Subgroup with language disorder	n = 7	n = 5	n = 2	n = 0		
FSIQ	76 (23)	75 (24)	81 (27)	—	0.105	.760
VIQ	69 (19)	69 (19)	69 (28)	—	0.001	.978
PIQ	85 (26)	83 (29)	92 (23)	—	0.157	.709
VMI	85 (31)	87 (32)	79 (42)	—	0.079	.790

Values are presented as means (standard deviation). ASO, Arterial switch operation; ASO/VSD, arterial switch operation with ventricular septal defect repair; FSIQ, full-scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; VMI, visual-motor integration.

Comparing psychologic tests for those 61 without autism and 4 with autism shows the following: FSIQ—97 (16; without autism) versus 67 (19; with autism), $t = 3.706$, $P < .001$; VIQ—97 (18; without autism) versus 64 (17; with autism), $t = 3.722$, $P < .001$; PIQ—96 (15; without autism) versus 75 (26; with autism), $t = 2.721$, $P = .008$; and VMI—95 (16; without autism) versus 76 (21; with autism), $t = 2.410$, $P = .019$.

Prediction of Outcomes for Children With and Without Autism

Data of 4 children with autism were removed before analysis of predictor variables for psychologic test results. For the 61 children without autism, Table 4 shows the variables from

Table E1 associated with psychologic test results at a P value of .10 or less. After adjusting, few variables remain significantly related to the psychologic scores (Table 5). These remaining variables were sequentially entered into stepwise multiple regression analyses to show changes in the percentage of variance explained by each additional variable and the cumulative variances explained by the combination of these variables (Table 5). Of the variables in Table E1, only mother's education, gestational age, and day 1 highest plasma lactate value combine to explain intelligence scores. This latter variable, the only likely modifiable variable, explains less than 10% of the variance of these scores. The variables that combine to explain VMI scores are similar to those predicting the intelligence quotients but include septostomy,

TABLE 3. Characteristics of 7 normal-hearing preschool children after the neonatal arterial switch operation who had language disorders diagnosed clinically by speech-language pathologists

Characteristics	Children						
	1	2	3	4	5	6	7
Normal first neurodevelopmental assessment (mo)*	7	8	7	6	7	10	7
Language tests used for assessments							
PLS 3 or 4/CELF 3 or 4/TOLD-P-	+	+		+	+	+	+
PLAI II/TLC-E	+						
REEL-2/PPVT-III/BBCA-R/SPELT-P	+	+	+	+			
CSBS/CCC-2	+		+			+	+
Clinical diagnosis of communication disorder	+	+		+	+	+	+
Testing done for possible autism spectrum disorder	+		+	+	+	+	+
Assessment supporting the diagnosis of autism spectrum disorder							
DSM-IV	+		+	—	—	+	+
ADOS/ADI-R	+		+	—	—	+	+
GADS/CARS			+		+		
Behavioral history suggestive of social interaction difficulties	+	+	+	+	+	+	+
Sibling with history of autism spectrum disorder†				+		+	+

See Table E2 for language test reference list and definition of test abbreviations. *First follow-up visit: patient seen by neurodevelopmental pediatrician, nurse, audiologist, physical therapist. †Each has an older brother with Asperger's syndrome. +, Positive test response; —, negative test response. DSM-IV, Diagnostic and Statistical Manual of Mental Disorders—fourth edition²⁰; ADOS, Autism Diagnostic Observation Schedule¹⁸; ADI-R, Autism Diagnostic Interview—Revised.¹⁹ (see Table E2 for reference list).

TABLE 4. Significant ($P < .10$) variables found by means of linear regression analysis to be associated with 5-year psychologic test results after the neonatal arterial switch operation for the 61 children without autism spectrum disorder

