Neonatal hematological and biochemical complications in TTTS and TAPS

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Chapter 6
Hypoalbuminemia in donors with twin anemia-polycythemia sequence: a matched case-control study

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Abstract

Objective: To determine the differences in albumin levels between donors and recipients with twin anemia-polycythemia sequence (TAPS).

Methods: We included all consecutive monochorionic twins with TAPS with double survivors. Each twin pair was matched for gestational age at birth with 2 control monochorionic twin pairs unaffected by TAPS or twin-twin transfusion syndrome. We measured levels of albumin, total protein, and hemoglobin on the first day of life in donors and recipients (TAPS group) and the control group.

Results: A total of 25 TAPS twin pairs and 50 control twin pairs were included in the study. The median gestational age at birth was 32 weeks in both groups. In the TAPS group, median levels (IQR) of albumin in donor twins were significantly lower than in recipient twins, i.e. 28.0 g/l (24.0-32.0) versus 32.0 g/l (30.0-34.5) ($p = 0.008$). Median levels (IQR) of total protein in donor twins were also lower than in recipients, i.e. 44.0 g/l (36.5-49.0) versus 49.0 g/l (46.5-51.0), respectively ($p = 0.004$). The median (IQR) intertwin albumin difference was significantly higher in the TAPS group than in the control group, i.e. 4.0 g/l (2.5-10.5) versus 2.0 g/l (1.0-4.0) ($p = 0.003$). The rate of hypoalbuminemia (<20 g/l) and hypoproteinemia (<40 g/l) in donor twins with TAPS was 20% (5/25) and 32% (8/25).

Conclusions: In addition to lower hemoglobin levels, donor twins with TAPS also have significantly lower albumin and total protein levels compared to recipient twins.

Introduction

Vascular anastomoses are almost invariably present in all monochorioric twin placentas and may lead to several complications including twin-twin transfusion syndrome (TTTS) and twin anemia-polycythemia sequence (TAPS) [1]. TTTS occurs in 9% of monochorionic twins and is characterized by the development of twin oligo-polyhydramnios sequence (TOPS) [2]. In contrast, TAPS is characterized by large intertwin hemoglobin differences without signs of TOPS [3]. TAPS can be detected in 2-13% of TTTS pregnancies treated with laser surgery (postlaser TAPS) [4,5] and can also occur spontaneously in about 3-5% of monochorionic twin pregnancies (spontaneous TAPS) [6]. TAPS placentas are characterized by the presence of only few minuscule arteriovenous placental anastomoses allowing slow but chronic intertwin blood transfusion, resulting in chronic anemia (with reticulocytosis) in donors and polycythemia in recipients [3].

Knowledge on biochemical differences between donors and recipients in TAPS is sparse but important. Hypoalbuminemia in neonates is an independent risk factor for mortality and morbidity [7,8] and has been associated with various adverse clinical conditions like necrotizing enterocolitis, respiratory distress syndrome, intracranial hemorrhage, sepsis, chronic lung disease, and edema [9,10,11]. In analogy to hypoproteinemia in donors with TTTS, we hypothesize that similar differences may be detected in TAPS twins.

The aim of this study was to determine the differences in albumin and total protein between donor and recipient twins with TAPS compared to a control group of uncomplicated monochorionic twins matched for gestational age at birth.

Methods

We conducted a retrospective analysis of consecutive monochorionic twin pairs with TAPS (TAPS group) and uncomplicated monochorionic twins (control group) delivered at the Leiden University Medical Center (The Netherlands) between August 2003 and August 2012. The Leiden University Medical Center is a tertiary care center managing all types of complications of monochorionic pregnancies and a national referral center for fetoscopic laser treatment for TTTS.

