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Twin-twin transfusion syndrome: neurodevelopment of infants treated with laser surgery

Síndrome de transfusão feto-fetal: neurodesenvolvimento de lactentes tratados com cirurgia a laser

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ABSTRACT

Objective: To assess the neurodevelopmental functions of survivors of twin-twin transfusion syndrome (TTTS) treated by fetoscopic laser coagulation (FLC), during the first year of life, comparing them to a control group; and to verify the influence of specific variables on neurodevelopment. **Method:** This was a prospective, longitudinal study. The sample comprised 33 monochorionic diamniotic twins who underwent FLC for treatment of TTTS and 22 full-term infants of single-fetus pregnancies. Bayley Scales of Infant and Toddler Development Screening Test were used for evaluation. Prenatal, perinatal and postnatal information were obtained. **Results:** There was an increased frequency of infants in the TTTS group with inadequate performance compared to the control group. The identified variables (fetal donor, low economic income and cardiorespiratory disease) negatively impacted expressive communication and fine motor skills. **Conclusion:** Although through follow-up is recommended in all TTTS survivors, particular attention is required for the high-risk group as defined in this study.

Keywords: diseases in twins; fetofetal transfusion; child development; risk factors.

RESUMO

Objetivo: Avaliar o desenvolvimento neurológico de sobreviventes da síndrome de transfusão feto-fetal (STFF) submetidos à coagulação a laser por fetoscopia (CLF), durante o primeiro ano de vida, comparando estes ao grupo controle; e verificar a influência de variáveis específicas no desenvolvimento. **Método:** Tratou-se de estudo prospectivo, longitudinal. A amostra foi composta por 33 gêmeos diamnióticos monocoriônicos submetidos à CLF para tratamento da STFF e 22 lactentes a termo de gestação única. Bayley Scales of Infant and Toddler Development Screening Test foram utilizadas para avaliação. Informações pré-natal, perinatal e pós-natal foram coletadas. **Resultados:** Houve maior número de lactentes com desempenho inadequado no grupo STFF do que no controle. As variáveis identificadas (feto doador, baixa renda econômica e doença cárdio-respiratória) influenciaram negativamente a comunicação expressiva e as habilidades motoras finas. **Conclusão:** Embora o acompanhamento seja recomendado para todos lactentes com STFF, especial atenção deve ser dada àqueles que apresentam fatores de risco.

Palavras-chave: doenças em gêmeos; transfusão feto-fetal; desenvolvimento infantil; fatores de risco.

Twin-twin transfusion syndrome (TTTS) is a serious condition that affects 9% to 15% of all monochorionic diamniotic twin pregnancies¹, and typically develops between 15 and 26 weeks of gestation². The syndrome is characterized by an unbalanced transfusion of blood across placental vascular anastomoses from one twin (donor) to the other (recipient)^{2,3,4}. Because of abnormal placental anastomoses, the donor pumps blood into the recipient. The donor twin becomes hypovolemic, with resultant oliguria, oligohydramnios, and sometimes growth restriction. The recipient

becomes hypervolemic, with polyuria, polyhydramnios, and cardiac dysfunction³.

Untreated, the risk of fetal death is approximately 90%^{3,4}. The optimal treatment for TTTS is fetoscopic laser coagulation (FLC) of placental anastomoses, which has led to improved single and dual twin survival. With this improvement in survival, there is a concern regarding risk factors to the neonatal neurologic status and later neurodevelopmental outcome^{5,6}.

Fetoscopic laser coagulation interrupts the blood flow between the fetuses and reducing the potential for major

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neurodevelopmental disability in survivors^{7,8}. Nevertheless, neurologic morbidity rates after antenatal treatment remain high (15% to 26%)¹. It is important to emphasize that information about the effects of TTTS in the infant development are still scarce, and risk factors associated with neurodevelopment impairment have not yet been established^{1,7,9,10}.

With this in mind, the questions posed by the present study were: what is the developmental profile of infants who suffered from TTTS? What are the factors that influenced the infant development? In order to answer these questions, the present study aimed to assess the neurodevelopmental functions (cognition, language and motor function) of survivors of TTTS treated by FLC during the first year of life, comparing them to a control group (full-term infants of single-fetus pregnancies); and to verify the influence of specific variables on neurodevelopment.

It was hypothesized that detailed assessment during the first months of life would provide important information for identifying early developmental disadvantages in TTTS infants. Considering that there are few studies that have documented in detail the long-term outcome of TTTS pregnancies, this study contributes to increase the current knowledge about neurodevelopment of an understudied group, and discusses possible clinical perspectives of early detection.