Variable	Psychologic test			
	FSIQ	VIQ	PIQ	VMI
	Unadjusted effect size and probability	Unadjusted effect size and probability	Unadjusted effect size and probability	Unadjusted effect size and probability
Mother's schooling (y)	2.03 (0.54 to 3.53), $P = .009$	2.26 (0.65 to 3.87), $P = .007$	1.69 (0.25 to 3.12), $P = .022$	1.43 (−0.09 to 2.95), $P = .06$
Birth gestation (wk)	3.69 (1.72 to 5.66), $P = .000$	3.35 (1.06 to 5.65), $P = .005$	3.13 (1.23 to 5.03), $P = .002$	3.80 (1.87 to 5.72), $P = .000$
Birth weight (kg)				7.73 (1.48 to 13.98), $P = .016$
Preoperative base deficit (mmol/L)				−0.93 (−1.76 to −0.10), $P = .028$
Cardiopulmonary bypass time (min)	−0.06 (−0.11 to −0.00), $P = .035$	—	−0.06 (−0.10 to −0.01), $P = .028$	−0.06 (−0.11 to −0.01), $P = .023$
Crossclamp time (min)	−0.19 (−0.37 to −0.01), $P = .035$	—	−0.23 (−0.39 to −0.06), $P = .008$	−0.31 (0.47 to −0.14), $P = .000$
Postoperative, <24 h highest plasma lactate value	−2.22 (−3.75 to −0.73), $P = .004$	−1.97 (−3.69 to −0.25), $P = .025$	−2.07 (−3.48 to −0.66), $P = .005$	−1.61 (−3.13 to −0.08), $P = .039$
Postoperative, <24 h lowest base deficit (mmol/L)	1.37 (0.16 to 2.58), $P = .028$	—	1.65 (0.53 to 2.76), $P = .004$	1.12 (0.09 to 2.34), $P = .069$
Postoperative, >24 h, highest dopamine dosage used ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	—	−1.01 (−1.92 to 0.09), $P = .032$	—	—
Postoperative, >24 h, highest plasma lactate value (mmol/L)	−6.32 (−10.42 to −2.22), $P = .003$	−4.16 (−8.99 to 0.66), $P = .089$	−7.59 (−11.26 to −3.92), $P = .000$	−3.78 (−8.03 to 0.47), $P = .080$
Postoperative, >24 h, base deficit (mmol/L)	1.46 (0.24 to 2.68), $P = .019$	—	1.50 (0.37 to 2.64), $P = .010$	1.37 (0.16 to 2.57), $P = .027$
Days of ventilation	−0.63 (0.98 to −0.27), $P = .001$	−0.50 (−0.91 to −0.08), $P = .020$	−0.61 (−0.94 to −0.28), $P = .000$	−0.46 (0.82 to −0.09), $P = .015$
Days of hospitalization	0.37 (−0.50 to −0.24), $P = .000$	−0.37 (−0.52 to −0.21), $P = .000$	−0.32 (−0.45 to −0.19), $P = .000$	−0.27 (−0.41 to −0.12), $P = .000$
Cardiopulmonary resuscitation required	—	—	—	−21.97 (−43.80 to −0.13), $P = .049$

FSIQ, Full-scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; VMI, visual-motor integration.

TABLE 5. Sequential stepwise multiple regression analysis of predictor variables* for each psychologic test for the 61 five-year-old children without autism spectrum disorder after the neonatal arterial switch operation

	FSIQ		VIQ		PIQ		VMI	
	Adjusted effect size and probability	Change in % variance	Adjusted effect size and probability	Change in % variance	Adjusted effect size and probability	Change in % variance	Adjusted effect size and probability	Change in % variance
Mother's schooling (y)	1.38 (0.04 to 2.80), $P = .057$	11.1%, $P = .009$	1.56 (0.15 to 3.26), $P = .072$	9.6%, $P = .015$	—	—	1.44 (0.07 to 2.81), $P = .040$	5.7%, $P = .06$
Birth gestation (wk)	2.63 (0.65 to 4.62), $P = .010$	11.7%, $P = .004$	2.25 (0.12 to 4.63), $P = .063$	6.9%, $P = .032$	2.78 (0.95 to 4.61), $P = .004$	15.5%, $P = .002$	—	—
Birth weight (kg)	—	—	—	—	—	—	6.46 (0.70 to 12.21), $P = .029$	8.4%, $P = .02$
Septostomy	—	—	—	—	—	—	9.01 (1.95 to 16.07), $P = .013$	7%, $P = .03$
Postoperative, <24 h highest plasma lactate value (mmol/L)	−1.96 (−3.31 to −0.60), $P = .005$	9.9%, $P = .005$	−1.74 (−3.37 to −0.12), $P = .036$	6.3%, $P = .036$	−1.78 (−3.11 to −0.44), $P = .010$	9.2%, $P = .01$	−1.65 (−3.04 to −0.26), $P = .021$	7.2%, $P = .02$
Percentage of variance explained by the multiple regression model		32.7%		22.8%		24.1%		28.3%

FSIQ, Full-scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; VMI, visual-motor integration. *Adjusted effect size and probability after linear regression of variables are associated with psychologic test results from Table 4.

which explains an additional 7% of the variance, as well as birth weight instead of gestational age.

