Chapter 8

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

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Abstract

Objective

To evaluate the long-term neurodevelopmental outcome in children who developed twin anemia-polycythemia (TAPS) after 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 between 2004 and 2011 and complicated by post-laser TAPS. Primary outcome was neurodevelopmental impairment (NDI), a composite outcome including any of the following: cerebral palsy, bilateral deafness, blindness, severe motor and/or cognitive developmental delay (< -2 SD). 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 NDI was 4/47 (9%), occurring in one donor (1/20, 5%) and three recipients (3/27, 11%) (P = .63). Risk factors for low cognitive scores are low gestational age at birth (P = 0.02) and low birth weight (P < = 0.01). 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 was found in almost 1 in 5 children surviving post-laser TAPS. Better treatment and ideally prevention of this complication after laser for TTTS is urgently warranted.

Introduction

Twin anemia-polycythemia sequence (TAPS) is a chronic form of feto-fetal transfusion in monochorionic (MC) twins through small anastomoses at the placental surface.[1] TAPS is characterized by large inter-twin hemoglobin (Hb) difference without signs of twin oligo-polyhydramnios sequence (TOPS). TAPS may occur spontaneous (spontaneous TAPS) or after twin-twin transfusion syndrome (TTTS) treated with laser (post-laser TAPS). The incidence varies between 1-5% in spontaneous TAPS and 1-16% 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 in the donor twin, suggestive of fetal anemia, and decreased velocities in the recipient twin, suggestive of polycythemia, without concomitant signs of TOPS. Postnatal diagnosis is based on inter-twin Hb 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 this study was to evaluate long-term neurodevelopmental outcome in post-laser TAPS survivors and to compare outcome between donors and recipients.

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 national referral center for fetal therapy in the Netherlands, 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.

TAPS was identified using previously published criteria and staging system.[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 co-twin, in the absence of TOPS. Postnatal TAPS diagnosis is based on inter-twin hemoglobin (Hb) 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.[2] Antenatal and postnatal TAPS is staged 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 and cord coagulation), gestational age at birth, birth weight, 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 ≥ grade 2, retinopathy of prematurity ≥ stage III or severe cerebral injury. Severe cerebral injury was defined as at least one of the following: intraventricular hemorrhage (IVH) ≥ grade III,[12] cystic periventricular leukomalacia (cPVL) ≥ grade II,[13] ventricular dilatation ≥ 97th percentile,[14] porencephalic cysts, arterial or venous infarction detected on cerebral imaging.

A follow-up visit was performed at a minimum age of 24 months and included a neurologic 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 the age ≥ 3 years were tested with the Wechsler Preschool and Primary Scale of Intelligence scale third edition (WPPSI-III).[17] These three tests (BSID-II, BSID-III and WPPSI-III) provide cognitive scores that follow a normal distribution with a mean of 100 and a standard deviation (SD) of 15. BSID-II and BSID-III also provide motor development scores. When each separate score was below 70, > 2 SD below the mean, this was indicative of a severe delay in either cognitive or motor development. Cerebral palsy (CP) 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 (NDI), including at least one of the following: CP, cognitive development score of less than 70 (< - 2 SD), motor development score of less than 70 (< - 2 SD), bilateral blindness, or bilateral deafness requiring amplification. The primary aim of our study was to assess the incidence of NDI in post-laser TAPS cases and to compare outcome between donors and recipients. Secondary outcome was estimation of risk factors associated with lower cognitive scores including gestational age at birth, birth weight, gestational age at TAPS diagnosis, TAPS management in the antenatal detected

TAPS cases and severe neonatal morbidity (including severe cerebral injury).
Data are reported as means with standard deviation (SD) or as medians with range, as appropriate. Statistical analysis was performed using the t-test and Mann-Whitney test for continuous variables. 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. Analyses were conducted using the Generalized Estimated Equation (GEE) module to account for the effect that observations within twins are not independent. Results are expressed as *P*-values. A *P*-value of less than 0.05 was considered significant. All statistical data were analyzed using SPSS version 20.0 (IBM, Armonk, NY, USA).

Results

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

Table 1 Baseline characteristics of post-laser TAPS survivors for follow-up.

