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Neurodevelopmental Trajectories of Preterm Born Survivors of Twin–Twin Transfusion Syndrome: From Birth to 5 Years of Age

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Objective To investigate the neurodevelopmental outcome at age 2 and 5 years in survivors of twin–twin transfusion syndrome (TTTS) treated with fetoscopic laser surgery and born premature and/or small for gestational age.
Study design At 2 and 5 years of age, standardized neurologic, motor, and cognitive assessments were performed by a neonatologist, a pediatric physical therapist, and a psychologist. Behavior was assessed using a validated questionnaire completed by parents.
Results Neurodevelopmental assessment at both time points was available for 73 survivors of TTTS. Mild to moderate neurodevelopmental impairment (NDI) was detected in 34% of survivors (25 of 73) at 5 years, compared with 25% (18 of 73) at 2 years ($P = .178$). Severe NDI was observed in 12% (9 of 73) at 5 years and in 3% (2 of 73) at 2 years ($P = .035$). Mean cognitive score was lower at the 5-year follow-up (90.7 ± 12.3 vs 95.6 ± 13.1 at 2 years; $P = .001$), and more children were diagnosed with mild cognitive impairment at 5 years (29% vs 11% at 2 years; $P = .007$). When comparing individual outcomes at both time points, 35% (25 of 71) moved from a normal outcome or mild to moderate impairment at 2 years toward more severe impairment at 5 years.
Conclusions A high rate of mild to moderate cognitive impairment and severe NDI at age 5 years was not identified at age 2 years. Our data highlight the importance of longitudinal follow-up of survivors of TTTS beyond age 2 years and emphasize the precautions that should be taken when diagnosing an absence of impairment before school age. *(J Pediatr 2022;240:51-7)*.

Twin–twin transfusion syndrome (TTTS) is a complication in monochorionic twin pregnancies caused by an imbalance in blood flow through the anastomoses on the shared placenta. It usually occurs between 16 and 26 weeks of pregnancy. Without timely intervention, TTTS is lethal in 73%-100% of cases.[1] Fetoscopic laser coagulation of the intertwin anastomoses is the preferred treatment.[2] Although intervention has increased the survival of both twins from 50% to 70% and survival of at least 1 twin from 81% to 92%, TTTS is associated with high mortality and morbidity in survivors.[3]

One important aspect of morbidity is long-term neurodevelopmental impairment (NDI). The reported prevalence of severe NDI is approximately 10%, and minor NDI occurs in an additional 14%.[4] However, these outcomes are based primarily on studies in toddlers and preschoolers, using different outcome measures and often without validated tests.[5-11] Favorable outcomes at an early age do not always reflect a child's abilities later in life. With increasing age and additional demands on the child's functioning, particularly at school age, the presence of developmental impairments is likely to become more visible.[12]

Knowledge of neurodevelopmental outcome beyond age 2 years and at least until school age is important, as it will benefit the counseling of parents of twins with TTTS and support early intervention strategies to improve outcomes. The aims of the present study were to investigate the rate of NDI in survivors of TTTS treated with fetoscopic laser surgery and born before 30 weeks of gestation and/or small for gestational age (SGA) at 2 and 5 years of age and to compare individual outcomes between the 2 time points.

Bayley-III-NL	Bayley Scales of Infant and Toddler Development, third Dutch edition
CBCL	Child Behavior Checklist
CP	Cerebral palsy
GMFCS	Gross Motor Functioning Classification Scale
M-ABC-II-NL	Movement Assessment Battery for Children, second Dutch edition
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit
SGA	Small for gestational age
TTTS	Twin–twin transfusion syndrome
WPPSI-III-NL	Wechsler Preschool and Primary Scale of Intelligence, third Dutch edition

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Methods

All survivors of TTTS treated with fetoscopic laser surgery and born between 2009 and 2014 at the Leiden University Medical Center were eligible if they were born before 30 weeks of gestational age and/or at SGA (ie, <10th percentile [$P < 10$] on the Perined [Hoftiezer] growth chart of 2008) with a birth weight <1500 g.[13] In The Netherlands, all children born at <30 weeks of gestational age and/or SGA with a birth weight below 1500 g undergo a standardized neurodevelopmental assessment at 2 and at 5 years of age, according to the national guideline of the Dutch Neonatal Working Group on Follow-Up. If only 1 of the twins is born SGA, the appropriate grown co-twin is tested as well. For this study, only survivors of TTTS with completed follow-up data at both time points were included. Children who could not be assessed owing to severe motor, neurosensory, or cognitive impairments were assigned the corresponding lowest score. Some of the children had been included in a previous study reporting neurodevelopmental outcome at 2 years of age.[11] The Medical Ethics Committee of Leiden-The Hague-Delft reviewed the protocol of this anonymized retrospective study with prospectively gathered follow-up data and issued a statement of no objection (G20.010).