The variable DHCA was not included in Table 4 because the duration of DHCA did not reach a significant level of unadjusted effect size on univariate analysis. However, all 5 of the children with PIQ scores of less than 70 had DHCA. Of the 33 children requiring DHCA, 5 (15%) had PIQ scores of less than 70 compared with no PIQ scores of less than 70 for those 32 children without DHCA (exact sig = .053).

Children With Autism

All variables from Table E1 were compared for the children with and without autism. Differences were found only in preoperative highest plasma lactate values (7 [6] mmol/L [with autism] vs 4 [7] mmol/L [without autism], $t = -2.215$, $P = .03$) and DHCA time ($n = 33$; 7 [3] minutes [with autism] vs 19 [20] minutes [without autism], $t = 2.945$, $P = .006$). All 4 children with autism had intact ventricular septum and the ASO, resulting in a prevalence of 11% in this subgroup. Three of the 4 children with autism had septostomy, and 2 of these required DHCA. The fourth child had DHCA without septostomy. None of the 4 with autism had an antenatal diagnosis of TGA; required repeat CPB in the operating room, extracorporeal membrane oxygenation, cardiopulmonary resuscitation, or reintervention; or had convulsions. Two children with autism and 1 child with an LD without autism have a sibling with Asperger's syndrome. A retrospective review of charts revealed no other child had a sibling with autism. Genetic investigations were negative for karyotype, Fragile X, del 22q.11.2 in 4 children with autism and also for Rett syndrome in 1 girl. Three children with autism had a normal magnetic resonance image on hospital discharge, and 1 had a small subependymal hemorrhage; this latter child and one of the other children with autism had repeated normal magnetic resonance image results.

We assessed whether any variables were predictive for autism. The only variables significantly related to autism at a P value of less than .10 in univariate logistic regression analysis were having a sibling with autism and highest preoperative plasma lactate value. In the multiple logistic regression model the odds for autism were 7.18 times higher for patients having a sibling diagnosed with autism (odds ratio, 7.18; confidence interval, 3.71–1389.41; $P = .005$). After adjusting for children having a sibling with autism, the odds ratio of autism corresponding to the highest preoperative plasma lactate value was 1.27 (confidence interval, 0.99–1.61), with marginal significance ($P = .057$).

DISCUSSION

This article confirms the low mortality previously reported^{13,22} and adds to previous publications^{3,6} on the preschool outcomes after the ASO by presenting data from a later surgical era. In keeping with past publications,^{3,13} children with diagnoses such as postdischarge meningitis and au-

tism considered to be unrelated to the perioperative period were excluded from predictive analysis. The finding that 4 (6%) of the 65 children in the cohort had autism is unusual.

This article suggests that after the ASO for TGA, children at 5 years of age are similar to their peers in terms of growth and health parameters, with few exceptions. Two (3%) of 65 children had motor impairment linked to preoperative complications, and 17 (26%) children had speech difficulties, language difficulties, or both. Seven (11%) of 65 children had LD. Cognitive ability for the total cohort, and more specifically for those without LD, compares favorably with the published literature.^{3,6,9,10} Those with LD differed significantly from those without LD on their FSIQ and VIQ measurements, which is in keeping with their diagnosis. They demonstrated relative strength but with wide variability in nonverbal areas. Four of the 7 children with LD were given diagnoses of autism characterized by deficits in social interaction, impaired communication, and restricted or repetitive interests and behaviours.²⁰ These children differed significantly from the remainder of the cohort on all psychologic measures, including the nonverbal measures.

Stepwise multiple regression analyses of the 5-year psychologic scores for children without autism show that less than one third of the variance within the scores can be explained by the studied variables. Mother's education is a predictor. Low birth weight is also related to outcomes, which is consistent with other reports.²² The highest plasma lactate value within the first postoperative day explains 6% to 10% of the variance in intelligence scores and supports previous findings.²³ Because this is a potentially modifiable variable, further investigation into causes of high lactate values could lead to improved outcomes. Similar to the prediction of intelligence scores, only 26% of the variation in VMI scores was explained by the studied variables; the use of septostomy contributed 7% and was associated with lower scores. There is potential for improvement with further study of brain insult associated with septostomy²⁴ or the underlying hypoxia contributing to its use.

