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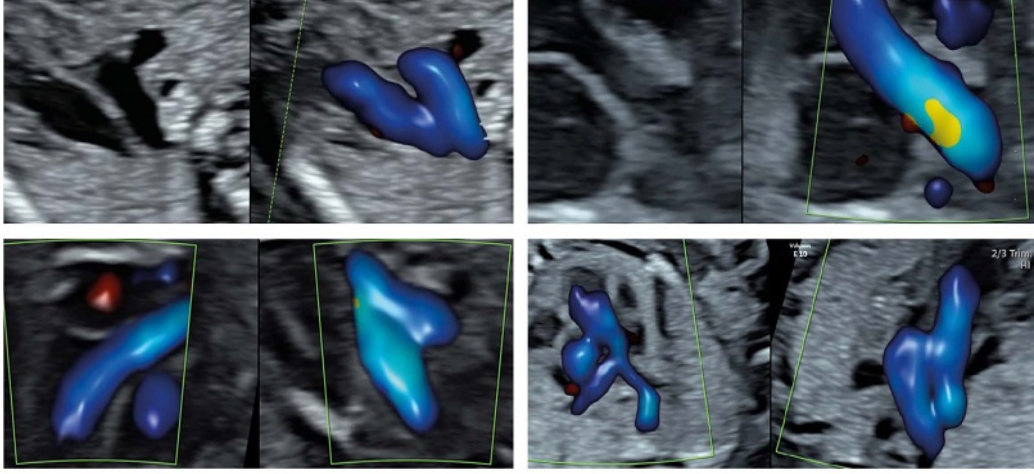

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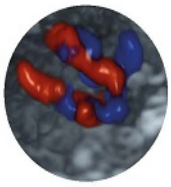

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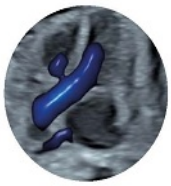

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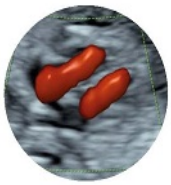

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Neurodevelopmental outcome in twin anemia–polycythemia sequence after laser surgery for twin–twin transfusion syndrome

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KEYWORDS: cognitive development; laser surgery; neurodevelopmental outcome; twin anemia–polycythemia sequence; twin–twin transfusion syndrome

ABSTRACT

Objective *To evaluate the long-term neurodevelopmental outcome in children who developed twin anemia–polycythemia sequence (TAPS) after fetoscopic laser surgery for twin–twin transfusion syndrome (TTTS).*

Methods *Neurological, motor and cognitive development was assessed in a consecutive cohort of TTTS survivors treated with laser surgery between 2004 and 2011 and complicated by post-laser TAPS. Primary outcome was neurodevelopmental impairment, a composite outcome including any of the following: cerebral palsy, bilateral deafness, blindness, severe motor and/or cognitive developmental delay (>2 SD below the mean). A risk analysis on cognitive outcome was performed.*

Results *During the study period, 33/306 (11%) monochorionic twin pairs developed TAPS after laser surgery for TTTS. Survival was 53/66 (80%). Long-term outcome was assessed in 47/53 (89%) children. The incidence of neurodevelopmental impairment was 4/47 (9%), occurring in one donor (1/20; 5%) and three recipients (3/27; 11%) (*$P = 0.63$*). Mild-to-moderate cognitive delay, i.e. scores below 85, was detected in 8/47 (17%) children. Risk factors for low cognitive scores were low gestational age at birth (*$P = 0.02$*) and low birth weight (*$P < 0.01$*). The lowest cognitive scores were detected in the subgroup of TAPS survivors treated with intrauterine transfusion (median score, 82.5).*

Conclusions *Neurodevelopmental impairment and cognitive delay were found in almost one in five children surviving post-laser TAPS. Better treatment and, ideally, prevention of this complication after laser treatment for TTTS is urgently needed.*

