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The relationship between preoperative fetal head circumference and 2-year cognitive performance after laser surgery for twin-twin transfusion syndrome

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Abstract

Objective—To determine the relationship between preoperative fetal head circumference (HC) and cognitive performance among children treated with laser surgery for twin-twin transfusion syndrome (TTTS).

Methods—Donor and recipient twin HCs were measured preoperatively (16 – 26 weeks' gestation) and at 2 years corrected age. Multilevel multivariate regression models were used to test pregnancy and child-level risk factors for lower Battelle Developmental Inventory 2nd Edition (BDI-2) scores. A repeated-measures ANOVA was used to examine HC growth among recipients and donors between preoperative and two years.

Results—Ninety-nine children were evaluated. The average BDI-2 score for the cohort was 101.4 (SD=12.2). After controlling for covariates, larger preoperative HC percentiles were significantly associated with an increase in total BDI-2 scores ($\beta=0.29$; $p<0.001$), where a 12.5% increase in preoperative HC percentile was associated with 1-point increase in total BDI-2 score. The mean recipient and donor twin HC percentiles preoperatively and at age 2 years were 51st percentile vs. 20th percentile ($p=.050$) and 60th percentile vs. 49th percentile ($p=.676$), respectively.

Conclusion—Smaller preoperative HC percentiles identified children at risk of lower, but still within normal range, total BDI-2 scores. The discordance in HC percentiles between the donor and recipient twin decreased after laser surgery.

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Introduction

Twin-twin transfusion syndrome (TTTS) occurs due to an unequal exchange of blood through placental vascular communications resulting in volume depletion with oligohydramnios in the donor twin and volume overload with polyhydramnios in the recipient twin. Selective laser photocoagulation of communicating vessels (SLPCV) performed between 16 and 26 weeks' gestational age (GA) is the preferred treatment for TTTS because it results in decreased perinatal morbidity and mortality.^{1–3} Perinatal survival and long-term outcomes including neurodevelopmental impairment have previously been studied.^{4–6}

We previously found that, in children that had laser surgery for TTTS, a smaller head circumference at 2 years of age was associated with lower overall cognitive performance.⁴ However, the relationship between preoperative fetal head circumference (HC) and cognitive performance has not been studied. Understanding the impact of fetal HC on neurodevelopmental outcomes may be useful in understanding the importance of fetal brain growth in the setting of the pathophysiological stresses of TTTS, and will aide in preoperative counseling and postnatal management of survivors.

The purpose of this study was to determine the relationship between preoperative fetal HC and cognitive performance among children treated with SLPCV for TTTS.

Material and Methods

This was a retrospective analysis of a prospectively enrolled cohort study.⁴ All consecutive patients treated for TTTS at a single center between 2007 and 2010 were eligible. The same inclusion and exclusion criteria were used.⁴ In brief, each patient underwent a detailed ultrasound examination including maximum vertical pocket (MVP) of amniotic fluid, fetal Doppler waveforms, fetal anatomy, placental location, and cervical length. TTTS was diagnosed at initial assessment if the monochorionic diamniotic multiple gestation had a MVP of fluid ≥ 8 cm in the recipient's sac and ≥ 2 cm in the donor's sac. The patients were staged prospectively according to the Quintero staging system.⁷ Laser surgery was performed within 24 hours of preoperative ultrasound evaluation. Cases were treated exclusively by SLPCV performed between 16 and 26 weeks' gestational age with or without sequential technique, as described in detail previously.⁶ Patients with gross intracranial abnormalities on preoperative ultrasound evaluation were not offered laser surgery.

The estimated fetal weight (EFW) prior to laser surgery was calculated using Hadlock's formula.⁸ Fetuses measuring less than the 10th percentile according to Hadlock standards for singleton gestations were designated as having intrauterine growth restriction (IUGR). The fetal HC was measured in the axial plane parallel to the base of the skull through the third ventricle, with the thalami located centrally and cavum septi pellucidi anteriorly. The ultrasound calipers were placed on the outer margins of the calvarium. The preoperative fetal HC measurements were converted into percentiles adjusted for gestational age based on Hadlock reference ranges. HC measurements $\leq 1^{st}$ percentile for gestational age were recorded as the 1st percentile. The definitions for prenatal and postnatal microcephaly are

not standardized.⁹ Some authors define microcephaly as less than 2 SD below the mean (<3rd percentile).^{9–11} Other authors define microcephaly as less than 3 SD below the mean (<0.1st percentile).^{12, 13} For the purposes of this paper, microcephaly was defined as less than 2 SD below the mean (<3rd percentile).