Baseline Characteristics of the Study Population

Perinatal data were collected from patient records, including TTTS stage according to internationally accepted staging criteria (I-V),[14] donor or recipient status, gestational age at fetoscopic laser surgery (in weeks), fetal demise, gestational age at birth (in weeks), birth weight, sex, neonatal mortality (within 28 days after birth), and severe cerebral injury. Severe cerebral injury was defined as the presence of at least 1 of the following: cystic periventricular leukomalacia grade ≥2, intraventricular hemorrhage grade ≥3, ventricular dilatation >97th percentile, porencephalic or parenchymal cysts, and arterial or venous infarction or other severe cerebral lesions associated with adverse neurologic outcome.[15-17] Maternal education was classified into 3 categories: primary and general secondary education, intermediate, and higher vocational education and university.

Outcome Assessment and Measures

Children and their parents were invited for follow-up visits at our outpatient clinic at corrected ages (for prematurity) of 2 and 5 years. All children were seen by our neonatal follow-up team of pediatric psychologists, pediatric physical therapists, and neonatologists. At age 2 years, cognitive and motor development was assessed with the Bayley Scales of Infant and Toddler Development, third Dutch edition (Bayley-III-NL).[18] At age 5 years, cognitive development was assessed using the Wechsler Preschool and Primary Scale of Intelligence, third Dutch edition (WPPSI-III-NL).[19] Results of both tests were interpreted according to the Dutch norms. The Bayley-III-NL cognitive and motor composite scores and WPPSI-III-NL verbal, performance, and total IQ scores follow a normal distribution, with a normed mean of 100 and an SD of 15. Children had mild to moderate cognitive or motor impairment with scores of 70-84 (between −1 and −2 SD) or severe impairment with scores <70 (−2 SD).

Motor development at age 5 years was examined with the Movement Assessment Battery for Children, second Dutch edition (M-ABC-II-NL).[20] According to the M-ABC-II-NL, children had either mild to moderate motor impairment with scores between the 5th and 15th percentiles or severe motor impairment with scores below the 5th percentile. At both time points, a neurologic examination was performed by a neonatologist. Cerebral palsy (CP) was classified as grade I-V according to the Gross Motor Function Classification System (GMFCS).[21]

Parents reported on behavioral problems at both time points using the Child Behavior Checklist (CBCL).[22] Age-standardized *t*-scores were obtained for internalizing (withdrawal, somatic complaints, anxiety/depression), externalizing (delinquent or rule-breaking and aggressive behavior) and total problem behavior, with higher scores indicating higher levels of problem behavior. Children were classified as having mild to moderate behavioral problems with *t*-scores in the borderline clinical range (≥84th percentile) or severe behavioral problems with *t*-scores in the clinical range (≥90th percentile).

Severe NDI, a composite outcome score for both time points, was defined as at least 1 of the following: Bayley-III-NL cognitive and/or motor score <70, WPPSI-III-NL full scale, verbal, or performance score <70, M-ABC-II score ≤5th percentile, CP GMFCS grade ≥2, and blindness or severe visual impairment and/or severe hearing impairment (ie, bilateral deafness, treatment in an audiologic center, severe neurosensory hearing loss or hearing loss requiring amplification). Mild to moderate NDI was defined as Bayley-III-NL cognitive and/or motor score <85 or WPPSI-III-NL full scale, verbal, or performance scores <85, M-ABC-II scores between the 5th and 15th percentiles, CP GMFCS grade 1, mild hearing loss (up to 30 dB), and/or mild visual impairment (defined as needing correction with > +4 or < −4 optical amplification). If a child already had been tested for follow-up elsewhere, the test results were requested with written permission from the parents.

Statistical Analysis

Results are presented as number of cases and percentage, mean ± SD, or median (IQR), depending on the distribution of the variable. Perinatal factors of survivors of TTTS with and without follow-up at both time points were compared to assess whether selective loss to follow-up occurred. Proportions were compared using the χ^2 test or Fisher exact test. Continuous variables were calculated using the independent *t* test or Mann–Whitney *U* test. To account for the fact that observations between co-twins are not independent, these analyses were performed using generalized estimating equations. To assess for a difference in the group distribution of the composite NDI (mild-moderate and severe) score and for each developmental domain (CP, cognitive scores, vision, hearing, and behavior) separately, the marginal homogeneity

test was conducted (to adjust for the effect of paired testing). In the event of a significant difference ($P < .05$), the McNemar test was conducted post hoc. Characteristics of the group with NDI (mild-moderate or severe) and the group without NDI were compared using the χ^2 test, Fisher exact test, or independent *t* test. All statistical analyses were performed using SPSS version 25.0 (IBM).