INTRODUCTION

Twin anemia–polycythemia sequence (TAPS) is a chronic form of fetofetal transfusion in monochorionic twins through small anastomoses at the placental surface[1]. TAPS is characterized by a large intertwin hemoglobin difference without signs of twin oligo–polyhydramnios sequence (TOPS). TAPS may occur spontaneously (spontaneous TAPS) or after twin–twin transfusion syndrome (TTTS) treated with fetoscopic laser surgery (post-laser TAPS). The incidence varies between 1% and 5% in spontaneous TAPS and 1% and 16% in post-laser TAPS[2–7]. Antenatal diagnosis is based on Doppler ultrasound abnormalities showing an increased peak systolic velocity in the middle cerebral artery of the donor twin, suggestive of fetal anemia, and decreased velocity in the recipient twin, suggestive of polycythemia, without concomitant signs of TOPS. Postnatal diagnosis is based on intertwin hemoglobin difference ≥ 8.0 g/dL and at least one of the following criteria: reticulocyte count ratio > 1.7 or small anastomoses (< 1 mm) at the placental surface. Perinatal mortality and morbidity rates in TAPS are not well known, and outcome may vary from two healthy neonates to severe neonatal morbidity, including severe cerebral injury, or neonatal death[2,7,8].

In TTTS treated with laser surgery the risk of adverse long-term neurodevelopmental outcome is increased, ranging from 6% to 18%[9–11]. Whether TTTS survivors who developed TAPS after laser surgery are also at increased risk of adverse long-term outcome is not known. The aim of this study was to evaluate long-term neurodevelopmental outcome in post-laser TAPS survivors and to compare outcome between donors and recipients.

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METHODS

All consecutive TTTS pregnancies treated with fetoscopic laser surgery at our center between 2004 and 2011 were eligible for this study. The Leiden University Medical Center is the Dutch national referral center for fetal therapy, including laser surgery for TTTS. All TTTS cases complicated with TAPS after laser surgery (post-laser TAPS) were included in this follow-up study. The study was approved by the institutional review board at the Leiden University Medical Center, and all parents gave written informed consent for their children to participate.

TAPS was identified using previously published criteria[2]. In brief, antenatal TAPS was diagnosed when Doppler ultrasound examination revealed an increase in peak systolic velocity in the middle cerebral artery of > 1.5 multiples of the median (MoM) in one fetus that coincided with a decreased velocity of < 1.0 MoM in the cotwin, in the absence of TOPS. Diagnosis of postnatal TAPS was based on an intertwin hemoglobin difference of ≥ 8.0 g/dL and at least one of the following criteria: reticulocyte count ratio > 1.7 or small anastomoses (< 1 mm) at the placental surface[2]. Antenatal and postnatal TAPS was classified from Stage 1 to 5 according to a previously published staging system[2].

The following antenatal and neonatal data were recorded: gestational age at laser treatment, Quintero stage of TTTS, fetal demise, age at detection of antenatal or postnatal TAPS, antenatal or postnatal TAPS stage, TAPS management in antenatally detected TAPS cases (expectant management, intrauterine transfusion, laser treatment or cord coagulation), gestational age at birth, birth weight and severe neonatal morbidity including severe cerebral injury and neonatal death. Severe neonatal morbidity was defined as the presence of at least one of the following: respiratory distress syndrome requiring medical ventilation and surfactant, patent ductus arteriosus requiring medical therapy or surgical closure, necrotizing enterocolitis $\geq$ Grade 2, retinopathy of prematurity $\geq$ Stage III or severe cerebral injury. Severe cerebral injury was defined as at least one of the following: intraventricular hemorrhage $\geq$ Grade III[12], cystic periventricular leukomalacia $\geq$ Grade II[13], ventricular dilatation $\geq$ 97th percentile[14], porencephalic cysts or arterial or venous infarction detected on cerebral imaging.