Pregnancy level data collected included maternal demographics (age, education, marital status, ethnicity), findings of the pre and postoperative ultrasounds, laser surgery characteristics (Quintero stage, gestational age, fetal growth restriction), and delivery information (birth in weeks, complications at delivery). A complete description of analyzed variables is available in our prior publication.⁴ At the child level, collected data included neurodevelopmental assessment and child growth parameters at 24 months (± 6 weeks) corrected age. The children underwent cognitive and developmental evaluation using Battelle Developmental Inventory, Second Edition (BDI-2).^{4, 14} The total BDI-2 developmental quotient standard score is computed as a sum of the 5 BDI-2 sub-domains, with a mean of 100 and standard deviation of 15. All scores, including abnormal scores, were included in this cohort. An abnormal standardized score was defined as a BDI-2 total developmental quotient of <70 or >130. The children also had HC measurements performed during the neurological examination. The postnatal HC was measured using a non-stretchable measuring tape as recommended by the Centers for Disease Control and Prevention (CDC) and performed by the nurse coordinator. The tape was securely wrapped around the widest possible circumference of the head across the forehead above eyebrows and ears and over the most prominent part of the back of the head. Based on the corrected age, HC measurements were converted into percentiles using World Health Organization (WHO) standards.¹⁵ The assessment at 24 months (± 6 weeks) corrected age was performed by a board-certified developmental-behavioral pediatrician in the outpatient setting as previously discussed.^{4, 16}

Statistical analyses

Descriptive statistics were first reported using IBM SPSS Statistics (version 23). Mplus version 7 (Muthén & Muthén, 2013) was used to run multilevel linear regression analyses to test preoperative HC and the pregnancy- and child-level covariates for BDI-2 scores. The multilevel framework was imposed for each of the linear regressions to allow for twins to be “nested” within pregnancy to account for shared and unshared variance among twin pairs. Multilevel bivariate linear regressions were first reported. Preoperative HC and covariates were all maintained in the multilevel multivariate linear regression analysis. Covariates that did not maintain significance in the multivariate model were systematically removed to allow for the most parsimonious possible final model.

A repeated-measures ANOVA was then used to chart differences between mean recipient and donor twin HC percentiles, both preoperatively and at 2-years corrected age for the total sample (singletons and twin pairs). Growth patterns were then plotted between recipients and donors solely for the twin pairs to demonstrate any catch-up head growth over time.

This study was approved by the institutional review boards of the Health Sciences Campus of the University of Southern California and Children’s Hospital Los Angeles.

Results

The study included 99 eligible children (56 families) treated with TTTS between 2007 and 2010. The majority of children were part of a twin pair ($n = 86$), with just over half of the children being recipients ($n = 51$). Thirteen co-twins from these families did not survive the prenatal or neonatal period and were unable to be assessed at the 2-year follow-up time point. The mean (M) preoperative and two-year head circumference percentile for all children was 36th percentile (SD = 30 percent) and 55th percentile (SD = 34 percent), respectively. The mean BDI-2 scores of the study group was 101.4 (IQR: 93, 109). Descriptive statistics for pregnancy-level and child-level factors are presented in Table 1.

Multilevel bivariate linear regressions for risk factors associated with BDI-2 scores are shown in Table 2. Preoperative HC was significantly associated with an increase in BDI-2 scores ($\beta = 0.07$, $p = .02$). Other child-level covariates used in the bivariate regressions were male gender (*ns*) and diastolic blood pressure (*ns*). Of the parent-level covariates, mother education ($\beta = 3.36$, $p < .001$) and GA at birth ($\beta = 0.79$, $p = .03$) were both associated with increased BDI-2 scores. Two years (± 6 weeks) age corrected for gestational age at birth ($\beta = -21.03$, $p = .08$), and Quintero stage ($\beta = -3.51$, $p = .06$) approached a significant association with BDI-2 scores.