Results

Study Group

Between 2009 and 2014, 133 survivors of TTTS were born preterm at <30 weeks or SGA with a birth weight <1500 g at our center after treatment with fetoscopic laser surgery for TTTS. The neonatal mortality rate was 7% in liveborn children (**Figure 1**; available at www.jpeds.com). Overall, 123 survivors of TTTS were eligible for long-term follow-up according to the Dutch Guideline for Neonatal Follow-Up. Follow-up assessment at age 2 years with Bayley-III-NL was available for 88% of survivors of TTTS (108 of 123) and follow-up at both time points for 68% of survivors (73 of 108). The perinatal characteristics of the group tested at both time points and the group tested only at 2 years were comparable (**Table I**).

Neonatal Outcome and Follow-Up Assessment at Age 2 Years

Table I presents the neonatal outcome and follow-up data at age 2 years for both groups. Bayley-III-NL motor index scores were significantly lower for the group tested at both time points compared with the group tested at 2 years (mean, 97.4 ± 12.7 vs 103.4 ± 13.6; $P = .039$). More children were diagnosed with mild NDI in the group tested at both time points compared with the group tested only at 2 years (25% [18 of 73] vs 3% [1 of 35]; $P = .022$). CP (GMFCS grade I) was diagnosed in 4% of children (3 of 73) tested at both time points and in 3% of children (1 of 35, GMFCS grade II) tested at age 2 years only.

Neurodevelopmental Outcomes in Survivors of TTTS from 2 to 5 Years of Age

Table II presents the results of the cognitive, motor, behavioral, and neurologic assessments of the survivors of TTTS tested at both time points. Cognitive scores were significantly lower at age 5 years compared with age 2 years (mean, 90.8 ± 12.3 vs 95.6 ± 13.1; $P = .001$). The percentage of children with cognitive scores within the normal range dropped from 88% (64 of 73) at age 2 years to 64% (47 of 73) at reassessment ($P = .000$). Significantly more children were diagnosed with mild-moderate cognitive impairment at age 5 years than at age 2 years (29% [21 of 73] vs 11% [8 of 73]; $P = .007$). Severe cognitive impairment was present in 7% of the children (5 of 73) at age 5 years.

At the 5-year reassessment, fewer children were diagnosed with a mild-moderate motor impairment than were seen at 2 years (6% [4 of 68] vs 17% [12 of 73]). Significantly more children had a severe motor impairment at 5 years (7% [5 of 68] vs 1% [1 of 73]). The individual CP diagnoses did not change from 2 to 5 years, with 4% (3 of 73) with GMFCS grade I. Neither blindness nor deafness was observed; 1 child had a mild visual impairment at both time points. At age 5 years, 14% of the children (10 of 70) had borderline to clinical behavioral problems, compared with 9% (6 of 70)

Table I. Perinatal characteristics and neonatal outcome and follow-up assessment at age 2 years of the survivors of TTTS tested at both time points vs survivors of TTTS tested at age 2 years only

