Impact of Prenatal Diagnosis on Neurocognitive Outcomes in Children with Transposition of the Great Arteries

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Objectives To assess the effect of prenatal diagnosis of congenital heart disease on neurocognitive outcomes in children with d-transposition of the great arteries (TGA) after surgical correction.

Study design A prospective study of children born with a TGA between 2003 and 2005 and aged 4 to 6 years was conducted. General intelligence, language, executive functions, and social cognition scores and preoperative, intraoperative, and postoperative factors were evaluated according to time of TGA diagnosis. Neurocognitive data were also compared with a control group.

Results Forty-five eligible patients (67% male) were examined; 29 had a prenatal diagnosis of TGA and 16 did not. All children were comparable in age, sex, and demographic variables. Diagnostic groups did not differ in preoperative, intraoperative, and postoperative variables. Preoperative acidosis was more frequent in the postnatal group (18% versus 3%). All patients had normal IQ scores, language, and verbal working memory. However, neurocognitive deficits were more prevalent and more severe in children with a postnatal-TGA. Prenatal diagnosis was associated with better outcomes in executive functions.

Conclusions Prenatal diagnosis of TGA is associated with better neurocognitive outcomes. Time of diagnosis may influence the development of early complex cognitive skills such as executive functions. *(J Pediatr 2012;161:94-8).*

See editorial, p 7

Prenatal diagnosis of congenital cardiac malformations has been associated with decreased neonatal morbidity because it allows for optimal early preoperative management.[1,2] Prompt treatment of the cardiac condition in a controlled environment has proven to reduce the risk of multiorgan failure, metabolic acidosis, and neurological preoperative insult in a large cohort of children in whom transposition of the great arteries (TGA) was prenatally diagnosed.[3] To date, data on the effect of prenatal diagnosis on neurocognitive development are limited to one study conducted in children at 1 year of age.[4] Long-term predictive validity of outcomes may be limited because normal development at 1 year does not always predict later cognitive outcomes.[5,6] Follow-up at an age at which cognitive deficits may be emerging is necessary to determine patient-specific risk factors for developmental dysfunction.

Children with d-transposition after surgical correction are at higher risk for specific neurocognitive deficits in domains such as language, visual-spatial skills, executive functions, and social cognition despite being of normal intelligence.[7-10] This study sought to evaluate the impact of time of TGA diagnosis on long-term cognitive outcomes in 4- to 6-year-old children who, as neonates, underwent an arterial switch operation between 2003 and 2005. Our study not only concerns general intellectual outcome, but also focuses on the emergence of early higher-order cognitive skills such as executive functions, receptive language, and social cognition that are known to be associated with important changes during the preschool years. We address these questions: (1) Does time of TGA diagnosis influence preoperative, intraoperative, and postoperative variables?; and (2) Is prenatal diagnosis of TGA associated with better long-term cognitive outcomes for IQ and specific higher-order cognitive skills such as executive functions and social reasoning?

Methods

All children born with a TGA between 2003 and 2005 were screened for enrollment in a single-center prospective study of neurocognitive outcomes conducted at Necker Children's Hospital (Paris, France). Eligibility criteria included a diagnosis of TGA with intact ventricular septum or ventricular septal defect (VSD) in

CHD	Congenital heart disease
TGA	Transposition of the great arteries
VSD	Ventricular septal defect

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Supported by the association for research in cardiology from Foetus to Adults (Association pour la Recherche en Cardiologie du Foetus à l'Adulte), Necker Children's Hospital, Paris, France. The authors declare no conflicts of interest.

 10.1016/j.jpeds.2011.12.036

children who underwent a neonatal arterial switch operation with a single method of vital organ support (continuous full-flow cardiopulmonary bypass grafting). Exclusion criteria were birth weight <2.5 kg, the presence of genetic syndromes (including 22q11 deletion), an associated extra-cardiac anomaly or cardiovascular anomalies requiring aortic arch reconstruction and the use of deep hypothermic circulatory arrest, or additional open surgical procedures. In addition, normal cardiac condition, age at evaluation (4-6 years), French as a first language, parent's consent to participation, and geographic location (region of Paris) were also taken in account for patients' enrollment in the study. This study was approved by the ethics committee of Necker Children's Hospital. Cognitive performance was compared with a control group of children (n = 45) recruited and examined in the same period and same geographic area. Parental educational level and socioeconomic status were recorded for all children.