For the purpose of this study, TAPS was diagnosed using the following proposed postnatal criteria: an intertwin Hb difference >8.0 g/dl and at least one of the following: reticulocyte count ratio >1.7 or placenta with only small (diameter <1 mm) vascular anastomoses [3]. Each twin pair with TAPS was compared with 2 uncomplicated monochorionic twin pairs unaffected by TAPS or TTTS and matched for gestational age at birth (±1 week). We excluded all twin pregnancies with single or double intrauterine death, TAPS cases treated with fetoscopic laser surgery, and cases with incomplete placental injection study. At birth, levels of hemoglobin, reticulocyte count, albumin, and total protein were measured routinely in all twins. Blood samplings were primarily obtained from umbilical cord. If umbilical cord blood was not available, venous blood samplings were obtained on day 1. We defined hypoalbuminemia at birth as an albumin level <20 g/l and hypoproteinemia as a total protein level <40 g/l [12,13,14].

We recorded the following perinatal variables: gestational age at birth, birth weight, birth weight discordance, individual placental territory, and placental territory discordance.

Birth weight discordance was assessed and calculated as follows: [(birth weight of the larger twin - birth weight of the smaller twin)/birth weight of the larger twin] × 100. The definition of small for gestational age was a birth weight <2 SD according to the growth charts for the Dutch population [15]. The percentage of individual placental territory was determined by dividing each individual placental territory by the sum of both territories. The following neonatal data were collected: respiratory distress syndrome, necrotizing enterocolitis, patent ductus arteriosus, sepsis, mortality, and cerebral injury. Cerebral injury was defined as the presence of at least 1 of the following findings: cystic periventricular leukomalacia ≥grade 2, intraventricular hemorrhage ≥grade 3, ventricular dilatation, arterial or venous infarct, or other severe cerebral dilatation detected with cranial ultrasound. Sepsis was defined as a clinically ill neonate with positive bacterial culture. Neonatal mortality was defined as death within 28 days after birth.

Primary outcome was the level of albumin and total protein at birth which was compared between donors and recipients in the TAPS group and between the smaller one (lowest birth weight) and the larger one in the control group. We also calculated the intertwin difference in levels of albumin, total protein, and hemoglobin and compared the results between the TAPS group and the control group.

Statistics

Data are reported as medians and IQR. Results of continuous variables within twin pairs were analyzed using a related-samples Wilcoxon signed rank test (when not normally distributed). Similarly, a Mann-Whitney test was used to compare continuous variables between the TAPS group and the control group. For analyses of paired nominal variables, the McNemar test was used. For statistical analyses, two-sided tests were used and $p < 0.05$ was considered statistically significant. Analysis was performed using SPSS version 17 (SPSS, Inc., Chicago, Ill., USA).

Results

During the 10-year study period, 216 monochorionic twins were born at our center. TAPS was diagnosed in 32 (15%) twins. Seven eligible twin pairs (22%) in the TAPS group were excluded because of incomplete biochemical data at birth. Of the remaining 25 TAPS twin pairs, 6 (24%) twins were spontaneous TAPS cases and 19 (76%) were postlaser TAPS cases. In the 19 postlaser TAPS twins the mean gestational age at laser treatment for TTTS was 21 weeks (IQR 18-25). Each TAPS twin pair (n = 25) was matched with 2 uncomplicated monochorionic twins (n = 50). The baseline characteristics in the TAPS and control groups are listed in table 1.

TABLE 1 Baseline characteristics in the twins with TAPS (TAPS group) and monochorionic twins uncomplicated by TAPS or TTTS (control group)

	TAPS group (N[c] = 50)	Control group (N[c] = 100)
Caesarean delivery - no. (%)	28 (56%)	44 (44%)
Female – no. (%)	24 (48%)	52 (52%)
Gestational age at birth – wk[a]	32 (29 – 34)	32 (29 – 33)
Birth weight difference - %[a,b]	10.4 (4.5 – 18.5)	10.4 (4.3 – 24.7)
Small for gestational age – no. (%)	2 (4%)	4 (4%)

[a]*Value given as median (IQR)*
[b]*Birth weight difference was calculated as follows: ((birth weight larger twin – birth weight smaller twin)/ birth weight larger twin) x 100*
[c]*Refers to the number of fetuses cq neonates*

