OBSTETRICS

Predictors of 2-year cognitive performance after laser surgery for twin-twin transfusion syndrome

Douglas L. Vanderbilt, MD; Sheree M. Schrager, MS, PhD; Arlyn Llanes, RN, BSN; Anita Hamilton, PhD; Istvan Seri, MD, PhD; Ramen H. Chmait, MD

OBJECTIVE: The purpose of this study was to determine risk factors for poor cognitive performance among children who are treated with in utero selective laser photocoagulation of communicating vessels for twin-twin transfusion syndrome.

STUDY DESIGN: This was a prospectively enrolled cohort study. Cognitive performance at age 2 years (±6 weeks) was assessed with the 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 examination. A priori power analysis determined that a sample of ≥100 children was required for adequate statistical power (0.80).

RESULTS: One hundred children (57 families) were evaluated. Total BDI-2 score was within normal range (mean, 101.3 ± [SD]12.2); 1 child had a BDI-2 score of <70. Individual child-level risk factors for lower BDI-2 included male sex ($\beta = -0.37$; $P < .01$), lower head circumference ($\beta = 0.28$; $P < .01$), and higher diastolic blood pressure ($\beta = -0.29$; $P < .01$). At the pregnancy level, lower maternal education ($\beta = 0.60$; $P < .001$), higher Quintero stage ($\beta = -0.36$; $P < .01$), and lower gestational age at birth ($\beta = 0.30$; $P < .01$) were associated with worse cognitive outcomes. Donor/recipient status, gestational age at surgery, fetal growth restriction, and co-twin fetal death 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 socioeconomic characteristics can identify at-risk children who need additional interventions.

Key words: laser surgery, neurodevelopment, twin-twin transfusion syndrome

Cite this article as: Vanderbilt DL, Schrager SM, Llanes A, et al. Predictors of 2-year cognitive performance after laser surgery for twin-twin transfusion syndrome. Am J Obstet Gynecol 2014;210:●●●●.

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

Although neonatal neurologic outcomes have been characterized, there is a lack of data on developmental outcomes after laser surgery in US patient cohorts. A recent systematic review and meta-analysis identified 8 international studies that reported long-term developmental outcomes after laser therapy for TTTS outside the perinatal period.[4] In this metaanalysis, prevalence of nonperinatal neurologic morbidity, abnormal standardized test of neonatal development, or both was 11.1%; rates of cerebral palsy were in the range of 4-6%.[4] In counseling mothers who carry fetuses with TTTS and who are eligible for SLPCV, a clear understanding of perinatal

From the Department of Pediatrics (Drs Vanderbilt and Seri); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology (Ms Llanes and Dr Chmait); and Department of Surgery (Dr Hamilton), Keck School of Medicine, University of Southern California, and the Division of Adolescent Medicine, Department of Pediatrics, Children's Hospital Los Angeles (Dr Schrager), Los Angeles, CA.

Received Dec. 22, 2013; revised Feb. 20, 2014; accepted March 21, 2014.

Supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through Grant Award numbers KL2RR031991 and UL1TR000130.

The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH.

D.L.V. is a KL2 Scholar awarded under the KL2 Mentoring Research Career Development Award through Southern California Clinical and Translational Science Institute at Keck School of Medicine, University of Southern California. The authors report no conflict of interest.

Presented at the 33rd annual meeting of the Society for Maternal-Fetal Medicine, San Francisco, CA, Feb. 11-16, 2013.

Reprints: Douglas Vanderbilt, MD Associate Professor of Clinical Pediatrics, 4650 Sunset Blvd. #76, Los Angeles, CA 90027. dvanderbilt@chla.usc.edu.

0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2014.03.050

neurologic 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 that are associated with poor developmental outcomes of survivors who were treated in utero with laser surgery in a large cohort of US patients at 2 years of age. Based on the previous research,[4] we hypothesized that lower gestational age at birth, later gestational age at time of procedure, higher Quintero stage, lower birthweight, and donor twin status will result in poorer cognitive performance.

Materials and Methods

Study population

All consecutive patients who were treated for TTTS between December 2007 and May 2010 were considered eligible and were 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 $\geq$8 cm in the recipient's sac and $\leq$2 cm in the donor's sac. Each case was classified prospectively according to the Quintero staging system.[5] All patients were given the options of expectant treatment, 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 treatment with laser surgery only for disease progression. Patients were not offered laser surgery if preoperative ultrasound scans revealed gross abnormalities of intracranial anatomy. Cases were treated exclusively by SLPCV with or without sequential technique, as described in detail previously.[3]

All consecutive laser-treated TTTS patients during the study period were contacted before the time their child was to reach 2 years old ($\pm$ 6 weeks) corrected for gestational age and invited to participate by a study nurse, who was blinded to the predictors. Reasons that 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, which is 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 neurologic 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, which included child height, weight, head circumference, and blood pressure, were collected at the 2-year-old visit.

A single board-certified neuropsychologist who was masked to the subjects' clinical characteristics evaluated the cognitive and developmental status of participants with 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 ($\pm$6 weeks). Consistent with standardized administration of the BDI-2, each participant was assessed in the presence of 1 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 examination 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 5 developmental subdomains (personal-social, adaptive, motor, communication, and cognition) comprising overall development. The total BDI-2 developmental quotient score is computed as a sum of the 5 BDI-2 subdomains, and it has a mean of 100 with standard deviation of 15. Individual item scores range from 0-2 points, with scores based on 1 of 3 predetermined criteria that include 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 examination), 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 with IBM SPSS Statistics software (version 19; SPSS Inc, Chicago, IL). Bivariate comparisons were also calculated between participating and not participating families and between donors and recipients (eg, *t* tests for continuous measures, chi-square tests for categoric variables). Multilevel linear regression analysis was conducted in Mplus software (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. 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

FLA 5.2.0 DTD ■ YMOB9750_proof ■ 16 May 2014 ■ 4:23 pm ■ ce