To allow for the most parsimonious multivariate model, preoperative HC and all covariates of interest were included in the initial model and systematically removed one at a time according to non-significance. The final multivariate model can be found in Table 2. Preoperative percentile HC ($\beta = 0.08$, $p = .003$), male sex ($\beta = -6.32$, $p = .01$), mother education ($\beta = 3.64$, $p < .001$), GA at birth ($\beta = 0.89$, $p = .001$), and Quintero stage ($\beta = -3.02$, $p = .03$) were all significantly associated with BDI-2 scores. The mean BDI-2 total score among the cohort was 101.4 (SD = 12.2). After controlling for Quintero stage, GA at birth, gender, and maternal education level, larger preoperative HC percentiles were significantly associated with an increase in total BDI-2 scores ($\beta = 0.08$; $p < .001$), where a 12.5% increase in preoperative HC percentile was associated with 1-point increase in total BDI-2 score. Holding all other variables constant, the bottom and top preoperative HC percentiles were associated with BDI-2 standard scores of 97.4 and 105.4, respectively.

A supplemental set of analyses was tested to determine whether the significant relationship between preoperative head circumference and BDI-2 scores could be explained by a cutoff percentile (i.e., 3rd percentile and 10th percentile). However, the relationship between BDI-2 scores and preoperative HC was linear, suggesting a steady increase in BDI-2 scores as head circumference percentile increases. (Figure 1) Bivariate analyses validated there were no statistically significant differences between patients with a preoperative HC < 10th percentile ($n=31$; $M = 96.7$, $SD = 12.7$) compared to those with a HC ≥ 10 th percentile ($n=68$; $M = 103.6$, $SD = 11.5$) or between patients with a preoperative HC < 3rd percentile ($n=18$; $M = 98.5$, $SD = 9.8$) compared to those with a HC ≥ 3 rd percentile ($n=81$; $M = 102.1$, $SD = 12.6$). Of the 18 patients with microcephaly, 15 (83.3%) also had IUGR, indicating symmetrical fetal growth restriction. In the remaining 3 patients with non-symmetrical growth restriction (HC < 3rd percentile and EFW ≥ 10 th percentile), the EFWs measured in the 14th, 36th, and 88th percentiles, and the BDI-2 scores in these patients were 103, 101, and 99, respectively.

To better understand the statistically significant relationship between preoperative HC percentile and BDI-2 scores, recipients and donor twins were compared; recipients (M = 51st percentile) were in a significantly higher percentile than donors (M = 20th percentile) preoperatively ($p = .05$). (Figure 2a) However, there was no significant difference in HC percentiles between recipients (M = 60th percentile) and donors (M = 49th percentile) at 2-years corrected age. Among the 86 dual survivors, the recipients had a mean 13 mm larger HC than their donor siblings at preoperative assessment, which decreased to a 5 mm difference at a corrected age of 2 years. (Figure 2b). Conversion to age-appropriate HC percentiles demonstrated that the net difference between the recipient and donor twin decreased from a 31st percentile difference preoperatively to a 6th percentile difference at 2 years of age. (Figure 2c)

Discussion

This is to our knowledge the first study investigating the relationship between preoperative fetal HC measurements and postnatal cognitive performance in a cohort of children treated by laser surgery for TTTS. Smaller preoperative HC percentiles identified children at risk of lower, but still within normal range, total BDI-2 scores at two years of corrected age. The bottom and top preoperative HC percentiles were associated with BDI-2 standard scores of 97.4 and 105.4, respectively. Within this range of BDI-2 scores, a 12.5% increase in preoperative HC percentile was associated with 1-point increase in total BDI-2 score. There was a linear relationship between preoperative fetal HC percentile and the total BDI-2 score. (Figure 1)

In our cohort, children with and without preoperative HC measurements < 3rd percentile did not have significantly different mean BDI-2 standard scores, 98.5 versus 102.1, respectively. Thus, despite the presence of microcephaly in the midtrimester, fetuses with TTTS treated with laser surgery had overall favorable neurological outcomes. We hypothesize that this lack of significant difference is due partly to the neuroplasticity of the developing brain,¹⁷ as well as to donor twin catch-up growth after laser surgery, both in overall weight¹⁶ and head circumference. In our cohort, there was no longer a statistical difference in the HC measurements between former recipient and donor twins at 2-years corrected age.

