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PREDICTORS OF TWO-YEAR COGNITIVE PERFORMANCE AFTER LASER SURGERY FOR TWIN-TWIN TRANSFUSION SYNDROME

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Abstract

Objective—To determine risk factors for poor cognitive performance among children treated with in utero selective laser photocoagulation of communicating vessels for twin-twin transfusion syndrome (TTTS).

Methods—This was a prospectively enrolled cohort study. Cognitive performance at age 2 years (± 6 weeks) was assessed via Battelle Developmental Inventory 2nd Edition (BDI-2). Multilevel regression models evaluated risk factors for poor cognitive performance at shared (“pregnancy”) and individual (“child”) levels. In addition to development, blindness, deafness and cerebral palsy were assessed based on physical exam. A priori power analysis determined that a sample of 100 children was required for adequate statistical power (0.80).

Results—100 children (57 families) were evaluated. Total BDI-2 score was within normal range (mean=101.3, SD=12.2), with one child having a BDI-2 of <70. Individual child-level risk factors for lower BDI-2 included male sex ($\beta=-0.37$, $p<0.01$), lower head circumference ($\beta=0.28$, $p<0.01$), and higher diastolic blood pressure ($\beta=-0.29$, $p<0.01$). At the pregnancy level, lower maternal education ($\beta=0.60$, $p<0.001$), higher Quintero stage ($\beta=-0.36$, $p<0.01$), and lower GA at birth ($\beta=0.30$, $p<0.01$) were associated with worse cognitive outcomes. Donor/recipient status, GA at

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surgery, fetal growth restriction, and co-twin fetal demise were not risk factors. The rate of neurodevelopmental impairment (blindness, deafness, cerebral palsy, and/or a BDI-2 score <70) was 4%.

Conclusion—Overall cognitive performance quotients were in the normal range, with risk factors for poor outcomes seen at the pregnancy and child levels. Clinical and socio-economic characteristics can identify at-risk children needing additional interventions.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) arises in monochorionic twin gestations due to unequal exchange of blood through the placental vascular communications. Selective laser photocoagulation of communicating vessels (SLPCV) is the preferred treatment for TTTS resulting in improved prenatal and perinatal survival.¹⁻³ With enhanced survival, identification of risk factors to later cognitive performance and outcomes becomes critical. However, few studies have reported risk factors associated with long-term developmental outcomes among infants with TTTS post laser surgery and none in the United States.

While neonatal neurologic outcomes have been characterized, there is a lack of data on developmental outcomes after laser surgery in U.S. patient cohorts. A recent systematic review and meta-analysis identified eight international studies that reported long-term developmental outcomes after laser therapy for TTTS outside the perinatal period.⁴ In this meta-analysis, prevalence of non-perinatal neurologic morbidity, abnormal standardized test of neonatal development or both was 11.1% with rates of cerebral palsy in the range of 4-6% (cf. Rossi et al. 2011).⁴ In counseling mothers carrying fetuses with TTTS and eligible for SLPCV, a clear understanding of perinatal neurological morbidity and longer-term developmental outcomes is needed. Elucidation of the antecedent risk factors would enhance clinical and parental decision making regarding treatment and prospective screening.

To that end, the aim of this study was to describe the risk factors associated with poor developmental outcomes of survivors treated in utero with laser surgery in a large cohort of U.S. patients at two years of age. Based on the previous research⁴, we hypothesized that lower gestational age at birth, later gestational age at time of procedure, higher Quintero stage, lower birth weight, and donor twin status will result in poorer cognitive performance.