All medical data were extracted from hospital records. Time of diagnosis (prenatal-TGA versus postnatal-TGA), presence or absence of a VSD, birth weight, gestational age, Apgar score at 5 minutes, hemodynamic condition (metabolic acidosis), and the need for balloon-atrial septostomy were part of the preoperative data. Metabolic acidosis was defined with a pH level <7.2. Age at the arterial switch operation, total bypass time and total cross-clamp time, and postoperative intensive care unit stay were examined.

All tests were administered by a single examiner (J.C.) who did not review patient-related medical factors, including time of diagnosis, before conducting the evaluations.

General intelligence was assessed with the Columbia Mental Maturity Scale.[11] Receptive language was evaluated with a comprehension subtest from the Neuropsychological Assessment.[12] The executive function domain included a thorough evaluation of 5 principal components. Cognitive inhibition was assessed with the Animal Stroop Test[13]; behavioral inhibition was evaluated with the knock and tap subtest from the Neuropsychological Assessment[12]; working memory was measured with the digit span task from the Wechsler Intelligence Scale for Children 4th edition[14] and with a spatial span task[15]; and cognitive flexibility was evaluated with the Dimensional Card Sorting Test,[16] a well-known neuropsychological test for preschool children. Social cognition development was measured with 3 tests of Theory of Mind, which assessed children's comprehension of false belief.[17] These tasks are commonly used in clinical settings and have age-standardized scores on the basis of scores of the general population. For these tests, children had to infer a character's false belief to correctly predict their behavior, beliefs, and knowledge (**Appendix**; available at www.jpeds.com).

Statistical Analyses

One-way ANOVA with post hoc testing (Tukey HSD [Honestly Significant Difference] test) for specific comparisons across groups was used to compare patients' results for continuous variables that were distributed normally. Nonparametric χ^2 tests were used for dichotomous variables. A discriminant function analysis was conducted to determine the patient-specific factors that differentiated the prenatal from the postnatal group the most. Linear multiple regression analyses were used to compare both groups of patients according to time of diagnosis for continuous variables, and logistic regression analyses were used on dichotomous variables. Adjustments for socioeconomic status and parental educational level were applied to all models of regression. Values were considered significant when P value <.05. Statistical analyses were performed with Statistica software (version 6.1; StatSoft Inc, Maisons-Alfort, France).

Results

Sixty eligible children were identified in the database. Parents of 6 children declined to participate in the study, and two children were excluded because of developmental disorders not previously identified (autism spectrum disorder and severe language disability). Six families could not be contacted because of a change of address, and one child refused to cooperate with the administration of the tests. Therefore, 45 eligible children (75%) participated in the study. No significant differences were found between participants (n = 45) and non-participants (n = 15) for all medical-related variables ($P > .05$). Twenty-nine children had a prenatal diagnosis of TGA (64%), and 16 children did not (36%).

We compared children with and without a prenatal diagnosis for preoperative, intraoperative, and postoperative variables and demographic characteristics (**Table I**). The percentage of children who were currently using remedial school services (psychologist, language therapist, special school aids) is reported in **Table I**.

The two groups did not differ significantly in the incidence of any of the preoperative, intraoperative, and postoperative

Table I. Characteristics of children with TGA according to time of diagnosis

	Prenatal diagnosis (n = 29)	Postnatal diagnosis (n = 16)
Birth weight, g	3210 (449)	3280 (476)
Gestational age, weeks	38.57 (1.92)	39.54 (1.15)
Apgar score, 5 minutes	8.9 (1.1)	8.7 (1.8)
Associated diagnosis of VSD, %	31	31
Acidosis, %	3	18
Atrial septostomy, %	58	62
Age at surgery, days	7.5 (3.9)	6.6 (2.9)
Bypass time, minutes	131 (22)	138 (19)
Aortic clamp time, minutes	86.6 (15)	84 (11)
Intensive care unit stay, days	6.5 (5)	6.3 (3)
Family socioeconomic status*	2.1 (0.90)	1.69 (0.94)
Father's educational level†	3.3 (1.44)	2.9 (1.61)
Mother's educational level†	3.5 (1.57)	2.8 (1.75)
Children receiving remedial school services, %	45%	69%

Values are means (SD). Analyses were calculated by using the independent-sample t test and χ^2 tests. No significant differences were found for any of the variables.