In the general literature, serial HC measurements in preterm and term-born children with appropriate growth have been positively associated with cognitive development, while microcephaly and poor HC growth has been associated with poor neurodevelopmental outcomes.^{18, 19} Microcephalic preterm infants at 38 to 42 weeks' corrected gestational age have been shown to have significantly decreased cerebrospinal fluid, cortical gray matter, deep nuclear gray matter, myelinated white matter and unmyelinated white matter compared to infants with a normal HC.¹⁸ However, a major limitation of previously published studies assessing HC and neurodevelopment outcome has been combining all etiologies of microcephaly into a single cohort. There are numerous genetic abnormalities, structural anomalies, or perinatal insults that can affect brain development resulting in microcephaly.^{20–22} In our cohort, the fetal growth restriction and lagging preoperative HC measurements was due to the underlying pathophysiology of TTTS.²³ This notion is further supported by the finding that the majority (83%) of fetuses with microcephaly also concurrently had

overall symmetrical IUGR. After laser surgery, the donor twin is permitted catch-up growth due to cessation of shunting of blood volume and nutrients to the recipient twin through vascular communications. Unequal placenta share with the donor twin having a smaller percentage of the total placental mass is often a co-contributing factor to inter-twin weight discordance.²⁴ Laser surgery does not correct the unequal placental share factor and this could be a reason for incomplete catch-up growth of the donor twin HC.

As previously demonstrated, higher Quintero stage was associated with slightly lower BDI-2 scores.⁴ TTTS Quintero stage III and IV have donor and/or recipient twins with critically abnormal Doppler waveforms. There is evidence in singleton pregnancies suggesting that placental dysfunction in fetal growth restriction is a risk factor for neurodevelopmental impairment.²⁵ The increased villous vascular resistance may lead to fetal cardiovascular changes reflected in the Doppler waveforms of the umbilical artery, umbilical vein, ductus venosus and middle cerebral artery.²⁵ Depending on the degree of placental villous obliteration, the umbilical artery end-diastolic flow may be decreased, absent, or reversed.²⁶ With progressive hypoxia, 'brain-sparing' can be seen with increased blood flow to the fetal brain in order to compensate for decreasing oxygen availability.²⁵ If fetal cardiac function becomes impaired, central venous pressure increases and abnormalities within the venous circulation can also be demonstrated by a pulsatile umbilical vein and/or absent or reversed a-wave in the ductus venosus. The hemodynamic alterations that occur as a result of placental insufficiency may adversely impact neurodevelopment by impairing nutrition and oxygen transport.^{25, 26} Although the type of placental dysfunction described in singletons with fetal growth restriction and in TTTS differ, the resultant fetal effects from poor placental function may be similar. However, unlike singletons with placental dysfunction, twins with treated TTTS have an opportunity for *in utero* recovery, which may translate to relatively improved neurological prognosis.

There were limitations of the study. First, although the data in this study were collected prospectively, this remains a retrospective study. Also, a control group of uncomplicated monochorionic twins was not available to determine the degree to which blood flow through shared vascular communications contributed to our findings. Second, oligohydramnios and the stuck position of the donor twin can limit the accuracy of ultrasound images and measurements. Third, the HC measurements at birth were not collected in order to minimize the variability in measurements performed by multiple providers. Furthermore, the children did not undergo serial formal postnatal evaluations at our institution to assess whether or not shifts in HC percentiles and/or BDI-2 scores exist as the children continue to develop. Many postnatal environmental factors known to impact neurodevelopment such as living conditions, infections, and nutrition were not assessed in this study.^{27, 28} Fourth, parental HC, intelligence quotient, and psychiatric disorders were not collected, and therefore we are unable to control for these potential confounders.^{29, 30} Fifth, the number of patients with fetal HC measurements < 3rd percentile was relatively small (n = 18), the possibility of a negative affect from *in utero* microcephaly cannot be ruled out. In addition, the small number of patients within this subset limits our ability to make a meaningful comparison between those with a HC < 3rd and < 10th percentile. Most likely, those with a HC measurement < 3rd percentile do not actually have a mean BDI-2 score that is higher than those with a HC measurement < 10th percentile. Sixth, the effect of slowed fetal head growth

on developmental abilities is controversial. While some evidence suggests that lagging fetal head growth is associated with developmental impairment,³¹ other studies have not found such an association.^{30, 32} As demonstrated in Figure 1, the low BDI-2 scores were not limited to the group with lower preoperative HC percentiles. This wide dispersion of BDI-2 scores likely exists because HC is just one of many factors involved in neurodevelopmental impairment. Hence, our finding on HC is limited by the lack of uniform postnatal neuroimaging to rule out co-existing abnormalities such as periventricular leukomalacia, intraventricular hemorrhage, or aberrant myelination. We recently published the results of the 56 children in this cohort that were ‘high-risk survivors’ and had neonatal cerebral imaging.³³ Ten twins (18%) had at least one cerebral lesion, which was a significant risk factor for neurodevelopmental impairment among these ‘high-risk survivors’.³³ Finally, given the neurodevelopmental outcome of fetuses with HC measurements is largely dependent on the underlying etiology and associated anomalies, the findings of this study should be applied to survivors of TTTS after laser surgery. Importantly, growth restricted fetuses in TTTS have symmetrically decreased biometric parameters, not just the HC, as would be in other conditions in which only the HC is decreased (e.g. ‘primary microcephaly’). Primary microcephaly is often associated with intracranial structural anomalies and other significant neurological abnormalities.^{34–36}