	N=47 children
TAPS donor	20 (43)
Gestational age at laser (weeks)	21 (15-27)
Quintero stage	2 (1-4)
Antenatal TAPS stage[a]	2 (1-5)
Stage 1	4 (14)
Stage 2	11 (39)
Stage 3	4(14)
Stage 4	7 (25)
Stage 5	2 (7)
Postnatal TAPS stage[b]	2 (1-4)
Stage 1	8 (42)
Stage 2	9 (47)
Stage 3	0 (0)
Stage 4	2 (11)
Stage 5	0 (0)
Gestational age at birth (weeks)	32 (26-41)
Birth weight (grams)	1635 (750-3667)
Female	22 (47)
Severe cerebral injury[c]	2/46 (4)
Severe neonatal morbidity[d]	18/47 (38)

TAPS, twin-anemia polycythemia sequence; *N,* number. Data are presented as median (range) or n (%).
[a]TAPS stage in the antenatal detected TAPS cases (*n* = 28)
[b]TAPS stage in de postnatal detected TAPS cases (*n = 19)*
[c]Denominator is the number of children who underwent cranial ultrasound.
[d]Severe neonatal morbidity was defined as any of the following characteristics: respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis≥ stage II or severe cerebral injury.

TAPS was detected antenatally in 28/47 (60%) cases and postnatally in the remaining 19/47 (40%) cases. Median gestational age at birth in TAPS cases detected antenatally and postnatally was 32 (26-37) and 32.5 (26-41) completed weeks, respectively (*P* = 0.62). Of the 28 antenatally detected post-laser TAPS cases, 17 were managed expectantly, eight underwent IUT, two were treated with re-laser surgical intervention and in one case cord coagulation of the co-twin was performed. Intrauterine treatment was offered in all cases of TAPS stage 3 and 4. In TAPS stage 1 or 2, intrauterine treatment was offered only in case TAPS was rapidly progressing (within a couple of days), or when the fetus showed other signs of severe anemia not meeting criteria for stage 3, such as increasing heart size or prehydropic signs. In case of treatment, laser surgery was the first choice of treatment if this appeared technically feasible. Laser surgery in TAPS can be more challenging due to the absence of the oligo polyhydramnios sequence. Intrauterine transfusion was chosen in case laser was not perceived feasible. Cord coagulation was performed in one case where we observed severe cerebral injury in

the ex TTTS recipient (new TAPS donor)[19]. Median gestational age at birth of the cases treated intrauterine (IUT, laser or cord coagulation) was 29 (26-33) weeks compared to 33 (27-41) weeks in the cases treated expectantly (P = 0.07).

Of the 47 children neonatal cranial ultrasound was performed in all but one case (46/47, 98%). This child was born at term age in the referral hospital where cranial ultrasound was not part of standard procedure. Two children were diagnosed with severe cerebral injury. In one case, the TAPS donor (former TTTS recipient) was diagnosed with cystic PVL grade III. In the other case, a TAPS recipient (former TTTS recipient), cerebral imaging showed venous infarction and IVH grade II.

Long-term neurodevelopmental outcome in the 47 children was assessed at a median age of 28 (24-96) months. Twenty-nine Children completed were assessed with the BSID tests using either the second edition (n = 9) or third edition (n=20). In three (3/29, 10%) children motor development could not be assessed due to child's refusal. 16 Children completed WPPSI-III. One twin pair was already tested elsewhere, due to behavioral difficulties, with the Snijders Oomen Non-Verbal Intelligence Scale (SON). Previous assessment with the WPPSI failed and the SON was used to obtain a reliable view of their capacities. One twin had mild-to-moderate cognitive delay and the co-twin scored within the normal range of intelligence.

The incidence of NDI in the studied cohort was 4/47 (9%), occurring in one donor (1/20, 5%) and three recipients (3/27, 11%) (P = 0.63). CP was diagnosed in one (1/47, 2%) case. Severe cognitive delay was detected in two (2/47, 4%) children and severe motor delay, in one (1/47, 2%) child. The long-term outcome is reported in Table 2. Patient characteristics of the 4 children with NDI are presented in Table 3.

Table 2 Long-term outcome in the post-laser TAPS group

	Overall N=47	**Donor N=20**	**Recipient N=27**	***P***
Cerebral palsy	1/47 (2)	1/20 (5)	0/27 (0)	0.43
Cognitive score	95.3 ± 12.5	94.5 ± 11.3	95.8 ± 13.4	0.74
Cognitive development < -2 SD	2/47 (4)	0/20 (0)	2/27 (7)	0.50
Cognitive development < -1 SD	8/47 (17)	3/20 (15)	5/27 (19)	1.0
Motor score[a]	93.9 ± 12.4	93.2 ± 7.8	94.4 ± 15.3	0.81
Motor development < -2 SD[a]	1/26 (4)	0/11 (0)	1/15 (7)	1.0
Motor development < -1 SD[a]	5/26 (19)	1/11 (9)	4/15 (27)	0.36
Bilateral blindness/deafness	0/47 (0)	0/20 (0)	0/27 (0)	-
Neurodevelopmental impairment[b]	4/47 (9)	1/20 (5)	3/27 (11)	0.63

SD, standard deviation; Data are expressed as n (%) or mean ± SD.