This study found a high percentage of children with speech and language difficulties. Children who have undergone the ASO for TGA have been reported to have significantly greater language difficulties compared with the general population, despite cognitive abilities in the average range.^{3,4,6,8,9} Although structural aspects of language (vocabulary and syntax) appear intact, specific difficulties with symbolic talk during play and storytelling, particularly with describing the story character's internal affective states, are at risk.^{11,12}

We found an unexpectedly high rate of autism in our sample of children undergoing the ASO, roughly 10 times higher than current prevalence estimates of 6 per 1000.²⁵ Diagnosable medical conditions, syndromes, and single-gene disorders make up less than 10% of autism diagnoses.^{25,26} Evidence from family and twin studies suggests that "idiopathic"

autism is highly inheritable because of interactions of multiple genes modified by epigenetic and environmental factors.²⁶ In this study 2 of the 4 children with autism had an older sibling with Asperger's syndrome. Hence the increased rate of autism in our cohort might partly be related to overrepresentation of related disorders among siblings. In addition, 1 of the 3 children with LD had a sibling with autism.

Several studies have investigated prenatal and perinatal risk factors associated with autism.^{27,28} High preoperative plasma lactate values, a surrogate measure of tissue hypoperfusion, was the only medical variable that was more abnormal among children with autism in this study. This variable had marginal predictive significance in multivariate analysis. However, all 4 children with autism had TGA with an intact ventricular septum, a group at risk for increased hypoxia. The septostomy received by 3 of the 4 children with autism is also linked to preoperative brain injury.²⁴ Specific brain injury is not supported for these children because brain imaging was within normal limits. In children with TGA, abnormal fetal circulation and brain oxygenation, neonatal hypoxia, and surgical risks are well known.²⁹ Abnormal brain microstructure and metabolism have been reported in newborns with congenital heart disease.³⁰ Any of these insults can interact with a genetic predisposition to lead to autism. TGA is generally considered an isolated cardiac malformation that is rarely associated with genetic syndromes. However, should the association of TGA and autism in this article be confirmed, this might indicate a shared genetic susceptibility or shared environmental insult during development.

The strengths of this study are the high proportion of children, 95.5% of survivors, available at 5 years for individual assessment and the prospectively collected predictive variables. Although follow-up occurred at 5 centers, all assessors were certified, protocols were closely followed, and the centers have worked as a multisite research team since 1996. A limitation of this article is the small number of subjects with complex forms of TGA; however, some studies do not include these children,^{3,4} and this study provides an opportunity to view their outcomes. The major limitation of the study is that not all children were seen by a speech-language pathologist, and thus the speech and language diagnoses might underestimate the proportion of children with these difficulties. Also, not all parents were asked about a family history of autism, although all were asked whether there were child development or mental health concerns in the extended family. No comparison subjects are available for this study, but standardized measures with population-normative data are used throughout.

CONCLUSIONS

After the ASO, preschool children have cognitive skills within population norms. However, we report an increased incidence of LD, supporting concern about discourse abilities. Follow-up of children after the neonatal ASO should

include a complete speech and language evaluation, with particular attention to social use of language and family history of LD, autism, or both. Investigation into a possible genetic link between TGA and autism is recommended. The importance of mother's schooling as a predictor of psychologic test results, the link of TGA with autism, and the minimal effect of intraoperative variables on cognitive scores support a strong genetic influence in the outcome of these children.

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TABLE E1. Characteristics of 65 survivors undergoing the neonatal arterial switch operation in relation to complexity of cardiac anomaly