*Socioeconomic status was scored according to the index from the French National Demographic Statistical Institute in a scale from 0 to 3, with a higher score indicating a higher socioeconomic status.

†Parental educational level was scored according to the French National Education Diploma classification (0 = primary school education; 1 = middle education; 2 = high school diploma; 3 = college undergraduate; 4 = college graduate/masters degree, and 5 = postgraduate/doctoral degree).

variables. Demographic characteristics, including the family's socioeconomic status and parental educational level, were higher in the prenatal group, but again without reaching statistical significance. However, the parametric *t* test used lacked sufficient power to detect significant differences in family's socioeconomic status and parental educational levels in both TGA subgroups. In addition, to further examine the possible patient-specific factors (medical and demographic) that may contribute the most to group differentiation (prenatal versus postnatal TGA), a discriminant function analysis was conducted. Results from this multivariate model indicate that only the presence of metabolic acidosis at birth significantly predicts group membership (Wilks Lambda test = 0.82; P = .04).

Table II shows neurocognitive mean scores of patients with TGA as a group, TGA according to time of diagnosis, and control subjects. Comparisons were made for the TGA group as a whole to the control group and for each TGA diagnosis subgroup (prenatal and postnatal) independently to the control group. Moreover, comparisons between prenatal-TGA and postnatal-TGA are also presented. All scores for the control group are in the reference range. When the TGA group, regardless of time of diagnosis, is compared with the control group, significant differences are observed for most cognitive domains. Children with TGA had significantly lower scores in response motor inhibition, made more errors, and had longer reaction times in the Stroop test. Performances in spatial working memory, cognitive flexibility, and all tests of social cognition are also significantly lower for the TGA group regardless of time of diagnosis. However, children with TGA as a group did not significantly differ from control subjects in IQ, verbal working memory, and receptive language scores.

When comparing children with a prenatal diagnosis alone with the control group, significant differences are limited to cognitive inhibition for reaction times and performance in one test of social cognition: theory of mind unexpected transfer. Conversely, in comparison with control values, children with a postnatal diagnosis of TGA performed significantly lower in all executive functions (except response motor inhibition and verbal working memory) and in all social cognition tests. Furthermore, children in whom TGA was diagnosed before birth showed significantly better performances than children with a postnatal diagnosis in cognitive flexibility and in two tests of social cognition: unexpected contents and unexpected transfer theory of mind.

To determine the severity of deficits observed in both groups (prenatal- and postnatal-TGA), the percentage of children who obtained scores −2 SD below normal control values were compared. Scores for IQ, verbal working memory, and language were in the reference range for all children, regardless of time of diagnosis. However, in the executive function domain, children with a prenatal diagnosis, compared with children without, had significantly fewer scores −2 SD below normal values for cognitive inhibition for number of errors (10% in the prenatal group versus 56% in the postnatal group). Moreover, children in the prenatal group obtained significantly fewer scores −2SD below normal values in two social cognition tasks: in appearance/reality task (20% versus 49%) and in unexpected content task (13% versus 72%).

We performed multivariate regression analyses to determine the possible influence of preoperative, intraoperative, and postoperative factors including time of TGA diagnosis on cognitive outcomes. All medical factors aforementioned with adjustments for socioeconomic status and parental educational levels were included in the analyses, with each cognitive variable as the dependent variable. Results show that prenatal diagnosis of TGA is significantly associated with better scores at cognitive flexibility and social cognition tests. Lower scores at spatial span were significantly associated with lower gestational age. Also, the presence of a VSD was significantly associated with fewer errors in the Stroop test.