MATERIALS AND METHODS

Study population

All consecutive patients that were treated for TTTS between December, 2007 and May, 2010 were considered eligible and contacted for this study. TTTS was diagnosed at initial assessment at Los Angeles Fetal Therapy (University of Southern California) if the monochorionic-diamniotic multiple gestation had a maximum vertical pocket of fluid 8 cm in the recipient's sac and 2 cm in the donor's sac. Each case was prospectively classified according to the Quintero staging system.⁵ All patients were given the options of expectant management, pregnancy termination, amnioreduction, laser surgery, or selective reduction (at another center). Patients with Stage I TTTS were informed of the controversy of undergoing laser surgery, and were offered the option of expectant management with

laser surgery only for disease progression. Patients were not offered laser if preoperative ultrasound revealed gross abnormalities of intracranial anatomy. Cases were exclusively treated via SLPCV with or without sequential technique, as described in detail previously.³

All consecutive laser-treated TTTS patients during the study period were contacted prior to the time their child was to reach age 2 years (± 6 weeks) corrected for gestational age and invited to participate by a study nurse, who was blinded to the predictors. Reasons for why patients declined participation were recorded. All subjects were evaluated in the Southern California Clinical Translational Science Institute's Clinical Trials Unit at Children's Hospital Los Angeles, an institution independent and physically separated from Los Angeles Fetal Therapy. Families were given an incentive per child of \$25 for their participation. There was no travel budget.

This study was approved by the Institutional Review Board of the Health Sciences Campus of the University of Southern California and the Committee on Clinical Investigations at Children's Hospital Los Angeles.

Measures

The Amiel-Tison Neurodevelopmental Examination was used to determine cerebral palsy by a board-certified developmental-behavioral pediatrician. This test is based on the clinical presence of gross and/or fine motor delay together with neurological signs such as abnormal persistence of primitive reflexes, muscle tone, motor developmental progression or coordination.⁶ Hearing and vision impairment was determined through the same examination or previous clinical report. Additionally, parent and child demographics, including child height, weight, head circumference, and blood pressure, were collected at the 2-year-old visit.

A single board-certified neuropsychologist, masked to the subjects' clinical characteristics, evaluated the cognitive and developmental status of participants using the Battelle Developmental Inventory, Second Edition (BDI-2).⁷ This tool was selected on the basis of availability of normative data, targeted age range, and the availability of standardized versions in both English and Spanish languages. A Spanish translator assisted the neuropsychologist with the administration of the BDI-2 as needed. Patients and their twin cohort (if applicable) were assessed consecutively on the same day at approximately 2 years of age (± 6 weeks). Consistent with standardized administration of the BDI-2, each participant was assessed in the presence of one primary caretaker. In a few cases, the participant was unable to tolerate physical separation from their twin, who was then allowed to be present (playing separately) in the exam room.

The BDI-2 involves direct individual assessment and parental interview to measure key developmental skills in children from birth to 95 months (7 years, 11 months). Based on widely accepted developmental milestones for children, the BDI-2 assesses five developmental subdomains (personal-social, adaptive, motor, communication, and cognition) comprising overall development. The total BDI-2 developmental quotient (DQ) score is computed as a sum of the five BDI-2 subdomains, and it has a mean of 100 with standard deviation of 15. Individual items' scores range from zero to two points, with scores

based on one of three pre-determined criteria including observation, parent interview and/or performance on a structured task.

Neurodevelopmental impairment (NDI) was defined as having bilateral blindness (unable to fix on or track an object), bilateral deafness (requiring amplification), cerebral palsy (based on physical exam), and/or a BDI-2 Total Developmental Quotient of <70 (standardized score), in accordance with previous TTTS literature.⁸