METHOD

The research design was an observational, prospective, longitudinal study of monochorionic diamniotic twins who underwent FLC for treatment of TTTS, compared to full-term infants of single-fetus pregnancies, with birth weight appropriate for gestational age during the first year of life. This project was approved by the Research Ethics Committee of the Medical School of the State University of Campinas (UNICAMP) (process n° 935/2011).

Infants were selected using the following inclusion criteria: 1) infants from monochorionic diamniotic twin pregnancies who had TTTS stages I, II, III or IV according to the classification of Quintero et al.¹¹ and underwent FLC, composing the study group (TTTS group); 2) the control group was composed of infants born at the Neonatology Service of the Center of Integral Attention to Women's Health – UNICAMP, of single-fetus pregnancies, considered to be in good health allowing them to go home within two days of birth, with gestational age categorized as full-term (37–41 weeks) according to the Capurro method, and showing expected birth weight appropriate for gestational age (between the 10th and 90th percentiles) according to the Alexander method; 3) parents agreed to sign the informed consent; and, 4) infants who were between one month and 12 months of age. Infants who presented with any other malformation unrelated to TTTS were excluded. Considering that we do not have validated Bayley scales, third edition in Brazil, we included a control

group of normal infants, to observe the behavior of Brazilian infants with the scale. Our aim was to create a comparison group that might represent Brazilian infants (as much as possible). We considered that we would have a more reliable instrument after that.

All FLC procedures were performed by the same surgeon (CFAP, who had seven years experience in fetoscopic laser surgeries) at the Professor José Aristodemo Pinotti Hospital, from 2009 to 2012, according to the endoscopic laser dichorionization of the placenta procedure. The placental chorionic plate vessels were initially mapped through the amniotic sac of the recipient twin; the vascular equator was identified; a line of ablation of the chorionic plate was created from one edge of the placenta to the other, including the arterio-venous anastomoses and vessels with unknown courses (those crossing the inter-twin membrane from the recipient to the donor side and concealed behind the fixed twin). Caution was taken to preserve the vessels originating from and returning to the same fetus, which were surrounded by this line of ablation. At the end of the photocoagulation process, polyhydramnios fluid was drained through the fetoscopy sheath so that the deepest amniotic fluid pocket was less than 8 cm deep.

From initial selected sample (40), 33 infants (82.5%) survived after laser treatment and participated in this study. Development was assessed using the Bayley Scales of Infant and Toddler Development Screening Test, third edition¹², which included 33 items for testing cognition, 24 items for receptive communication, 24 items for expressive communication, 27 items for fine motor skills and 28 items for gross motor skills.

Each subtest (cognition, receptive language, expressive language, gross motor and fine motor skills) has a starting point consistent with the age or adjusted to the child's age. Every child is given an item score of zero or one. A zero score (0) refers to a child who did not carry out the item or failed to meet the criteria established by the test. The score of one (1) refers to a child who met the criteria established by the test, showing adequate performance on the item.

To start the test, the child is required to achieve a score of one (1) on the first item of his/her starting point previously determined by chronological or adjusted age. The reversal rule is applied when the child is given zero (0) in the first item, requiring the examiner to revert to the previous starting point. The test is completed when the child receives four consecutive zeros.

At the end of the assessment a raw score is obtained for each subtest, which classifies children into three categories: competent (low risk for delay), emerging (requires subsequent reviews) and risk (should be referred for diagnostic assessment)¹². To perform statistical analyses, the three categories of the Bayley Scale were grouped into two types of responses: appropriate responses (consisting of the competent category), and inadequate responses (comprising emerging and risk categories).

Neurological examination was performed by a pediatric neurologist following our standard protocol¹³.

The infants were assessed at the Center for Investigation in Pediatrics of UNICAMP from July, 2011 to July, 2013. The infants were evaluated twice, at the age of one to six months for the first evaluation and seven to 12 months for the second evaluation. The adjusted age for prematurity was considered in the neurodevelopmental assessments, using 40 weeks of gestation as a reference. The testers included a developmental neurologist and three physiotherapists. Infants who presented with developmental disorders were referred to a program for habilitation/rehabilitation.

Prenatal, perinatal and postnatal information were obtained through medical records and parent interviews. The following data were recorded: TTTS classification (donor or recipients), TTTS stage (I or II/III/IV), gestational age at surgery, type of delivery (vaginal or cesarean), gender (female or male), fetal growth (SGA or AGA), gestational age at delivery (pre-term or at term), Apgar score at first and fifth minutes (< 7 or ≥ 7), cardiorespiratory disease (present or absent), oxygen administration (present or absent), maternal education (< 9 or ≥ 9), maternal occupation (work outside or work at home), marital status (without partner or with partner), maternal age, number of children and adults in the home, and economic class according to the Brazilian Association of Research Companies¹⁴, an instrument of economic segmentation that uses the survey of household characteristics (presence and number of household items and education of the household head) to differentiate the population. The criterion assigns points according to each household characteristic. At the end of the questionnaire, a total score is obtained, which classifies families into eight categories: A1, A2, B1, B2, C1, C2, D, E¹⁴.