A follow-up visit was performed at a minimum age of 24 months and included a neurological examination and an assessment of cognitive and motor development using the Dutch version of the Bayley Scales of Infant and Toddler Development (BSID). Before 2006, the second edition of the BSID was used (BSID-II), while the third edition (BSID-III) was used from 2006 onwards[15,16]. Children at age 3 years or older were tested with the Wechsler Preschool and Primary Scale of Intelligence third edition (WPPSI-III)[17]. These three tests provide cognitive scores that follow a normal distribution with a mean of 100 and an SD of 15. BSID-II and BSID-III also provide motor development scores. When each separate score was below 70, i.e. > 2 SD below the mean, this was indicative of severe delay in either cognitive or motor development. Scores below 85, i.e. > 1 SD below the mean, were indicative of mild-to-moderate delay. Cerebral palsy was defined according to the European CP Network and classified as diplegia, hemiplegia, quadriplegia, dyskinetic or mixed[18].

The primary outcome measure was a composite outcome termed neurodevelopmental impairment, including at least one of the following: cerebral palsy, cognitive development score of less than 70 (> 2 SD below the mean), motor development score of less than 70 (> 2 SD below the mean), bilateral blindness or bilateral deafness requiring amplification. The primary aim of our study was to assess the incidence of neurodevelopmental impairment in post-laser TAPS cases and to compare outcomes between donors and recipients. The secondary outcome was an estimation of risk factors associated with lower cognitive scores including gestational age at birth, birth weight, gestational age at diagnosis of TAPS, TAPS management in the antenatally detected TAPS cases and severe neonatal morbidity (including severe cerebral injury).

Data are reported as mean $\pm$ SD or as median (range), as appropriate. Statistical analysis was performed using Student's *t*-test and the Mann–Whitney *U*-test for continuous variables. The chi-square test and Fisher's exact test were used for categorical variables, as appropriate. Analysis for risk factors possibly contributing to cognitive outcome was conducted using univariate and multivariate regression methods. The potential risk factors for cognitive outcome were studied in a univariate logistic regression model. The multivariate logistic regression model included all variables that showed significant association in the univariate analysis. Analysis was carried out using the Generalized Estimated Equation module to account for the effect that observations within twin pairs are not independent. All statistical data were analyzed using SPSS version 20.0 (IBM, Armonk, NY, USA), and $P < 0.05$ was considered as indicating statistical significance.

RESULTS

A total of 306 monochorionic twin pregnancies were treated at our center with fetoscopic laser surgery for TTTS between 2004 and 2011. In total, 33/306 (11%) monochorionic twin pairs were diagnosed with TAPS after laser surgery for TTTS. Fetal death occurred in 7/66 cases (11%), neonatal death in five cases (5/59; 8%) and in one case (1/59; 2%) sudden (unexplained) infant death occurred at the age of 2 months. Overall survival rate in the post-laser TAPS group was 53/66 (80%). Six children (6/53, 11%) were lost to follow-up owing to consent being declined or loss of contact information. Follow-up assessments were performed in 47/53 children (89%). Baseline characteristics of the TAPS survivors included for follow-up are presented in Table 1.

TAPS was detected antenatally in 28/47 cases (60%) and postnatally in the remaining 19/47 cases (40%). Median gestational age at birth in TAPS cases detected antenatally and postnatally was 32 (range, 26–37) and 32.5 (range, 26–41) completed weeks, respectively ($P = 0.62$). Of the 28 antenatally detected post-laser TAPS

Table 1 Baseline characteristics of post-laser twin–anemia polycythemia sequence (TAPS) survivors assessed at follow-up ($n = 47$)

Characteristic	*Value*
TAPS donor	20 (43)
Gestational age at laser (weeks)	21 (15–27)
Quintero stage	II (I–IV)
Antenatally detected TAPS stage ($n = 28$)	2 (1–5)
Stage 1	4 (14)
Stage 2	11 (39)
Stage 3	4 (14)
Stage 4	7 (25)
Stage 5	2 (7)
Postnatally detected TAPS stage ($n = 19$)	2 (1–4)
Stage 1	8 (42)
Stage 2	9 (47)
Stage 3	—
Stage 4	2 (11)
Stage 5	—
Gestational age at birth (weeks)	32 (26–41)
Birth weight (g)	1635 (750–3667)
Sex female	22 (47)
Severe cerebral injury*	2/46 (4)
Severe neonatal morbidity†	18 (38)

