Neurodevelopmental Outcome and Health-related Quality of Life in Children With Single-ventricle Heart Disease Before Fontan Procedure

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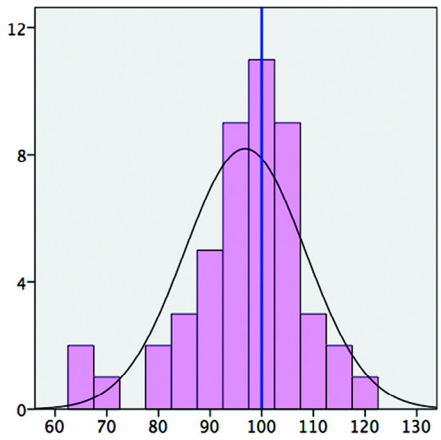
Neurodevelopmental impairment and impaired quality of life constitute a major source of morbidity among children with complex congenital heart disease, in particular for single-ventricle (SV) morphologies. Risk factors and quality of life determining clinical and neurodevelopmental outcome at 2 years of age are examined. In a 2-center cohort study, 48 patients with SV morphology (26 hypoplastic left heart syndrome and 22 other types of univentricular heart defect) have been examined before Fontan procedure between 2010 and 2015. Patients were assessed with the Bayley Scales of Infant and Toddler Development, Third Version (Bayley-III), and the Preschool Children Quality of Life (TAPQOL) questionnaire. A total of 44 patients underwent hybrid procedure (n = 25), Norwood procedure (n = 7), or shunt or banding procedure (n = 12) as first surgery before subsequent bidirectional cavopulmonary anastomosis (n = 48). Median cognitive, language, and motor composite scores on the Bayley-III were 100 (range 65-120), 97 (68-124), and 97 (55-124), respectively. The language composite score was significantly below the norm ($P = 0.025$). Risk factors for poorer neurodevelopmental outcome were prolonged mechanical ventilation, longer days of hospital stay, and more reinterventions (all $P < 0.05$). Parents reported a good quality of life for their children. Children undergoing Fontan procedure show a favorable development and good quality of life. More complicated postoperative course and reinterventions constitute risk factors for impaired neurodevelopment. Improving postoperative management and implementing routine follow-up assessments aremeasures to further improve the neurodevelopmental outcome of this high-risk patient population.



Cognitive Composite Score in 2-3 y/o children with SV.

Central Message

Single-ventricle children show a favorable neurodevelopment and quality of life before Fontan procedure. Prolonged hospital stay and multiple reinterventions predicted outcome whereas surgical approaches did not.

Perspective

Extended neuroprotective strategies, further improvement of peri- and postoperative management, and reduction of pathologic hemodynamics leading to recurrent catheter interventions are important tools in the treatment of children with single ventricles. Nationwide routine follow-up assessments are warranted to further improve neurodevelopmental outcome.

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INTRODUCTION

Children with complex congenital heart disease (CHD), especially those with single-ventricle (SV) morphologies, are at the highest risk of developing neurodevelopmental impairment.[1] Advances in prenatal diagnosis, birth and perinatal treatment in pediatric heart centers, improved perioperative care including brain protective strategies (selective head perfusion and moderate hypothermia), and brain monitoring (near-infrared spectroscopy and amplitude-integrated electroencephalography) have increased survival rates to 80%-90% even for most complex variants of CHD.[2] However, only modest improvement of short- and long-term outcomes of palliated patients with univentricular heart morphology has been described over the past decades.[3] Results of the Infant Single Ventricle Trail[4] and of the Single Ventricle Reconstruction Trial[5] demonstrated that patients between 2004 and 2008 had mean psychomotor and mental developmental indices significantly lower than normative means.

These groups concluded that neurodevelopmental impairment in SV survivors might be more associated with innate patient factors (eg, genetic predisposition and intrauterine conditions) and overall morbidity in the first year than with intraoperative management strategies.[5] It is well described that neonates with complex congenital heart defects show neurologic abnormalities even before cardiac surgery.[6] Hypoxic conditions, risk of intracerebral hemorrhages, strokes and inflammatory processes caused by cardiovascular surgeries, and catheter interventions in the first year of life might further delay brain maturation and increase the likelihood of secondary acquired structural brain injury. In fact, it has been shown that the maturational delay of the brain is a risk factor for consequent brain injury and developmental delay.[7]

The aim of the present study was to investigate the neurodevelopmental outcome and quality of life of patients with SV morphology in the pediatric heart surgery era between 2010 and 2015 and to describe predictive risk factors determining outcome in children before Fontan procedure at 2-3 years of age.

MATERIALS AND METHODS

Study Population

Between April 2010 and July 2015, 76 consecutive patients with univentricular heart defects were prospectively enrolled at the University Pediatric Heart Center of Giessen, Germany (center A), or at the University Children's Hospital of Zurich, Switzerland (center B) and examined before Fontan surgery until July 2015. Two patients with genetic comorbidity were excluded. From 74 eligible patients, 9 were followed up in a heart center different from the study centers, of whom 2 were living abroad. In 9 cases, the parents refused participation. One patient underwent a heart transplant before the Fontan procedure and another underwent biventricular surgery. Two patients were excluded, as examinations according to the study protocol were not feasible (1 patient was too old for the inclusion criteria, and 1 patient was examined with the Bayley Scales of Infant Development-II). In 4 patients, the parents opted for palliative care.

Finally, 48 patients met all the study inclusion criteria. Baseline characteristics of the excluded population did not differ from those of the included children. The demographic data and perioperative parameters were prospectively collected at admission and during the hospital stay for each operation or intervention. Perinatal parameters were retrospectively collected from patient charts. Growth parameters was transformed into *z*-scores based on World Health Organization Child Growth Standards using the freely available Anthro Software, Version 3.2.2 (www.who.int/childgrowth/) or Pedz (www.pedz.de) for children born preterm. Socioeconomic status was evaluated with a short demographic questionnaire as proposed by Largo et al.[8] Total scores were calculated by adding the maternal education to the paternal occupation (each scored from 1 to 6). Low, intermediate, and high social classes were defined as total scores from 2 to 5, from 6 to 9, and from 10 to 12, respectively. All data were entered into a predefined database. The comprehensive study included also cerebral magnetic resonance imaging (MRI) and brain volumetric measurements, which will be reported separately.

The study was approved by the local ethics committee of the University of Giessen and Zurich, and written informed consent was obtained from the parents.

Early Childhood Assessments

Children were assessed aged 19.3-34.8 months with Bayley Scales of Infant and Toddler Development, Third Version (Bayley-III) by a certified pediatrician for each center. The test rates cognition (Cognitive Composite Scale [CCS]), language (Language Composite Scale [LCS]), and motor function (Motor Composite Scale [MCS]) on separate scales with 2 subscales for each of the latter 2 domains. The CCS estimates global cognition based on memory tasks, manipulation, and problem solving; the LCS assesses expressive and receptive communication; and the MCS investigates fine and gross motor functioning. Normative composite scores by age for each scale were calculated and compared to test norms (mean 100 points, standard deviation [SD] 15). For all scales, cut-off points of <85 and <70 were used to identify mild to moderate and severe delay.

Neurologic Examination

All children were examined for clinical neurologic abnormalities with a focus on motor functioning (graded as normal, reflex or tone abnormality, reflex and tone abnormality, or cerebral paresis) and sight or auditory disorders by a certified and trained pediatrician at each center at the same date as the Bayley-III assessment.

Preschool Children Quality of Life (TAPQOL)

The TNO-AZL (Netherlands Organisation for Applied Scientific Research Academic Medical Centre) Children's Quality Of Life