	Total (n = 65)	ASO (n = 36)	ASO/VSD (n = 19)	Complex (n = 10)	F or χ^2	P value*
Preoperative						
Socioeconomic status†	42 (12)	42 (14)	44 (10)	42 (12)	0.264	.769
Mother's schooling (y)	13 (3)	13 (3)	13 (5)	12 (2)	0.224	.800
Male sex	42 (65%)	23 (55%)	13 (31%)	6 (14%)	0.222	.895
Year of operation	1999.9 (2.0)	1999.5 (2.1)	2000.8 (1.7)	1999.5 (1.8)	3.106	.052
Antenatal diagnosis	6 (9%)	2 (6%)	4 (21%)	0 (0%)	4.766	.092
Age at operation (d)	11 (7)	10 (7)	10 (8)	14 (7)	1.336	.270
Birth gestation (wk)	39 (2)	39 (2)	39 (1)	38 (3)	0.972	.384
Birth weight (kg)	3.4 (0.6)	3.3 (0.5)	3.4 (0.5)	3.5 (1.0)	0.128	.880
Balloon septostomy	35 (54%)	24 (68%)	8 (42%)	3 (30%)	5.723	.057
Ventilation (d)	5 (4)	4 (4)	4 (3)	6 (8)	1.103	.338
Highest dopamine used ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	4.4 (7.2)	5.9 (8.2)	3.4 (5.9)	1.1 (3.2)	2.183	.121
Highest plasma lactate value (mmol/L)	3.6 (3.3)	4.0 (3.8)	3.5 (2.7)	2.0 (1.4)	1.610	.208
Lowest base deficit (mmol/L)	-4.4 (4.7)	-5.6 (4.3)	-4.1 (3.9)	-0.3 (5.6)	5.744	.005
Operative						
Cardiopulmonary bypass time (min)	137 (74)	123 (75)	136 (21)	190 (113)	3.463	.038
Lowest flow for >10 min ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	104 (30)	105 (34)	107 (29)	95 (14)	0.604	.550
Crossclamp time (min)	68 (22)	57 (16)‡§	74 (12)	96 (26)	21.979	<.001
Lowest temperature during CPB (°C)	25 (3); range, 19–29	25 (3)‡	26 (2)‡	23 (3)	4.855	.011
DHCA used	33 (50%)	27 (75%)	2 (11%)	4 (40%)	21.232	<.001
DHCA time (min; n = 33)	18 (19)	16 (18)	15 (10)	37 (24)	2.315	.116
Lowest temperature just before DHCA (°C)	23 (2); range, 19–27	23 (2)	21 (0.4)	22 (3)	1.059	.359
Need for re-CPB	7 (11%)	1 (3%)	1 (5%)	5 (50%)	19.008	<.001
Postoperative, <24 h						
Highest dopamine used ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	7.6 (4.7)	7.5 (3.8)	8.0 (5.8)	7.1 (5.8)	0.106	.900
Highest plasma lactate (mmol/L)	5.3 (2.6)	5.5 (2.3)	5.1 (3.0)	5.0 (2.6)	0.246	.783
Lowest base deficit (mmol/L)	0.88 (3.2)	1.7 (3.2)§	-1.0 (2.4)	1.5 (3.6)	5.093	.009
Postoperative >24 h						
Highest dopamine dosage used ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	7.1 (4.9)	7.4 (4.6)	6.4 (5.6)	7.6 (4.7)	0.293	.747
Highest plasma lactate value (mmol/L)	2.1 (0.9)	1.9 (0.8)	2.5 (1.2)	2.1 (0.7)	2.143	.126
Lowest base deficit (mmol/L)	1.4 (3.3)	2.1 (3.4)	0.1 (2.4)	1.6 (3.9)	2.187	.121
Overall						
Duration of ventilation (d)	9 (10)	8 (12)	9 (9)	11 (7)	0.378	.686
Duration of hospitalization (d)	27 (25)	27 (26)	26 (26)	29 (17)	0.065	.937
Clinical convulsions occurred	4 (6%)	3 (8%)	1 (5%)	0 (0%)	0.978	.613
Cardiopulmonary resuscitation required	2 (3%)	0 (0%)	0 (0%)	2 (20%)	11.349	.003
Extracorporeal membrane oxygenation used	2 (3%)	1 (3%)	0 (0%)	1 (10%)	2.221	.329
Reintervention	6 (9%)	1 (3%)	2 (11%)	3 (30%)	6.976	.031

Values are presented as means (standard deviations) or number (percentage). Note: After the Bonferonni correction, *P* values of .001 or less remain significant. ASO, Isolated arterial switch operation; ASO/VSD, ASO with ventricular septal defect repair; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest. *One-way analysis of variance or χ^2 analysis. †Mean (SD) = 43 (13); Blishen and colleagues.¹⁴ ‡Significant difference from the complex group (*P* < .01). §Significant difference from the ASO/VSD group (*P* < .01).

TABLE E2. References for language measures

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