Data are presented as median (range) or *n* (%). *46 children underwent cranial ultrasound. †Severe neonatal morbidity defined as any of the following characteristics: respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis ≥ Stage II or severe cerebral injury.

cases, 17 were managed expectantly, eight underwent intrauterine transfusion, two were treated with further laser surgical intervention and in one case cord coagulation of the cotwin was performed. Intrauterine treatment was offered in all cases of TAPS Stages 3 and 4. In TAPS Stage 1 or 2, intrauterine treatment was offered only in cases in which TAPS was rapidly progressing (within days), or when the fetus showed other signs of severe anemia not meeting the criteria for Stage 3, such as increasing heart size or prehydropic signs. When treatment was performed, laser surgery was the first choice if this appeared technically feasible. Laser surgery in TAPS can be more challenging owing to the absence of TOPS. Intrauterine transfusion was chosen when laser treatment was not considered to be feasible. Cord coagulation was performed in one case in which we observed severe cerebral injury in the ex-TTTS recipient (the new TAPS donor)[19]. Median gestational age at birth of the cases treated *in utero* (intrauterine transfusion, laser or cord coagulation) was 29 (range, 26–33) weeks compared with 33 (range, 27–41) weeks in the cases treated expectantly ($P = 0.07$).

Of the 47 children available for follow-up, neonatal cranial ultrasound was performed in 46 cases (98%). The remaining child was born at term in a referral hospital at which cranial ultrasound was not part of the standard procedure. Two children were diagnosed with severe cerebral injury. In one case, the TAPS donor (a former TTTS recipient) was diagnosed with cystic periventricular leukomalacia Grade III. In the other case, a TAPS recipient (a former TTTS recipient), cerebral imaging showed venous infarction and intraventricular hemorrhage Grade II.

Long-term neurodevelopmental outcome in the 47 children was assessed at a median age of 28 (range, 24–96) months. Twenty-nine children were assessed with the BSID using either the second edition ($n = 9$) or the third edition ($n = 20$). In three of these children (10%) motor development could not be assessed owing to the child's failure to cooperate. Sixteen children completed WPPSI-III. One twin pair had already been tested elsewhere because of behavioral difficulties, with the Snijders Oomen Non-Verbal Intelligence Scale. Previous assessment with the WPPSI failed and the Snijders Oomen scale was used to obtain a reliable view of their capacities. One twin had mild-to-moderate cognitive delay and the cotwin scored within the normal range of intelligence.

The overall incidence of neurodevelopmental impairment in the studied cohort was 4/47 (9%), occurring in one donor (1/20, 5%) and three recipients (3/27, 11%) ($P = 0.63$). Cerebral palsy was diagnosed in one case (2%). Severe cognitive delay was detected in two children (4%) and severe motor delay in one child (2%). Mild-to-moderate cognitive delay was detected in 8/47 (17%) and mild-to-moderate motor delay in five (19%) children in whom it could be assessed. Long-term outcomes are reported in Table 2. Patient characteristics of the four children with neurodevelopmental impairment are presented in Table 3.

We performed a subgroup analysis on cognitive outcome of the antenatal TAPS cases according to prenatal management (Table 4). We found that the subgroup of TAPS survivors treated with intrauterine transfusion had the lowest cognitive score compared with the other subgroups (Table 4).

We performed univariate analysis of potential risk factors for cognitive outcome in the whole cohort. Risk factors for low cognitive scores were low gestational age at birth ($P = 0.02$) and low birth weight ($P < 0.01$). Since these two risk factors are highly correlated ($r = 0.87$, $P < 0.01$), no multivariate analysis was performed. In the antenatal TAPS cases ($n = 28$), intrauterine transfusion was a significant risk factor for low cognitive scores ($P = 0.05$).