Discussion

Neurocognitive deficits in children with a d-TGA after surgical correction continue to be reported despite great progress in

Table II. Neurocognitive outcomes of patients with TGA as a group, prenatal TGA and postnatal TGA diagnosis subgroups, and control subjects

Cognitive domain	Test	TGA (n = 45)	Prenatal diagnosis (n = 29)	Postnatal diagnosis (n = 16)	Control group (n = 45)
IQ	Columbia Mental Maturity Scale	113 (8.3)	114.5 (8.50)	112.4 (8.06)	116 (8.85)
Receptive language	NEPSY-Comprehension	12.4 (0.80)	12.65 (0.55)	12.25 (1.12)	12.5 (0.81)
Response motor inhibition	NEPSY-Knock and tap	24.25 (3.81)*	24.31 (2.46)	24.14 (5.82)	25.97 (2.12)
Cognitive inhibition	Stroop test (number of errors)	3.08 (3.02)*	2.41 (2.48)	4.31 (3.59)*	1.42 (1.48)
	Stroop test (reaction time)	82.42 (31.61)*	77.82 (28.05)*	90.74 (36.71)*	61.03 (20.53)
Verbal working memory	Digit span Weschler Intelligence Scales for Children IV	2.84 (2.49)	2.96 (2.48)	2.62 (2.57)	3.64 (2.55)
Spatial working memory	BEM-144 blocks	3.06 (2.12)*	3.62 (2.0)	2.06 (2.01)*	4 (2.03)
Cognitive flexibility	Dimensional Card Sorting Test	7.28 (2.86)*	8.10 (2.65)	5.64 (2.61)*,†	8.66 (2.09)
Theory of mind 1	Appearance/reality distinction	2.02 (1.21)*	2.31 (1.03)	1.50 (1.36)*	2.68 (0.55)
Theory of mind 2	Theory of mind–unexpected contents	1.91 (1.23)*	2.34 (0.97)	1.12 (1.31)*,†	2.68 (0.59)
Theory of mind 3	Theory of mind–unexpected transfer	0.95 (1.27)*	1.31 (1.33)*	0.31 (0.87)*,†	2.15 (1.24)

NEPSY, a developmental neuropsychological assessment; *BEM-144*, battery of memory efficiency 144 blocks (batterie d'efficience mnésique).
Mean scores with SD in parentheses.
*P < .05 for comparisons in each group of patients with control subjects.
†P < .05 for comparisons between prenatal-TGA and postnatal TGA.

surgical management. Children with ductal-dependent lesions are at risk of ductal closure and therefore at high risk of acidosis, hypoxemia, and hypoxic-ischemic injury.[18] Several studies have demonstrated an association between prenatal diagnosis of congenital heart disease (CHD), including TGA, and a significant decrease in preoperative morbidity.[2,3,19] It has been argued that prenatal diagnosis of cyanotic cardiac defects allows for optimal management, such as planned delivery at a specialized cardiac center, prompt administration of prostaglandin, and balloon atrial septostomy when required. Prenatal diagnosis of CHD has been related to a minimized risk of metabolic acidosis and perhaps prevention of cerebral damage.[20] Potential long-term benefits of prenatal diagnosis on cognitive development have never been reported in children with TGA after the first year of life.[4]

Our results showed that time of diagnosis was not significantly related to medical or demographic variables when each variable was taken independently in between-group comparisons. However, when all patients' characteristics, including preoperative, intraoperative, and postoperative factors were analyzed simultaneously in a multivariate model, presence of preoperative acidosis significantly predicted group membership. The percentage of children with a postnatal diagnosis of TGA with a pH level <7.2 was 18%, compared with 3% in the prenatal group. In addition, children with a prenatal diagnosis obtained significantly better scores in 3 of the measures administered when compared with the postnatal group. They obtained significantly higher scores in cognitive flexibility and in 2 of 3 tests of theory of mind (social cognition). Furthermore, children with a prenatal diagnosis significantly differ from control subjects only for cognitive inhibition capacities and one-third tests of theory of mind. In contrast, children with a postnatal diagnosis demonstrated significantly worse performance in all tests except IQ, language, response motor inhibition, and verbal working memory. In addition, a higher percentage of children with a postnatal diagnosis had scores below −2 SD on executive and social cognition tests.

