Neurologic and psycho-intellectual outcome related to structural brain imaging in adolescents and young adults after neonatal arterial switch operation for transposition of the great arteries

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Objective: We studied brain structure abnormalities in adolescents and young adults who had undergone the neonatal arterial switch operation for transposition of the great arteries and related them to the neurologic and psycho-intellectual outcomes.

Methods: In a prospective longitudinal study, 60 unselected adolescents and young adults who had undergone surgery with combined deep hypothermic circulatory arrest and low flow cardiopulmonary bypass were re-evaluated at a mean age of 16.9 ± 1.7 years to determine their clinical neurologic status, intellectual development, and psychological condition. The results were related to population norms and anatomic structural abnormalities assessed by brain magnetic resonance imaging, with consideration of the risk factors in the preoperative and perioperative periods.

Results: Neurologic impairment was more frequent (10%) than in the normal population. Although the average full-scale, verbal, and performance intelligence quotients were not reduced, scores >2 standard deviations less than the expected mean were increased. Above average scores were found for analytical thinking, but the orthography testing results were reduced. The self-rated psychological condition was better than expected. Magnetic resonance imaging demonstrated moderate or severe structural brain abnormalities in 32% of the patients. Periventricular leukomalacia was detected in >50%; its severity correlated with the grade of neurologic impairment, which correlated significantly with reduced intelligence, analytical thinking, and orthography. Preoperative acidosis and hypoxia were the only independent patient-related risk factors for neurologic dysfunction, reduced intelligence, periventricular leukomalacia, and reduced brain volume.

Conclusions: Despite encouraging overall neurodevelopmental outcomes, a significant minority had performances below the expected level, emphasizing the need for ongoing surveillance. Considering the high frequency of structural brain abnormalities, prospective long-term studies are needed to define their prognostic value with respect to the neuropsychological outcomes in childhood and adolescence. (J Thorac Cardiovasc Surg 2014;148:2190-9)

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See related commentary on pages 2199-200.

Although the neonatal arterial switch operation (ASO) to correct transposition of the great arteries (TGA) has been accepted for >25 years as the method of choice because of the low mortality and good long-term cardiologic results, longitudinal examination of the neurodevelopmental outcomes in adolescents and young adults has been very rare.[1]

Within our institution's prospective arterial switch reassessment program, the patients had been evaluated at a mean age of 5.4 years[2,3] and 10.5 years[4-6] after neonatal ASO, when they had presented with increased neurologic impairment but normal average intelligence scores. The parent-rated, but not self-rated, psychosocial stress was also elevated.

The purpose of the present study was to reassess our patients' neurologic status, formal intelligence, and psychological condition and to perform structural brain imaging. Our patients were adolescents and young adults from a large homogeneous group of unselected patients. Limited information is available concerning the risk factors for structural brain abnormalities, and the possible relations to neuropsychological outcomes in this age group need additional assessment.

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Abbreviations and Acronyms

ASO = arterial switch operation
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
IQ = intelligence quotient
MRI = magnetic resonance imaging
MRT = Mannheimer Rechtschreib test
PVL = periventricular leukomalacia
SD = standard deviation
SP = Spearman's correlation coefficient
TGA = transposition of the great arteries
tMRI = total structural brain MRI

METHODS

Demographic Data

From 1986 to 1992, 96 neonates with TGA had undergone ASO. The present study group consisted of 60 unselected adolescents and young adults (67% of the 89 long-term survivors), who had been re-evaluated at a mean ± standard deviation (SD) age of 16.9 ± 1.7 years (range, 14.0-21.1), 78.3% of whom were male. Of the 60 patients, 54 (90%) had participated in both preceding studies at a mean age of 5.4 years[2,3] and 10.5 years,[4-6] and 6 (10%) had participated in the study at a mean age of 5.4 years and had been re-evaluated by questionnaire at a mean age of 10.5 years. Of the 60 patients, 74% had had simple TGA, and 18% had also had a nonimportant ventricular septal defect, and an additional 5% had an important ventricular septal defect that had been closed during ASO. Two patients had had coarctation of the aorta corrected during later infancy. Finally, 87% had undergone atrial balloon septostomy, and all had been treated with prostaglandin E_1 before surgery to keep the arterial duct open. At re-evaluation, all patients, except for 2 with spastic tetraplegia and 1 with distinct scoliosis, had a normal endurance capacity as assessed by spiroergometry, and none was taking cardiac or psychiatric medication. The rate of attendance to special schools and the lack of a final school examination was 12% each. The socioeconomic status, evaluated according to the income producer's profession, was not different from that of a normal population.[7]

The present study was designed as a case series with published controls and prognostic factor analyses. The demographic data and risk factors for neurodevelopmental outcome are listed in Table 1. The ethical medical committee of the Aachen University of Technology (Aachen, Germany) approved the study, and all patients and their parents provided written informed consent.