[a]Total number of children with assessment of motor development with Bayley scales, 11 donors and 15 recipients.

[b]Neurodevelopmental impairment included any of the following: Cerebral Palsy, cognitive development < 2 SD, motor development < 2 SD, bilateral deafness or blindness.

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

We also performed univariate analysis of potential risk factors for cognitive outcome in the whole cohort. Risk factors for low cognitive scores are 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 ($P = 0.05$).

Table 3 Patient characteristics of the 4 post-laser TAPS survivors with NDI

Case	TAPS donor/ recipient	Highest TAPS stage	Treatment TAPS	GA birth weeks	Birth weight	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-I	Cognitive delay < -2SD
2	Recipient (former TTTS donor)	2	IUT	29	1009	RDS	No abnormalities	Cognitive delay < -2SD
3	Recipient (former TTTS donor)	3	Cord coagulation co-twin	28	955	RDS	No abnormalities	Motor delay < -2SD
4	Donor (former TTTS recipient)	2	IUT followed by re-laser surgery intervention	32	1635	No	cPVL-III	CP: quadriplegia

TAPS, twin anemia polycythemia sequence; GA, gestational age; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; SD, standard deviation; IUT, intrauterine transfusion; cPVL, cystic periventricular leukomalacia; CP, cerebral palsy.

Table 4 Cognitive scores in the 28 post-laser TAPS survivors diagnosed antenatally.

Treatment antenatal TAPS	N	Antenatal TAPS stage	Gestational age at birth	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)

TAPS, twin anemia polycythemia sequence; N, number
Data are expressed as n (%) or median (range)

Discussion

This is the first study evaluating long-term neurodevelopmental outcome in TTTS survivors who developed TAPS after laser surgery. NDI was detected in 9%, with no difference 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 NDI reported in case series of TTTS treated with laser (range 6% to 18%).[9-11] Unfortunately due 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 treated with laser. Larger studies, possibly with a case-control study design, are needed to determine if post-laser TAPS leads to an increased risk of impairment compared to uncomplicated TTTS cases.

The incidence of CP of 2% in our series was similar to previously published TTTS follow-up studies, ranging from 3 to 12%.[9-11] In the general population, CP occurs in approximately 6% at 28 to 31 weeks, 0.7% at 32 to 36 weeks, and 0.1% in term infants.[20] Severe cognitive delay (4%) and severe motor delay (2%) was 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 2.3% rate in the general population.

Cerebral injury and neurologic impairment in TAPS survivors can theoretically be due to several factors, including among others, 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 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[21] and impaired neurodevelopmental outcome.[22] In a subgroup analysis on antenatal detected/managed TAPS cases, we found that the TAPS subgroup treated with IUT had the lowest median cognitive score (82.5) compared to the other subgroups. A possible explanation for the low cognitive scores could be that these cases were born at a lower gestational age at birth of 29 weeks (IQR 27.5-33) due to induced labor or planned caesarean for severe anemia or polycythemia. IUT may temporarily improve the condition of the donor, allowing prolongation of the pregnancy. However, IUT may also worsen the polycythemia in the recipient twin and lead to possible severe complications such as severe cerebral injury.[8] Additionally IUT is a symptomatic treatment, not a causal 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 3 children with severe developmental delay, 2 were tested with BSID-III and one with BSID-II. Children at the age ≥ 3 years were tested with WPPSI. With advanced age a more reliable view of capacities can be obtained. Two children were already tested elsewhere with the Snijders Oomen Non-Verbal Intelligence Scale due to failure of previous WPPSI assessment. The most important limitation of this study was the relatively small sample size. Although this is the largest study to date reporting on neurodevelopmental outcome in post-laser TAPS our data should be interpreted with care.

Since post-laser TAPS is caused by small residual anastomoses that might have been missed at initial laser treatment for TTTS, it is of high importance to reduce the amount of these residual anastomoses. A recent published randomized controlled trial showed a significant reduction of 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, where 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 NDI and 17% incidence of mild-to-moderate cognitive delay, without difference between donors and recipients. Risk factors for lower cognitive score are lower gestational age at birth and birth weight. Antenatal TAPS management consisting of IUT was a risk factor for lower cognitive scores. Larger studies are needed to reliably investigate 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 utmost importance to increase sample size.

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