In the TAPS group, median albumin levels at birth in donors were significantly lower compared to those of the recipient twins, i.e. 28.0 versus 32.0 g/l (p = 0.008) (table 2). Hypoalbuminemia (albumin level <20 g/l) was detected in 5 donors (20%). Skin edema was present in 2 of the donors with hypoalbuminemia. The first infant had an albumin level of 16 g/l (and required several albumin infusions) while her cotwin sister had an albumin level of 27 g/l. In the second case the donor had an albumin level of 11 g/l, and received several albumin infusions, while his cotwin brother had an albumin level of 33 g/l. On day 8 the infant died of severe respiratory and circulatory failure and persistent pulmonary hypertension of the newborn. In another donor with hypoalbuminemia (albumin of 13 g/l), fetal hydrops at birth was diagnosed. His cotwin brother had an albumin of 34 g/l. Albumin infusions were given in combination with diuretics to treat the hypoalbuminemia. The donor died due to multiorgan failure. In the 2 other infants with hypoalbuminemia no fetal hydrops was present and treatment with albumin transfusions was not administered.

TABLE 2 Hematological and biochemical differences at birth between donors and recipients (TAPS group) and smaller and larger twins (control group)

	TAPS group			Control group		
	Donors (N = 25)	Recipients (N = 25)	p-value	Smaller twins (N = 50)	Larger twins (N = 50)	p-value
Hemoglobin – g/dL[a]	9.5 (7.7 – 11.2)	22.6 (20.6 - 24.5)	0.000	16.3 (14.7 – 18.5)	16.5 (15.3 – 18.1)	0.882
Albumin – g/L[a]	28.0 (24.0 – 32.0)	32.0 (30.0 - 34.5)	0.008	31.0 (29.0 – 33.0)	31.0 (28.8 – 35.0)	0.692
Albumin < 25 g/L – no. (%)	6 (24%)	0 (0%)	0.031	1 (2%)	5 (10%)	0.375
Albumin < 20 g/L – no. (%)	5 (20 %)	0 (0%)	0.063	1 (2%)	0 (0%)	1.000
Total protein – g/L[a]	44.0 (36.5 – 49.0)	49.0 (46.5– 51.0)	0.004	46.0 (43.0– 1.5)	47.0 (42.3–53.0)	0.656
Total protein < 40 g/L – no. (%)	8 (32%)	1 (4%)	0.039	4 (8%)	7 (14%)	0.453

[a]*Data given as median (IQR)*

All of the recipients in the TAPS group had an albumin level >25 g/l. One infant in the control group had a albumin level <20 g/l.

Median levels of total protein in donors were lower than in recipients, i.e. 44.0 g/l versus 49.0 g/l (p = 0.004). Hypoproteinemia was detected in 32% (8/25) of the donor twins and in 4% (1/25) of the recipient twins (p = 0.039). Intertwin hematological and biochemical differences at birth between the TAPS group and control group are shown in table 3.

TABLE 3 Inter-twin hematological and biochemical differences at birth between the TAPS group and the control group

	TAPS group	Control Group	p-value
Inter-twin hemoglobin difference – g/dL[a]	12.2 (9.7–15.3)	1.2 (0.3–3.7)	0.000
Inter-twin albumin difference – g/L[a]	4.0 (2.5–10.5)	2.0 (1.0–4.0)	0.003
Inter-twin total protein difference – g/L[a]	7.0 (3.0–14.0)	3.0 (2.0–6.8)	0.012

[a]*Data given as median (IQR)*

Clinical and placental characteristics in twins in the TAPS group and control group are presented in table 4. We found no differences in neonatal mortality and morbidity between donors and recipients in the TAPS group. Donors in the TAPS group had a lower birth weight than recipients, but larger individual placental territories, whereas the lower birth weight in the smaller twins in the control group was correlated with a smaller placental share.