Statistical analyses were performed using the Statistical Analysis System (SAS 9.2). The probability level adopted for rejection of the null hypothesis was $p < 0.05$. The data were presented using position and dispersion measurements for numerical variables and frequencies for categorical variables. The comparison of categorical variables between groups was investigated with the Chi-Square or Fisher's Exact Tests. The comparison of paired proportions was examined with McNemar Test. Multiple logistic regression analysis with "stepwise criterion of variable selection" was used to measure the independent effects of prenatal, perinatal and postnatal factors on infant development of TTTS group.

RESULTS

We present an observational, prospective, longitudinal study of 55 infants (33 infants in the TTTS group and 22 infants in the control group). The mean age of the infants in the first and second assessment were 5.5 (± 1.4) and 9.8 (± 1.9) months respectively.

The descriptive analysis of the characteristics of the two groups is presented in Table 1. In the TTTS group the mean birth weight was 1671 grams (± 689.3) and the

mean gestational age was 32.4 weeks (± 3.5). Following the Quintero classification, 5 children were classified in stage I (15.2%), 4 in stage II (12.1%), 18 in stage III (54.5%) and 6 in stage IV (18.2%). In the control group, the mean birth weight was 3387.9 grams (± 285.8), and the mean gestational age was 39.2 weeks (± 0.9). Considering the family characteristics, in the TTTS and control groups, there was a greater frequency of mothers who had low income (around US\$ 1840 for the TTTS group and US\$ 1068 for the control group).

All infants of the TTTS group underwent neurological examination, which revealed three infants with strabismus (9.1%), one infant with microcephaly (3.0%), and six infants with spastic cerebral palsy (18.1%), four of them with tetraparesis and two with diparesis. Table 2 describes in more detail the situation of each infant with cerebral palsy. Most infants were graded as severe by Quintero classification (III), were small for gestational age, and had Apgar scores at one minute ≤ 7 .

Regarding the assessment with the Bayley Scales, most infants were classified as appropriate for development. In our study the frequency of inappropriate performance in both evaluations for the TTTS group was around 18.2% for the cognitive domain, 9.1% for receptive communication, 21.2% for expressive communication, 24.2% for fine motor and 24.2% for gross motor skills. Tables 3 and 4 show comparative analysis between the groups in the first and second assessments respectively. In the first assessment, there were significant differences between the groups only in the cognitive and fine motor domains. In the second assessment, there were significant differences between the groups in all domains (cognitive, receptive and expressive communication, gross and fine motor skills). In both evaluations there were more infants in the TTTS group with inadequate performance in relation to the control group. We found no significant differences in neurodevelopmental outcomes between the first and second assessment of the TTTS group.

Multiple logistic regressions were carried out to measure the association between neurodevelopment and various clinical parameters. The analysis revealed that TTTS classification (OR 6.8, 95%CI 1.0–44.6, $p = 0.04$) and economic class (OR 1.1, 95%CI 1.0–1.3, $p = 0.01$) were significantly associated with expressive communication. Infants classified as donors in TTTS had a higher risk of abnormality (6.8 times) than the recipients; and infants whose families had a lower economic score displayed a higher risk of abnormality (each point decreases the risk of abnormality by 16.0%). Moreover it was found that the cardiorespiratory disease variable (OR 5.6, 95%CI 1.1–27.5, $p = 0.03$) was significantly associated with fine motor function. Infants with cardiorespiratory disease had a higher risk of abnormality (5.6 times) than those without the disease.

The TTTS Quintero stage, gestational age at surgery, type of delivery, gender, fetal growth, gestational age at delivery, Apgar score at first and fifth minutes, oxygen administration, maternal education, maternal occupation, marital status,

Table 1. Demographic characteristics of the two groups.