DISCUSSION

This is the first study evaluating long-term neurodevelopmental outcome in TTTS survivors who developed TAPS after laser surgery. Neurodevelopmental impairment was detected in 9%, with no differences between donors and recipients. Our results suggest that impairment in post-laser TAPS cases is frequent but is within the range of the incidence of neurodevelopmental impairment reported in case series of TTTS treated with laser (range 6% to 18%)[9–11]. Unfortunately owing to logistic reasons we did not have the opportunity to perform follow-up in the years 2006–2007. This is the reason why our cohort could not be compared with the whole cohort of TTTS cases treated with laser therapy. Larger studies, possibly with a case–control study design, are needed to determine

Table 2 Long-term outcomes of 47 children with post-laser twin anemia–polycythemia sequence (TAPS)

Outcome	*Overall (n = 47)*	*TAPS donor (n = 20)*	*TAPS recipient (n = 27)*	P
Cerebral palsy	1 (2)	1 (5)	—	0.43
Cognitive score	95.3 ± 12.5	94.5 ± 11.3	95.8 ± 13.4	0.74
Cognitive score < −2 SD	2 (4)	—	2 (7)	0.50
Cognitive score < −1 SD	8 (17)	3 (15)	5 (19)	1.0
Motor score*	93.9 ± 12.4	93.2 ± 7.8	94.4 ± 15.3	0.81
Motor score < −2 SD*	1/26 (4)	—	1/15 (7)	1.0
Motor score < −1 SD*	5/26 (19)	1/11 (9)	4/15 (27)	0.36
Bilateral blindness/deafness	—	—	—	—
Neurodevelopmental impairment†	4 (9)	1 (5)	3 (11)	0.63

Data are expressed as *n* (%) or mean ± SD. *Number of children with assessment of motor development with Bayley scales, 11 donors and 15 recipients. †Neurodevelopmental impairment included any of the following: cerebral palsy, cognitive development > 2 SD below the mean, motor development > 2 SD below the mean, bilateral deafness or blindness.

Table 3 Patient characteristics of the four post-laser twin anemia–polycythemia sequence (TAPS) survivors with neurodevelopmental impairment

Case	*TAPS donor/recipient*	*Highest TAPS stage*	*Treatment of TAPS*	*GA at birth (weeks)*	*Birth weight (g)*	*Neonatal morbidity*	*Cerebral imaging*	*Long-term outcome*
1	Recipient (former TTTS donor)	4	Expectant management	29	1080	RDS, renal failure (transplant at 3 years)	IVH Stage I	Cognitive score < −2SD
2	Recipient (former TTTS donor)	2	IUT	29	1009	RDS	No abnormalities	Cognitive score < −2SD
3	Recipient (former TTTS donor)	3	Cord coagulation cotwin	28	955	RDS	No abnormalities	Motor score < −2SD
4	Donor (former TTTS recipient)	2	IUT followed by re-laser surgery intervention	32	1635	No	cPVL Stage III	CP: quadriplegia

CP, cerebral palsy; cPVL, cystic periventricular leukomalacia; GA, gestational age; IUT, intrauterine transfusion; IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome; TTTS, twin–twin transfusion syndrome.

Table 4 Cognitive scores in 28 post-laser twin anemia–polycythemia sequence (TAPS) survivors diagnosed antenatally

Treatment antenatal TAPS	n	*Antenatal TAPS stage*	*GA at birth (weeks)*	*Cognitive score*
Expectant management	17	2 (1–5)	33 (27–41)	93 (69–109)
Intrauterine transfusion	8	3.5 (2–4)	29 (26–33)	82.5 (67–105)
Laser surgery	2	2 (2–2)	32 (32–32)	112.5 (100–125)
Cord coagulation	1	3 (3–3)	28 (28–28)	99 (99–99)

Data are expressed as *n* or median (range). GA, gestational age.

if post-laser TAPS leads to an increased risk of impairment compared with uncomplicated TTTS cases.