Statistical analyses

Descriptive statistics and bivariate comparisons were produced using IBM SPSS Statistics (version 19; SPSS Inc, Chicago, IL).⁹ Bivariate comparisons were also calculated between participating and not participating families and between donors and recipients (e.g., t-tests for continuous measures, chi-square tests for categorical variables). Multilevel linear regression analysis was conducted in Mplus (version 6; Muthén & Muthén, Los Angeles, CA), with twins grouped or “nested” within pregnancy and missing data were subject to listwise deletion in the regression model.¹⁰ Unlike logistic regression, which describes the relationship between the presence or level of a predictor and the odds of obtaining a ‘yes’ or ‘1’ on the binary outcome variable, linear regression coefficients quantify the relationship between a predictor and the expected level or amount of a continuous outcome. Specifically, a standardized linear regression coefficient denotes the expected change in the (standardized) outcome for one standard unit change in the predictor. The multilevel approach extends the general linear regression model by accounting for the genetic and environmental experience shared by twins of the same family (the shared or “pregnancy” level), and the experiences unique to each child (the individual or “child” level). Multilevel regression allows for simultaneous inclusion of the effects of both child-level and pregnancy-level risk factors of cognitive performance; further, it supports the inclusion of families with two (twin) children as well as families with only one surviving child.

Due to the small number of children with neurodevelopmental impairment, total BDI-2 DQ score was considered the primary outcome for analysis. Child-level risk factors for development tested in the regression models included donor status (donor=1, recipient=0), male sex (male=1, female=0), height (cm), weight (kg), head circumference (cm), systolic and diastolic blood pressure (mm Hg), and heart rate (bpm). Pregnancy-level risk factors included gestational age (GA) at surgery and birth in weeks, the twins’ current corrected age in years, Quintero stage, presence (1) or absence (0) of fetal growth restriction, fetal demise, and complications at delivery, maternal and paternal age in years, maternal and paternal education (some college or more=1, high school or less=0), number of adults and children in the home, parents’ marital status (married=1, other=0), minority race/ethnicity (minority=1, Caucasian=0), and whether the twins’ mother or father smokes tobacco (yes=1, no=0). Although all potential risk factors for poor cognitive performance were initially incorporated into the adjusted model, it was expected that some demographic covariates would not be related to the outcome. Thus, non-significant predictors were systematically removed to arrive at the most parsimonious possible final model. The study was powered on the basis of assuming a relatively parsimonious random effects regression model with at most 10 predictors at either level. In such a model with $\alpha=0.05$ and adequate power=0.80, α

priori power analysis determined that a total sample of 100 children was required to detect small-to-moderate regression effects.

RESULTS

One hundred thirty consecutive TTTS cases were treated via SLPCV between December 2007 and May 2010; ninety families resided in California. Fifty-seven families comprising 100 eligible children enrolled in the study. Fourteen 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 rate of study participation for in-state families was 58% versus 13% for out-of-state families ($p<0.001$). The reasons the remaining 73 families did not participate in the study were as follows: lived too far ($n=32$), unable to contact ($n=21$), no survivors ($n=8$), unable to accommodate ($n=5$), uninterested ($n=3$), language barrier ($n=2$), last minute cancellation ($n=1$), and motor vehicle accident ($n=1$). Table 1 presents the characteristics of families by study participation. There were no statistically significant differences seen in numbers of donors and recipients, Quintero Stage distribution, pregnancies with IUFD, pregnancies with donor IUGR, or gestational ages at surgery or birth between families that did and did not participate.

Descriptive statistics for parent factors are presented in Table 2 and child risk factors and cognitive performance are shown in Table 3 by donor/recipient status and overall designation. Recipients weighed more at the two-year visit (donors: mean=11.65 kg, SD=1.38 kg; recipients: mean=12.62 kg, SD=1.75 kg; $t(98)=3.095$, $p<0.01$). However, there were no other significant differences between donor and recipient twins.

The NDI rate was 4%. One child had a BDI-2 score greater than 2 standard deviations below the mean (<70) but did not have other abnormal developmental findings. Three children were diagnosed with cerebral palsy: two had mild spastic diplegia, and the third had moderate to severe cerebral palsy.