The effect of prenatal diagnosis on long-term cognitive outcomes can provide an ideal opportunity to determine the potential influence of preoperative factors, including timely medical management, on children's development. This population had a low incidence of co-existing anomalies including genetic syndromes, underwent corrective surgery at a very early age, and usually had normal cardiac function after the operation. The only earlier study on development in children with TGA according to time of diagnosis did not find significant differences in outcomes with the Bailey Scales of infant development at 1 year of age.[4] In that study, however, children with a prenatal diagnosis were less likely to have Psychomotor index scores at least 2 SD below normative values, even when this difference did not reach statistical significance. Only 7% of the children had a prenatal diagnosis of TGA. In our study, 64% of the children had a prenatal diagnosis of their malformation, which allowed us to compare more proportionally equivalent groups of children born during a limited and recent period (2003-2005). Furthermore, children who are at risk for poor cognitive development may not be identified on the basis of 1-year test scores.[6] This particularly applies for complex cognitive function, which is known to have progressive development throughout early childhood. It has been shown that children with TGA may be vulnerable to diminished executive function and may be at risk for impairments of social cognition.[10] Delays in diagnosis may expose these children to a higher prevalence of these deficits. In our study, children with a postnatal diagnosis exhibited generally more severe deficits, because a higher proportion obtained scores −2 SD below control values. More important, children with a prenatal diagnosis displayed only specific impairments in one executive domain, namely, cognitive inhibition capacities. This shows that all executive components are not compromised and that deficits may be limited for this group.

Executive function and social cognition are known to have a great influence on school achievement and social adaptation. These core components of cognition are necessary to produce goal-directed behaviors and to develop the ability to understand other people's mental states and emotions. These abilities involve the protracted development of prefrontal brain structures.[21,22] Recent research shows that early brain insult during the first months of life is strongly related to cognitive long-term sequelae in a variety of pediatric populations.[23] During early brain development, including the prenatal period, processes such as synaptogenesis, dendritization, and myelination, which are critical for brain connectivity and functional networks, are highly active.[24] Early insults, including hypoxic-ischemic moderate injuries, may potentially lead to disruption of these processes that can affect optimal future maturation.[23] Executive function appears to be highly compromised in the long-term when a very early brain insult has occurred, supporting the concept of early brain vulnerability.[23] Moreover, prefrontal brain structures that play a key role in the development of these skills have been described as highly sensitive to lack of oxygen supply.[25] The degree to which deficits are observable may also depend on the early onset of adverse oxygen-related risk. This may be the case for neonates with TGA who present a risk for hemodynamic instability and hypoxic-ischemic injury, especially when the diagnosis is delayed. In this study, higher-order cognitive skills appear to be affected in all children with TGA. However, the extent to which these deficits can be defined as severe and affecting broader and more numerous domains is modulated by a prompt diagnosis of TGA. Furthermore, early white matter abnormalities recently have been related to executive disfunctions in preschool children born preterm.[26] Similar cerebral anomalies have been found in children with TGA,[27] the deficits of which may resemble those found in preterm children.

Several limitations should be considered when interpreting this study. We studied a single cardiac defect successfully corrected in the neonatal period; therefore our results cannot be generalized to all children with CHD. Also, variability in preoperative, intraoperative, and postoperative factors may differ across centers, and results may only be applicable for children receiving similar treatment. Furthermore, although

acidosis was more common in children with a postnatal diagnosis, only 4 of 45 children had a pH level <7.2. Finally, we do not know whether these deficits reflect a maturational lag or a permanent impairment. Longitudinal research is ongoing to determine how these deficits evolve as children get older and the potential association of these deficits to time of diagnosis with time.

