**Letter to
the Editor**

Neurodevelopmental Outcome of Children with Hypoplastic Left Heart Syndrome at One and Four Years of Age Comparing Hybrid and Norwood Procedure

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Keywords: congenital heart defect, hypoplastic left heart syndrome, norwood, neurodevelopmental outcome, hybrid procedure

To the Editor

Long-term neurodevelopmental outcome of children treated for Hypoplastic Left Heart Syndrome (HLHS) may be impaired.¹⁾ As younger gestational age has been shown to be associated with poorer neurodevelopmental outcome after cardiac surgery related to impaired brain maturation,²⁾ we suggested the cerebral vulnerability to be more sensitive to cardiopulmonary bypass surgery immediately after birth compared to later infancy. Two different treatment strategies for HLHS exist including the Norwood and Hybrid procedure.³⁾ Our hypothesis was that the impact of Norwood and Hybrid procedure on long-term neurodevelopmental outcome may be different by delaying cardiopulmonary bypass surgery to the age of 3 to 5 months when performing the Hybrid procedure as first stage.

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Received: April 21, 2016; Accepted: May 30, 2016

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Recently, we reported the neurodevelopmental outcome at one year of age for children treated for HLHS comparing Hybrid and Norwood procedure.⁴⁾ Meanwhile, we further followed this patient group until the age of 4 years. Further data on long-term neurodevelopmental outcome comparing Hybrid and Norwood procedure are still missing. Therefore, we aimed to report the neurodevelopmental outcome of infants treated for HLHS either by the Norwood or the Hybrid procedure at 4 years of age. Furthermore, we analyzed the impact of a learning curve after start of a Hybrid program.

In all consecutive infants with HLHS undergoing Hybrid (2006–2008) and Norwood procedure (2004–2008), we evaluated mid-term (at 1 year of age) and long-term follow up (at 4 years of age) after implementation of both treatment options in a single centre setting (for details see⁴⁾).

For neurodevelopmental assessment we included different tests according to the age of the patients: Therefore, at 1 year of age, we used the Bayley Scales of Infant Development II, while, at 4 years of age, we used the Wechsler Primary Preschool Intelligence Scale–III and the Movement-ABC 2. Further analysis included a comparison of outcome of the early (within first year after implementation of the procedure) versus the late treatment period (after first year of implementation).

By that, 31 (18 male) infants were treated with Hybrid (n = 13) or Norwood (n = 18) procedure⁴⁾ Norwood stage I procedure was performed using cardiopulmonary bypass (alpha-stat) with moderate hypothermia (22°C–28°C) and selective cerebral perfusion. We performed either a

Fig. 1 Above (A, left), at 1 year, motor (PDI) and (B, right), cognitive (MDI) outcome were significantly impaired compared to the norm [PDI 57 (49–99), $p < 0.001$; MDI 91 (65–109), $p = 0.002$]. Below (C, left), at 4 years of age, comparable results after Hybrid and Norwood procedure for cognitive outcome [median IQ: Norwood 92 (80–104) vs. Hybrid 88 (76–116), $p = 1.0$], (D, right) lower IQ in the early period independent of performed procedure [IQ early period 87 (76–101) vs. late period 96 (80–116), $p = 0.03$]. PDI: psychomotor development index; MDI: mental development index; IQ: intelligence quotient

modified Blalock-Taussig shunt or a Sano shunt and used modified ultrafiltration after cardiopulmonary bypass. For hybrid procedure pulmonary arteries were banded bilaterally with a 3 mm long Goretex tube (body weight < 3 kg, 3 mm diameter tube; body weight > 3 kg, 3.5 mm diameter tube).³ For the catheter-based intervention self-expanding bare metal stents (Sinus Repo, Optimed Co., Ettlingen, Germany) were used for the arterial duct stenting and balloon atrioseptostomy was performed by static balloon dilatation (12 mm diameter) or Rashkind procedure.

Until the age of 1 year, 20 children survived. We recently reported on the neurodevelopmental outcome at mid-term follow up (at 1 year of age) with significantly lower psychomotor development index (PDI) and mental development

index (MDI) outcome compared to the norm [median PDI 57 (49–99), $p < 0.001$; median MDI 91 (65–109), $p = 0.002$], but, of interest, independent of the type of surgical treatment by comparing Hybrid ($n = 9$) and Norwood ($n = 11$) procedure [PDI: Norwood 56.5 (49–81) vs. Hybrid 65 (50–99), $p = 0.18$; MDI: Norwood 93 (65–109) vs. Hybrid 88 (71–102), $p = 1.0$].⁴ Now, we are able to report on the long-term follow up (at 4 years of age), including the remaining 16 of 20 children, due to late death ($n = 1$), or lost to follow up ($n = 3$). Comparable with the results at 1 year of age, cognitive and motor performance were poorer than the norm [median IQ: 89 (76–116), $p = 0.02$; total motor score: $p = 0.002$], and again not correlated with the type of surgical treatment by comparing Hybrid ($n = 7$) and Norwood ($n = 9$)

procedure [IQ: Norwood 92 (80–104) vs. Hybrid 88 (76–116), $p = 1.0$; motor outcome: $p > 0.8$]. Of note, cognitive performance of children treated in the early treatment period was significantly lower compared to children treated in the late period independent of performed procedure [IQ early period 87 (76–101) vs. late period 96 (80–116), $p = 0.03$], while this effect was not found for motor outcome, which was comparable between early versus late treatment period ($p > 0.8$).

The neurodevelopmental impairments in cognitive and motor function that have been described at one year of age persist at 4 years of age in children with HLHS. The severity of impairments seems to be less pronounced for the cognitive outcome, being mildly impaired with a median total IQ within one standard deviation of the norm (**Fig. 1**). But, the motor outcome is more severely affected with a median score at the 20th percentile compared to the 50th percentile in the norm. In our small study population, a delay of cardiopulmonary bypass surgery by performing the Hybrid procedure is not associated with a better outcome at 4 years of age in children with HLHS. It is well known that other in particular pre-operative factors, such as altered intrauterine hemodynamics,⁵⁾ delayed intrauterine cerebral growth^{6,7)} or perioperative events during intensive care⁸⁾ contribute significantly to neurodevelopmental outcome.

Further long-term follow up until adolescence is needed to examine whether cognitive and motor outcome remains stable until school age in this population. Other studies reporting on neurodevelopmental outcome of cohorts of preschool children with HLHS showed comparable outcome results after Norwood procedure.⁸⁾

The improvement of cognitive outcome during the observed time period cannot be completely explained by the available data sets obtained in this small observational case series. Therefore, we need a prospective clinical study, revealing standardized data sets comparing the peri- and postoperative course in a larger group of patients.

Furthermore, for a better understanding of the mechanism leading to an impaired motor and cognitive outcome in this patient group and the effect of the type of surgical intervention, brain imaging studies need to be combined with neurodevelopmental outcome assessment in a multi-center trial.

In conclusion, at 4 years of age there are no evident differences between Hybrid and Norwood procedure in a small cohort of patients with HLHS. Nevertheless, the cognitive outcome is influenced by the time period of

treatment and improves with increasing institutional experience and knowledge, which to some extent may be explained as an institutional learning curve.

Acknowledgment

The study was supported by a grant of the Foundation Mercator.

Disclosure Statement

There are no disclosure statements about potential conflicts of interest.

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