Surgical Management and Perfusion Methods

The age at ASO ranged from 1 to 39 days (mean 7.1 ± 5.1); 2 patients were >12 days old. ASO was performed under conditions of deep hypothermic circulatory arrest (DHCA) and combined low flow cardiopulmonary bypass (CPB) by 2 surgeons (B.J.M., S.H.D.). The standardized surgical technique using the Lecompte modification and bypass modalities has been previously described.[2] The CPB times are listed in Table 1.

Neurologic Examination

The clinical neurologic status was evaluated by an experienced examiner (H.H.H.-G.). The results were classified as normal or borderline without functional impairment (grade 0) or moderately (grade 1, functional impairment requiring therapy) or severely (grade 2, dependent on continued assistance) impaired. Neurologic dysfunction was diagnosed in patients who had ≥1 of the following abnormalities: abnormal head shape or growth, abnormal cranial nerves, motor dyspraxia, ataxia, sensory dysfunction, palsy, clinical seizures during the previous 5 years, and dysreflexia.

Psycho-Intellectual Testing

The battery of tests focused on the evaluation of formal intelligence, academic achievement, and psychological condition. The tests were normalized for age and/or gender and were conducted by 2 examiners on 2 consecutive days within the scope of a standardized operative sequence.

Intelligence. The Hamburg-Wechsler intelligence test (German version of the Wechsler Adult Intelligence Scale, revised),[8] with a possible mean score of 100 ± 15, was used to determine cognitive development and reduction of effort. Of the 60 patients, 56 were tested using 6 of 11 subtests (information, arithmetic, similarities, vocabulary, picture completion, and block design) to evaluate the verbal, performance, and full-scale intelligence quotient (IQ) (Table 2).

Analytical thinking. The Leistungsprüfsytem nach Horn[9] is a standardized German intelligence test consisting of 14 subtests with a mean possible score of 100 ± 15. Subtest 3 (geometric shapes) was given to 56 patients to analyze analytical thinking as an indicator of the so-called fluid intelligence, which has been assumed to be inherited rather than acquired.

Orthographic performance. The Mannheimer Rechtschreib test (MRT)[10] is a German standardized test of orthography, defined as the assessment of spelling skills and mistakes. We used the long form, which consisted of 120 items. The 6 subtests, consisting of 20 items each (Table 2), represent different categories to identify key aspects of orthographic performance. The results of the subtests and a summary range are expressed as percentages and were compared with published normal values from an age-, graduation-, and province-matched German population.

Psychological condition. The Brief Symptom Inventory[11] was used to obtain standardized information from 57 patients on their subjective psychological condition during the previous 7 days compared with that of healthy controls. In the Brief Symptom Inventory, 53 items have been subsumed into 9 symptom scales to provide psychometric information (somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism). From these scales, 3 global indexes can be derived: the Global Severity Index, measuring the overall psychological distress level and defining the patient's perception level of psychological problems; the Positive Symptom Distress Index, measuring the intensity of symptoms; and the Positive Symptom Total, indicating the number of self-reported symptoms. The test results are expressed as normalized T scores, with higher values representing increased psychological stress. The present study focused mainly on the Global Severity Index T score as the most sensitive factor for evaluating a patient's general psychological condition (Table 2).

Structural Brain Imaging

Structural brain magnetic resonance imaging (MRI) was performed in 54 patients to evaluate possible cortical and white matter abnormalities after exposure to an increased risk of preoperative, perioperative, and postoperative hypoxia and hypoperfusion of the brain. The exclusion criteria were a cardiac pacemaker or cochlea implant and noncompliance because of anxiety (n = 4).

MRI was performed using a 3.0 Tesla Arechiva magnetic resonance scanner (Philips Healthcare, Best, The Netherlands). The scanning protocol included acquisition of the following images: T2-fluid attenuated inversion recovery, diffusion, T2* fast field echo (axial orientation), T2-turbo spin echo, and T1* fast field echo (sagittal orientation).

The MRI scans were evaluated by a neuroradiologist (T.K.), who was unaware of all clinical data, by visual inspection. Anatomic abnormalities were classified with respect to the following criteria: reduced brain volume (intrinsic volume loss [ventricular dilatation] and extrinsic volume loss [increased width of sulci]—evaluated separately), periventricular leukomalacia (PVL), focal non–periventricular white matter lesions, encephalomalacia, and additional abnormalities. Brain volume loss and PVL were classified into 4 grades: no abnormality (grade 0), mild (grade 1), moderate (grade 2), and severe abnormality (grade 3) (Table 3). In addition, a summary score of all criteria was determined, the total structural brain MRI

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