Total BDI-2 scores were within normal range in this sample (mean=101.33, SD=12.18), with only one child scoring more than two standard deviations below the population average of 100. Total BDI-2 scores according to Quintero Stage are shown in Table 4. There were no differences in scores between Quintero Stage I and II. However, advanced Quintero Stage, particular Stage IV patients, appeared to have lower Total BDI-2 scores. Child-level risk factors for lower BDI-2 included male sex ($\beta=-0.37$, $p<0.01$), lower head circumference ($\beta=0.28$, $p<0.01$), and higher diastolic blood pressure ($\beta=-0.29$, $p<0.01$). At the pregnancy/family level, lower maternal education ($\beta=0.60$, $p<0.001$), higher Quintero stage ($\beta=-0.36$, $p<0.01$), lower GA at birth ($\beta=0.30$, $p<0.01$), married parents ($\beta=-0.25$, $p<0.05$), and older corrected age ($\beta=-0.20$, $p<0.05$) were associated with worse outcome. Younger fathers ($\beta=0.25$, $p<0.10$) and more adults in the home ($\beta=-0.23$, $p<0.10$) were nearly significant risk factors and were retained as covariates in the final regression model. Donor/recipient status, gestational age at surgery, fetal growth restriction, and fetal demise were not significant risk factors for developmental outcomes. For within level (i.e. child level), R-square was 0.297 and for between level (i.e. pregnancy/family level) R-square was 0.746. The intraclass correlation for total BDI-2 score showed that 65% of variance in the unadjusted total BDI-2

score and 56% of variance in the adjusted model are attributable to the pregnancy or family level rather than the child level factors, illustrating the strong effects of shared genetic, maternal, and social environments.

DISCUSSION

The primary objective of this study was to assess the cognitive performance and other developmental outcomes of an US cohort of 2-year-old TTTS survivors after in utero laser surgery and to identify predictive risk factors for lower developmental functioning. To the best of our knowledge, this is the first published study of a US cohort of children that received in utero laser therapy for TTTS and subsequently underwent formal developmental testing at 2 years of age. The mean BDI-2 scores for the entire cohort was 101.3 (SD=12.2), which was within normal range.¹¹ The neurodevelopmental impairment rate was 4%, as one child had a BDI-2 score < 70 and three children were diagnosed with cerebral palsy (two mild and one moderate to severe spastic diplegia). This cohort compares favorably with the other published international cohorts that were reviewed by Rossi et al. in regards to NDI rates (4% vs 11%) and provides more detailed exploration of factors associated with poor cognitive performance.⁴

A main goal of this study was to identify predictive risk factors for lower developmental functioning. Our study identified several important risk factors to later developmental outcomes at the individual and shared twin levels. Lower gestational age at birth was an expected risk factor¹² for lower scores, while male sex was the strongest risk factor identified for lower scores. The latter finding is consistent with the general population prevalence of higher risk in males of developmental disabilities.¹³ Our finding on head circumference suggests that in this cohort larger head size correlates with better development. More investigation is needed to fully understand whether this is due to an age effect or correlates with overall actual brain size. There was a donor vs. recipient difference in weight, but that did not correlate with a significant difference in overall development. The lack of donor vs. recipient difference was consistent with the findings of a previous meta-analysis.¹⁴ Finally, the higher diastolic blood pressure finding may be due to increased anxiety amongst those children with lower developmental scores or may represent a subtle cardiovascular risk factor that could be related to the TTTS exposure. Alternatively, higher diastolic blood pressure might be associated with lower gestational age and/or fetal growth restriction status.

Shared or pregnancy-level factors emerged as important determinants of the developmental outcome. These shared factors were responsible for over half the variance in predictive models. Like in previous studies, Quintero stage was associated with cognitive scores.⁸ This confirms a lasting effect of TTTS severity at the time of intervention on long-term developmental scores. As mentioned earlier, prematurity was an expected risk factor for lower cognitive score that is consistent with a wide literature.¹²

The strongest determinate of the lower cognitive outcome was related to maternal educational level. This variable is strongly linked to socio-economic status and long term cognitive outcomes across many pediatric studies.¹⁵ Though maternal education level is

critically important to understanding these outcomes, it is often omitted from TTTS longitudinal studies. In this study we have found that its impact is greater than other well described factors such as gestational age and Quintero stage. In studies of general populations, younger (<25 years) and older (>35 years) age of fathers has been found to be associated with higher risk of lower child scores.¹⁶ Our fathers were primarily in the older age range, and we speculate that their age might have had a positive effect due to their ability to provide appropriate socioeconomic support for the family. Interestingly, while it is expected that married parents and more adults in the home would be promoters of an enriched caregiving environment and child development, these were both risk factors. Further investigation of the complex interaction of stress in the family may help to clarify these socio-demographic findings.