The incidence of cerebral palsy of 2% in our series is similar to that in previously published TTTS follow-up studies, which range from 3% to 12%[9–11]. In the general population, cerebral palsy occurs in approximately 6% of infants born at 28–31 weeks' gestation, 0.7% of those born at 32–36 weeks and 0.1% of term infants[20]. Severe cognitive delay (4%) and severe motor delay (2%) were in the lower range compared to outcomes after TTTS in general (0% to 25%)[11]. According to the normal distribution of intelligence, severe cognitive delay occurs at a rate of 2.3% in the general population.

Cerebral injury and neurologic impairment in TAPS survivors can theoretically be due to several factors, including hematologic disorders (anemia and polycythemia, leading to impaired cerebral oxygenation), morbidity related to TTTS, preterm delivery or the type of antenatal TAPS treatment. In a univariate risk factor analysis on cognitive scores, we found that low gestational age at birth and low birth weight were important risk factors for cognitive delay. Low gestational age at birth and low birth weight are known to be independently associated with increased risk for severe cerebral lesions and impaired neurodevelopmental outcome[21,22]. In a subgroup analysis on antenatally detected/managed TAPS cases, we found that the TAPS subgroup treated with intrauterine transfusion had the lowest median cognitive score (82.5) compared with the other subgroups (Table 4). A possible explanation for the low cognitive scores could be that these cases were born at a lower gestational age of

29 weeks (interquartile range, 27.5–33.0) owing to induced labor or planned Cesarean section for severe anemia or polycythemia. Intrauterine transfusion may temporarily improve the condition of the donor, allowing prolongation of the pregnancy. However, intrauterine transfusion may also worsen polycythemia in the recipient twin and lead to possible severe complications such as severe cerebral injury[8]. Additionally intrauterine transfusion is a palliative treatment, not a curative treatment for TAPS.

One of the limitations of our study is the use of different developmental tests, that is BSID-II ($n = 9$), BSID-III ($n = 20$) and WPPSI-III ($n = 16$). Previous studies have reported a significant underestimation of developmental delay using the BSID-III compared to BSID-II assessment[23,24]. Of the three children with severe developmental delay, two were tested with BSID-III and one with BSID-II. Children aged 3 years or older were tested with WPPSI. With advanced age a more reliable view of capacities can be obtained. Also, two children had already been tested elsewhere with the Snijders Oomen Non-Verbal Intelligence Scale because of failure of previous WPPSI assessment.

The most important limitation of this study was the relatively small sample size. Thus, although this is the largest study to date reporting on neurodevelopmental outcomes in post-laser TAPS, our data should be interpreted with caution.

Since post-laser TAPS is caused by small residual anastomoses that might have been missed at initial laser treatment for TTTS, it is of great importance to reduce the number of these residual anastomoses. A recently published randomized controlled trial showed a significant reduction in the incidence of post-laser TAPS without any identifiable adverse outcomes[25]. To reduce the amount of residual anastomoses and the incidence of TAPS, we advise the use of the Solomon technique, in which the whole vascular equator is coagulated, for laser treatment in TTTS.

In conclusion, this is the first study reporting on neurodevelopmental outcome in post-laser TAPS. We report a 9% incidence of neurodevelopmental impairment and 17% incidence of at least mild-to-moderate cognitive delay, with no difference between donors and recipients. Risk factors for a lower cognitive score are lower gestational age at birth and lower birth weight. Antenatal TAPS management consisting of intrauterine transfusion was a risk factor for lower cognitive scores. Larger studies are needed to investigate reliably long-term neurodevelopmental outcome and evaluate risk factors for adverse outcome. Since TAPS is a rare disease, collaboration between international fetal therapy centers is of the utmost importance to increase sample size.

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