Variables	TTTS group		Control group	
TTTS classification – Recipients	19 (57.6%)		N/A	
Quintero stage – II / III / IV	28 (84.9%)		N/A	
Mode of delivery – Cesarean	32 (97.0%)		6 (27.3%)	
Gender – Female	22 (66.7%)		15 (68.2%)	
Fetal growth – AGA	19 (57.6%)		22 (100%)	
Gestational age at birth – Pre-term	29 (87.9%)		0	
Apgar score				
1st – ≥ 7	27 (81.8%)		22 (100%)	
5th – ≥ 7	31 (93.9%)		22 (100%)	
Present				
Cardiorespiratory disease	20 (62.5%)		5 (22.7%)	
Oxygen administration	21 (63.6%)		0	
Maternal education (years) – ≥ 9	30 (90.9%)		17 (77.3%)	
Maternal occupation – Work at home	17 (51.5%)		15 (68.2%)	
Marital status – with partner	31 (93.9%)		16 (72.7%)	
Numeric variable	Mean	SD	Mean	SD
Gestational age at surgery (weeks)	21.2	1.9	N/A	
Maternal age (years)	29.5	6.3	25.2	7.8
Number of children in the home	2.5	0.9	1.4	0.6
Number of adults in the home	2.8	1.1	3.0	1.1
Economic class (score)	29.9	7.9	24.6	0.6

SD: standard deviation; TTTS: twin-twin transfusion syndrome; AGA: .

Table 2. Characteristics of infants diagnosed with cerebral palsy.

Infants with cerebral palsy	TTTS classification	Quintero stage	Gestational age at surgery (weeks)	Gestational age at birth (weeks)	Fetal growth	Apgar 1	Apgar 5
1	donor	III	22.0	34.1	SGA	8	9
2	donor	III	19.4	28.0	SGA	6	9
3	donor	III	21.1	33.4	SGA	7	8
4	recipients	IV	25.0	26.4	AGA	6	8
5	recipients	III	17.0	28.4	AGA	8	9
6	recipients	III	20.0	27.6	SGA	7	8

TTTS: twin-twin transfusion syndrome; SGA: ; AGA: .

Table 3. Comparative analysis between groups in the first assessment.

Domains	TTTS Group		Control Group		p-value
	Inadequate	Appropriate	Inadequate	Appropriate	
Cognition	10 (30.3%)	23 (69.7%)	0	22 (100%)	0.003*
Receptive communication	05 (15.1%)	28 (84.9%)	01 (4.6%)	21 (95.4%)	0.384*
Expressive communication	11 (33.3%)	22 (66.7%)	09 (40.9%)	13 (59.1%)	0.567**
Gross motor	14 (42.4%)	19 (57.6%)	04 (18.2%)	18 (81.8%)	0.060**
Fine motor	16 (48.5%)	17 (51.5%)	02 (9.1%)	20 (90.9%)	0.002**

TTTS: twin-twin transfusion syndrome; * Fisher's exact test; **Chi-Square test.

Table 4. Comparative analysis between groups in the second assessment.

Domains	TTTS Group		Control Group		p-value
	Inadequate	Appropriate	Inadequate	Appropriate	
Cognition	10 (30.3%)	23 (69.7%)	0	22 (100%)	0.003*
Receptive communication	05 (15.1%)	28 (84.9%)	01 (4.6%)	21 (95.4%)	0.384*
Expressive communication	11 (33.3%)	22 (66.7%)	09 (40.9%)	13 (59.1%)	0.567**
Gross motor	14 (42.4%)	19 (57.6%)	04 (18.2%)	18 (81.8%)	0.060**
Fine motor	16 (48.5%)	17 (51.5%)	02 (9.1%)	20 (90.9%)	0.002**

TTTS: twin-twin transfusion syndrome; *Fisher's exact test; **Chi-Square test. Domains.

maternal age, number of children and adults at home were not risk factors for neurodevelopmental outcomes.

DISCUSSION

The focus of the present study was to assess the neurodevelopmental functions (cognition, language and motor function) of survivors of TTTS treated by FLC, and to verify the influence of specific variables on neurodevelopment. We were able to follow up the TTTS group during the first year of life, and compared them to a control group.

Our data showed a high rate of normal neurodevelopmental outcome in a group of infants who were treated for TTTS by FLC. This fact suggests that, although infants with TTTS have a high risk of morbidity, FLC treatment was an effective procedure to allow normal development in most infants⁸. The frequency of inappropriate performance in both evaluations for the TTTS group was around 18.2% for the cognitive domain, 9.1% for receptive communication, 21.2% for expressive communication, 24.2% for fine motor and 24.2% for gross motor skills. We also found six infants in our cohort who could be diagnosed as having cerebral palsy.

The neurodevelopmental outcome found in this study is in agreement with other outcome reported previously. The prevalence of cerebral palsy associated with TTTS managed with FLC has been reported to be 3%–16% and the prevalence of neurodevelopmental disabilities to be 12%–33%^{1,6,7,9,15,16,17}. The discrepancies in reported rates may partly be due to several methodological differences such as the use of different protocols and criteria for the definition of cerebral injury and neurodevelopmental impairment, including clinical or imaging scans at different ages^{6,18,19}.