The primary methodological strength in the design of this study was the large sample size sufficient to determine donor vs. recipient differences and identify risk factors to neurodevelopment. The use of an extensive, prospectively collected dataset with prenatal and perinatal variables also allowed assessment of early predictors. The assessments were done at a relatively narrow age range to allow us to perform between-subject comparisons. The assessments were conducted by independent and highly qualified personnel in a consistent research environment blinded to the recipient vs. donor status of the children. A final strength is the team of experienced and consistent healthcare providers that cared for these families from diagnosis to procedure to follow-up.

Despite these strengths, there were several study limitations. First, while differences were not seen in the measured risk factors between assessed and non-assessed groups, we were limited by resources to a 50% assessment rate. The major factor that limited recruitment was location of residence. Patients that did not live within driving distance from the study center were significantly less likely to participate in the study. Although there were no statistically significant differences in characteristics of study participants versus nonparticipants (except location of residence), it should be noted that the number of Quintero Stage IV patients in the nonparticipants was higher than those that did participate (16% vs. 7%, respectively). Thus, the overall Total BDI-2 score described for the study cohort potentially excluded some of the highest risk children. There were other possible sources of selection bias: We expected that families would be more incentivized to participate if they had a developmental concern and desired to learn more about their child's developmental level, as this type of assessment could run several hundred dollars if paid for out of pocket. Alternatively, families may have difficulty in travel if they had a child with extremely low cognitive performance. We also cannot exclude a social desirability bias in which the families self-selected to not participate if their child had developmental delays. With these limitations in mind, we caution against utilizing data from this study as a source of comparison to other studies due to the expected variability in study populations. Next, the study was not powered to answer many additional questions regarding blood pressure, growth, socio-demographic, or other risk factor findings more fully. A larger sample may have detected additional statistically significant findings (e.g., father's age, number of adults in the home), and such a large sample would also be needed to explore any interactions among these variables. Third, follow-up was at 2 years of age. Although this age allows for strong cognitive, language, personal-social and motor assessment, subtle learning, attention and behavioral problems

that may emerge at later ages were not assessed. Of note is that previous studies support stability of TTTS neurologic and neurodevelopmental outcomes from 2 to 6 years of age.¹⁷ Finally, while we did not have a control group, the standardized normed assessment tool allows for comparison with development levels of a general population sample.

In summary, this is the first study on a US cohort that has formally assessed cognitive and developmental outcomes at 2 years of age in children that underwent laser surgery for TTTS. The findings of this study have direct application to mothers with TTTS who are considering or have had laser ablation surgery. The findings support the notion that the prenatal care focus should be on prompt in utero treatment of TTTS to avoid progression to higher Quintero stage and on measures to minimize prematurity.¹⁸ Postnatal care should emphasize psychosocial support for the family, robust physical growth and an enriched caregiving environment. The clinical and socio-economic characteristics described in this study may be useful to identify at-risk children that may benefit from early clinical and psychosocial interventions such as quality child care.¹⁹