TABLE 4 Clinical outcome and placental characteristics in the TAPS group and control group

	TAPS group			Control group		
	Donors (N = 25)	Recipients (N = 25)	p-value	Smaller twins (N = 50)	Larger twins (N = 50)	p-value
Birth weight – gr[a]	1459 (1117–1815)	1695 (1208–1893)	0.016	1435 (1141–1733)	1671 (1385–2013)	0.000
Individual placental territory - %[a]	53.6 (47.2–64.0)	46.5 (36.0–52.8)	0.107	42.4 (36.0–51.7)	57.6 (48.4–64.0)	0.007
RDS– no. (%)	5 (20%)	6 (24%)	1.000	15 (30%)	20 (40%)	0.180
NEC– no. (%)	0 (0%)	0 (0%)	1.000	5 (10%)	4 (8%)	1.000
PDA– no. (%)	2 (8%)	0 (0%)	0.500	2 (4%)	2 (4%)	1.000
Cerebral injury – no. (%)[b]	1 (4%)	1 (4%)	1.000	3 (6%)	2 (4%)	1.000
Sepsis – no. (%)[c]	4 (16%)	4 (16%)	1.000	6 (12%)	6 (12%)	1.000
Mortality– no. (%)	2 (8%)	1 (4%)	1.000	1 (2%)	3 (6%)	0.500

[a]Data given as median (IQR)
[b]Cerebral injury is defined as any of the following: cystic periventricular leukomalacia grade 2 or higher, intraventricular hemorrhage grade 3-4, ventricular dilatation, arterial or venous infarct or other severe cerebral dilatation [c]Sepsis is defined as blood-culture proven clinical sepsis

Abbreviations: RDS = Respiratory distress syndrome, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus

Discussion

TAPS was first described in 2007 [16] and data on the pathophysiology of TAPS is mostly limited to reports on hematological features of TAPS [17]. This is the first study evaluating differences in biochemical variables in TAPS twins and showing that donor twins with TAPS have significantly lower levels of albumin and total protein levels at birth compared to recipients, in addition to lower hemoglobin levels. In a previous study, we and others found similar differences in albumin and total protein between donors and recipients with TTTS [18,19]. The intertwin albumin difference in the TTTS group in our previous study was slightly larger (5.0 g/l) compared to the TAPS group in the current study (4 g/l) [20].

Our data may suggest that placental vascular anastomoses in TAPS, such as in TTTS, allow intertwin transfusion not only of hemoglobin but also of albumin and total protein [16]. Another explanation could be that the lower albumin and total protein levels in donors may not only be due to loss of proteins into the circulation of the recipients but could also be due to a reduced production of albumin in donors.

An additional finding of this study concerns the correlation between birth weight and individual placental share. The smaller twins in the control group have a significantly lower individual placental territory, confirming the well-known association between placental function and birth weight [1]. In contrast, although donors in the TAPS group have larger placental shares than recipients, we found a trend in lower birth weights compared to recipients. This paradoxical finding was previously described by Lewi et al. [21]. It is tempting to speculate that the lower levels of albumin and total protein may play a role in the reduced growth of donors despite the larger placental share.

Albumin, which makes up 50% of the normal intravascular protein mass and is responsible for 75-80% of the plasma colloid pressure, has several important physiological properties. Albumin is involved in protein binding and transport of many endogenous and exogenous substances (e.g. drugs, bilirubin) and acts as a free radical scavenger. Furthermore, albumin inhibits platelet function and has antithrombotic effects and finally affects vascular permeability [9,22]. Serum albumin concentrations increase with gestational age. Possible explanations for this could be increased synthesis by the fetal liver [23] or the greater placental transfer of albumin towards term [24]. Serum levels of albumin may fall during periods of stress, trauma, or sepsis [25] despite its long half-life of 17-19 days [22].

Although hypoalbuminemia is associated with an increased risk of neonatal morbidity and mortality [7,8], we found no differences in morbidity or mortality between donors and recipients. However, our study was not designed to detect such differences.

The data in this study should be interpreted with care due to the known methodological limitations associated with retrospective study designs.

In conclusion, our data add to the understanding of the pathophysiologic characteristics of TAPS. Our findings confirm that placental vascular anastomoses in TAPS may allow transport not only of hemoglobin from donors to recipients but also of albumin and total protein.

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