In summary, preoperative HC percentiles were associated with overall cognitive performance at 2 years corrected age in children who underwent *in utero* laser surgery for TTTS. Despite smaller HC percentiles being associated with a lower total BDI-2 scores, it was reassuring that the majority of children remain within the normal range. Parents can be counseled that the majority of children after laser surgery for TTTS will not need additional behavioral and developmental assistance, outside of routine care for corrected postnatal age.

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Bulleted statements**What's already known?**

- Smaller head circumference (HC) at 2 years of age after laser surgery for twin-twin transfusion syndrome (TTTS) is associated with lower overall cognitive performance.

What does this study add?

- Smaller fetal HC at the preoperative ultrasound done before laser surgery for TTTS is also associated with lower overall cognitive performance.
- HC percentiles are smaller for the donor compared to the recipient at the preoperative assessment, but this discordance decreases significantly at 2 years of age.

Figure 1.
Scatter plot and linear trajectory of preoperative fetal head circumference (HC) percentile with the Battelle Developmental Inventory, Second Edition, (BDI-2) total standard score obtained at age 2 years corrected age.

Figure 2.

(a) Comparison of mean head circumferences acquired during fetal life prior to laser surgery (preoperative) and at two years corrected age. (b) Millimeter mean difference between the recipient and donor in twin pairs at preoperative and two years corrected age. (c) Age-adjusted percentile mean difference between the recipient and donor in twin pairs at preoperative and 2 years corrected age.

Table 1

Pregnancy and child-level characteristics. Results are n (%) or mean (standard deviation)

Pregnancy level	Overall (N=56)
Mother's education	
Some HS or less	5 (8.9%)
HS graduate or GED	8 (14.3%)
Some college	10 (17.9%)
AA degree or Pro Cert	8 (14.3%)
College graduate (BA/BS)	15 (26.8%)
Graduate/Pro education	10 (17.9%)
Quintero stage	
Stage I	10 (17.9%)
Stage II	13 (23.2%)
Stage III	29 (51.8%)
Stage IV	4 (7.1%)
GA (weeks) at surgery	20.51 (2.62)
GA (weeks) at delivery	33.12 (3.44)
Individual child level	Overall (N=99)
Sex	
Female	49 (49.5%)
Male	50 (50.5%)
HC measurement	
Preoperative (cm)	17.50 (3.10)
Preoperative (percentile)	35.66 (29.61)
2-year (cm)	47.98 (1.94)
2-year (percentile)	54.55 (34.41)
BDI-2 total score	101.4 (12.21)

HS, high school; GED, General Education Diploma; AA, Associates Degree; BA, Bachelor of Arts; BS, Bachelor of Science; GA, gestational age

Table 2

Multilevel multivariate regression to test pregnancy and child-level risk factors for lower Battelle Developmental Inventory 2nd Edition (BDI-2) scores.

	Unadjusted BDI-2 estimates (β)	p-value	Adjusted BDI-2 estimates (β)	p-value
Pregnancy-level				
Mother's Education	3.36 (1.76 to 4.96)	<.001	3.64 (1.94 to 5.33)	<.001
Two-year corrected age	-21.03 (-44.28 to 2.23)	.08	--	--
GA at Birth	0.79 (.09 to 1.49)	.03	0.89 (.37 to 1.41)	.001
Quintero Stage	-3.51 (-7.14 to .12)	.06	-3.02 (-5.72 to -.31)	.03
Individual child-level				
Male gender	-2.50 (-7.94 to 2.95)	.37	-6.32 (-11.08 to -1.56)	.01
Diastolic blood pressure	-0.18 (-.40 to .03)	.10	--	--
Preoperative HC	0.07 (.01 to .12)	.02	0.08 (.03 to .13)	.003

GA, gestational age; HC, head circumference