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Table 1

Characteristics of Study Participants vs. Non-participants

Number	Not Enrolled	Enrolled	Significance Test
Total Families	73	57	--
Total Eligible Children	106	100	
Donors	46 (43%)	49 (49%)	$\chi^2(1)=0.65, p=0.42$
Recipients	60 (57%)	51 (51%)	
Quintero Stages:			$\chi^2(3)=3.517, p=0.32$
1	8 (11%)	10 (18%)	
2	14 (19%)	13 (23%)	
3	39 (53%)	30 (53%)	
4	12 (16%)	4 (7%)	
Pregnancies with Fetal Demise	20 (27%)	9 (16%)	$\chi^2(1)=2.488, p=0.11$
Donors with Growth Restriction	32 (44%)	23 (40%)	$\chi^2(1)=0.159, p=0.69$
Gestational Age (mean, SD in weeks)			
Surgery	20.55 $\pm$ 2.20	20.47 $\pm$ 2.62	$t(128)=0.189, p=0.85$
Delivery	31.76 $\pm$ 4.57	32.96 $\pm$ 3.62	$t(128)=1.624, p=0.11$

Table 2

Pregnancy and Family Demographic Level Factors for Enrolled Families.

Pregnancy Factors	Overall N (%)
Quintero stage:	
I	10 (17.5%)
II	13 (23%)
III	30 (52.6%)
IV	4 (7%)
Any complications	41 (72%)
Vaginal delivery	9 (16%)
Mean (SD)	
GA delivery: (range: 24-38.7 weeks)	32.96 (3.62)
GA surgery: (range: 16.4-26 weeks)	20.47 (2.62)
Parent/Family Factors (N=57)	Overall N (%)
Married	43 (74%)
Maternal high school education or less	13 (23%)
Paternal high school education or less	20 (35%)
Maternal smoking	1 (2%)
Paternal smoking	5 (9%)
Mean (SD)	
Maternal age (range: 21-45)	32.30 (6.33)
Paternal age (range: 22-52)	35.59 (7.98)
# adults in home (range: 1-5)	2.37 (0.85)
# children in home (range: 0-6)	2.94 (1.33)

Table 3

Child Level Risk Factors and Comparison of Donors and Recipients.

Child Factors (N=100)	Donor N (%)	Recipient N (%)	Overall N (%)
Donor/Recipient status	49	51	100
Male sex	25 (51%)	26 (51%)	51 (51%)
Race			
White	22 (45%)	21 (41%)	43 (43%)
Hispanic	17 (35%)	20 (39%)	37 (37%)
Asian	5 (10%)	6 (12%)	11 (11%)
Black	2 (4%)	3 (6%)	5 (5%)
Other/decline to state	3 (6%)	1 (2%)	4 (4%)
Other developmental outcomes (any)	2 (4%)	2 (4%)	4 (4%)
Bilateral deafness	0 (0%)	0 (0%)	0 (0%)
Bilateral blindness	0 (0%)	0 (0%)	0 (0%)
Cerebral palsy	2 (4%)	1 (2%)	3 (3%)
BDI-2 quotient < 2 SD	0 (0%)	1 (2%)	1 (1%)
	Donor Mean (SD)	Recipient Mean (SD)	Overall Mean (SD)
Birth Weight (kg; range: 0.48 to 3.82)	1.68 (0.67)	1.99 (0.71)	1.84 (0.71)
Difference in Birth Weight (grams)			300.98 (443.15)
Current Weight ** (kg; range: 9.0-17.7)	11.65 (1.38)	12.62 (1.75)	12.14 (1.64)
Current Height (cm; range: 75-96)	84.46 (3.69)	85.95 (3.84)	85.20 (3.82)
Current Head circumference (cm; range: 43-69.5)	47.87 (3.71)	48.77 (3.47)	48.33 (3.60)
Total BDI-2 dev. quotient (range: 58-132)	101.16 (11.86)	101.49 (12.60)	101.33 (12.18)

**
 $p < 0.01$.

Table 4

Total BDI-2 Scores by Quintero Stage.

Quintero Stage	N	Mean	Standard Deviation	95% Confidence Interval for Mean	
				Lower Bound	Upper Bound
I	19	104.9	14.7	97.8	112.0
II	24	104.4	11.6	99.5	109.3
III	50	99.7	9.7	97.0	102.5
IV	7	92.6	18.3	75.7	109.5
Total	100	101.3	12.2	98.9	103.8