Higher-order cognitive skills such as executive function and social cognition reasoning appear to be impaired in patients with worse outcomes for children with a postnatal diagnosis of TGA. Longitudinal follow-up is necessary to determine long-term outcomes in this vulnerable population. ■

We thank all the parents and children for their participation and all teachers for their collaboration in the control group recruitment. We also thank Philippe Bonnet and Denis Corroyer for their statistical support.

Submitted for publication Jul 29, 2011; last revision received Nov 11, 2011; accepted Dec 20, 2011.

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Appendix

The Columbia Mental Maturity Scale[11] is an individually administered test designed to assess the general reasoning ability of children between the ages of 3 and 9 years. This test includes 100 pictorial and figural classification items arranged in levels of complexity. It evaluates general nonverbal intellectual abilities. Raw scores are converted to a standard IQ with a mean of 100 and a SD of 15.

Each subtest of the developmental neuropsychological assessement (NEPSY) assesses a specific neuropsychological domain for children from 3 to 12 years old. The Language Comprehension Subtest assesses receptive language through the comprehension of verbal instructions, with gradual increasing syntactic complexity. Reliability ranges from 0.73 to 0.89. The Knock and Tap Subtest assesses the capacity to control motor actions in response to a contradictory visual stimulus. The child learns a pattern of motor sequences and has to inhibit the automatic tendency to imitate the experimenter's contradictory motor actions. Validity studies show that there is a weak correlation between the executive function subtests of the NEPSY and tests of general intelligence. NEPSY is commonly used in clinical populations, including children with a diagnosis of attention-deficit/hyperactivity disorder. Subtests of executive functions have been described as good predictors of attention and hyperactivity disorders.

The Animal Stroop test[13] is used to assess cognitive inhibition capacities in young children from 3 years old. It consists of a pictorial version of the Stroop task, and it does not require reading abilities. It was designed to be sensitive to individual and age-related differences in impulse control and visual interference sensitivity. Visual stimuli (4 exemplar images of animals) are congruent in the first condition, neutral in the second condition and then incongruent in the third condition, in which each animal's head is substituted with another animal's head. Interference is elicited from the well-documented preferential processing of facial information over body information. Children are required to name the body and inhibit a preferred response on the basis of the identification of the animal's head. Scores are given for Reactions Times and the number of errors committed. Validity studies of populations with frontal lobe epilepsy, traumatic brain injury, or attention-deficit/hyperactivity disorder support this task as a sensitive measure of cognitive inhibition.

Digit Span is a subtest from the Wechsler Scales 4th edition.[14] It measures verbal working memory skills: retaining and manipulating information for a short time. It includes two parts: forward and backward. The forward part requires the child to repeat numbers as they were stated by the experimenter, whereas the backward part requires the child to repeat in the reverse order as they were stated. When scores in the forward part are within the reference range, Digit Span backward is taken as the reference for verbal working memory. In the spatial span task,[15] analogous to the verbal working memory task, the stimuli are visual (a set of small squares randomly positioned). Children reproduce a sequence of squares locations in the same order as they saw it and then backward.

The Dimensional Card Sorting Test[16] is a widely used measure of cognitive flexibility capacities in young children. Children are required to sort a series of bivalent cards, first according to one dimension (eg, shape), then according to the other (eg, color), and finally a combination of trials with rapid switches in dimensions. Performances progressively increase between 4 and 6 years and are commonly impaired in children with attention-deficit/hyperactivity disorder, prefrontal cortical damage, and autism.

Theory of Mind[17] was used to measure social cognition. Three standardized false belief tasks were used to test children's ability to attribute thoughts and intentions to others that differ from their own. They assess the ability to consider mental states as a cause for explaining behavior in others. Appearance/reality distinction, unexpected contents, and unexpected transfer measure the capacity to understand another person's mistaken belief on a situation in which the child knows the final outcome, but the character does not. Developmental studies show that these 3 tasks strongly correlate in both, typical and atypical populations. Children younger than 4 years old typically fail these tests by attributing their own egocentric perspective to the character. Deficits in theory of mind understanding are common in children with autism, and they refer to difficulties to determine the intentions of others, a lack of understanding of how their behavior affects others, and problems with social reciprocity.