The comparative analysis between groups showed significant differences at the first and second assessment. There was increased frequency of infants in the TTTS group with inadequate performance in relation to control group. These results are not surprising. Large population-based studies consistently show that the long-term neurodevelopmental outcomes of twins are worse than those of singletons¹⁶. Language and speech delays are more pronounced in multiples, as are cognitive delays, motor development, behavioral problems and

difficulties in parent-child interactions²⁰. In multiple gestations, factors such as preeclampsia, TTTS, and the competition between multiple infants for placental nutrient and oxygen delivery seem to place the twins at risk for growth and development problems²¹. TTTS is a well-recognized risk factor for adverse neurodevelopment outcome⁹, and appears to be associated with an increase in long-term cognitive and neuro-motor disabilities¹⁶. The exact mechanism responsible for neurodevelopmental deviation in infants who suffered from TTTS is not clear. The brain injury may result from hemodynamic imbalance and intertwin blood shifts, which lead to hypoxic-ischemic insults during pregnancy, or from postnatal injury associated with prematurity and low birth weight⁶.

Multiple risk factors can increase the risk of developmental disability, by either additive or multiplicative effects. Genetic factors, nutrition, health, environment in which the children grow up, and opportunities offered by their families are all determinants of child development²²⁻²⁴.

It seems that donor and recipient twins with TTTS treated with FLC are equally at risk for cerebral injury and long-term neurodevelopment impairment^{24,9}. However, our results showed an independent association between expressive communication disturbance and donor infants. This should be explored in following studies. Similar to our results Tosello¹ suggested that the risk of neurosensory sequel was significantly related to the status of donor. It is known that donor twins are significantly smaller at birth than recipient twins and remain shorter at two years of age¹⁸. Lower birth weight has been associated with an increased risk for developmental disturbance²⁵. So, this fact may have contributed to worse performance of donor twins in relation to recipient twins.

In the present study, the infants whose families had lower economic income showed a higher risk of expressive communication disturbance. These findings are in agreement with prior research, which has demonstrated strong associations between familial socioeconomic resources and children's health outcome, with especially poor health outcome among disadvantaged youth who experience a concentration of risks²⁶. Children from middle and low-income countries face an even greater challenge: in addition to being more susceptible to perinatal problems, these children are also subject to unfavorable household environments, in which

stimulation and social support are inadequate. This combination of events increases the risk of problems in cognitive, physical, and social development²⁷.

Another issue that needs to be addressed is the effect of cardiorespiratory disease on infant development. In the present study infants with cardiorespiratory disease had a higher risk of fine motor disturbance than those without the disease. The abnormal placenta that occurs in cases that develop TTTS contributes to abnormal fetal heart formation, primarily in recipient twins, such as ventricular hypertrophy, atrioventricular valve regurgitation, and abnormal right ventricular or left ventricular function. These cardiac abnormalities can contribute to the poor neurodevelopmental outcome¹⁷. Likewise, it has been suggested that children who develop chronic lung disease may be developmentally compromised by exposure to hypoxic episodes²⁸ and have abnormal motor outcome at one year²⁹ and at school-going age³⁰. According to the authors, early assessment and motor therapy is recommended for infants with chronic lung disease, because of its effect on motor performance.

The present study has certain limitations that should be taken into account when considering its possible contributions. First, the sample was small; this fact could have influenced the results, at least in part. A larger sample should be

considered in future research. Second, we used a non-standard assessment tool for the Brazilian population. However, the Bayley Scales have an overall acceptance, and we included a control group to observe the behavior of Brazilian infants with the scale. Third, we use a control group absolutely no risk, full-term infants of single-fetus pregnancies. Future researches should use a control group of infants from twin pregnancies without TTTS, matched for gestational age.

This study represents one of the few studies addressing the neurodevelopmental functions of monozygotic twins who underwent FLC for treatment of TTTS. Our study was conducted during the first year of life and included a control group. We identified three variables that jeopardize the outcome. Infants classified as donors and infants whose families had lower economic income showed higher risk for expressive communication disturbance. Moreover, infants with cardiorespiratory disease had a higher risk for fine motor disturbance.

In conclusion, we were able to establish specific variables (fetal donor, lower economic income and presence of cardiorespiratory disease) for neurodevelopment impairment in survivors of TTTS after FLC. Although thorough follow-up is recommended in all TTTS survivors, particular attention is required for the high-risk group as defined in this study.

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