Characteristics	2- and 5-year group (N = 73)	2-year group (N = 35)	*P* value
Gestational age at laser, wk, median (IQR)	20.0 (17.5-23.0)	19.0 (17.0-24.0)	.70
TTTS staging, n (%)			
Stage 1	14 (19)	4 (11)	.49
Stage 2	27 (37)	14 (40)	.94
Stage 3	28 (38)	17 (49)	.41
Stage 4	4 (6)	0 (0)	—
Donor, n (%)	38 (52)	17 (49)	.30
Female sex, n (%)	50 (69)	18 (51)	.19
Gestational age at birth, wk, median (IQR)	29.9 (28.3-32.1)	30.0 (28.6-31.9)	.84
Gestational age <28 wk, n (%)	16 (22)	4 (11)	.31
Gestational age <32 wk, n (%)	55 (75)	27 (77)	.55
Birth weight, g, median (IQR)	1280 (990-1600)	1330 (1205-1400)	.36
SGA ($P < 10$), n (%)	24 (33)	11 (31)	.32
Single survivor, n (%)	5 (7)	1 (3)	.40
Maternal education, n (%)			
Primary, general secondary	4 (6)	7 (20)	.13
Intermediate	32 (50)	15 (43)	.55
Higher vocational education, university	32 (44)	13 (37)	.75
Severe cerebral injury, n (%)	7 (10)	3 (9)	.86
Neonatal morbidity*, n (%)	30 (41)	11 (31)	.33
Bayley cognitive index, mean ± SD	95.64 ± 13.1	97.3 ± 18.2	.59
Cognitive scale score, mean ± SD	8.97 ± 2.7	9.57 ± 3.23	.31
Bayley motor index, mean ± SD	**97.4 ± 12.7**	**103.4 ± 13.6**	**.039**
Fine motor scale score, mean ± SD	**10.14 ± 2.85**	**11.4 ± 2.39**	**.044**
Gross motor scale score, mean ± SD	8.63 ± 2.8	9.57 ± 3.1	.14
Mild to moderate NDI, n (%)	**18 (25)**	**1 (3)**	**.022**
Severe NDI, n (%)	2 (3)	4 (11)	.09
CP, n (%)	3 (4)	1 (3)	.75
GMFCS grade I	3 (4)	—	—
GMFCS grade II-V	—	1 (3)	—

Significant values are in bold type.
*Neonatal morbidity was defined as the presence of one of the following complications: respiratory distress syndrome needing treatment with surfactant, patent ductus arteriosus requiring medical treatment or surgical closure, necrotizing enterocolitis grade ≥2, severe anemia requiring blood transfusion on the first day after birth, severe polycythemia requiring partial exchange transfusion on the first day after birth, severe cerebral injury.

Table II. Neurodevelopmental outcomes of the 73 survivors of TTTS at age 2 to 5 years

Outcomes	2-year assessment (N = 73)	5-year assessment (N = 73)	*P* value
Age, mo, median (IQR)	26 (25-27)	69 (67-71)	
Cognitive development, mean ± SD	Bayley-III-NL	WPPSI-III-NL	**<.001**
Cognitive index/full-scale IQ, mean ± SD	**95.64 ± 13.1**	**90.75 ± 12.3**	**.001**
Verbal IQ		94.4 ± 13.9	
Performance IQ		90.7 ± 11.7	
Normal range, n (%)*	**64 (88)**	**47 (64)**	**<.001**
Mild-moderate impairment*	**8 (11)**	**21 (29)**	**.007**
Severe cognitive impairment*	1 (1)	5 (7)	.10
Motor development, n (%)	Bayley-III-NL	M-ABC-II-NL (N = 68)	.88
Normal range	60 (82)	59 (87)	.32
Mild-moderate impairment	**12 (17)**	**4 (6)**	**.021**
Severe motor impairment	1 (1)	5 (7)	.10
Behavior, borderline to clinical, n (%)	CBCL (N = 70)	CBCL (N = 70)	.86
Internalizing problems	8 (11)	12 (17)	.32
Externalizing problems	9 (13)	9 (13)	.48
Total behavior problems	6 (9)	10 (14)	.53
CP, GMFCS grade I, n (%)	3 (4)	3 (4)	—
Neurodevelopment, composite, n (%)			**.005**
Normal	**53 (73)**	**39 (53)**	**.004**
Mild-moderate impairment	18 (25)	25 (34)	.18
Severe impairment	**2 (3)**	**9 (12)**	**.035**

Significant values are in bold type.
*Cognitive outcome at 5 years is based on WPPSI-III-NL Total IQ, Verbal IQ, and Performance IQ-scores.

at 2 years ($P = .527$). Only 2 children had borderline to clinical behavioral problems at both time points.

Rate and Course of Neurodevelopmental Impairment

The rate of NDI was significantly different between the 2 time points ($P = .005$), owing to an increase in the number of children with severe NDI at 5 years, from 3% (2 of 73) at 2 years to 12% (9 of 73) at the 5-year reassessment ($P = .035$). There was a decrease in the number of children with a normal neurodevelopmental outcome, from 73% (53 of 73) at 2 years to 53% (39 of 73) at 5 years ($P = .004$). Mild-moderate NDI was present in 34% of the children (25 of 73) at 5 years.

Neurodevelopmental Trajectories

Figure 2 shows the individual neurodevelopmental trajectories and change in severity of NDI from age 2 years to 5 years. Of the 53 children with a normal outcome at 2 years, 34 (64%) also had a normal outcome at 5 years (Figure 2), 16 (30%) moved from a normal neurodevelopmental outcome to mild NDI at the 5-year reassessment, and 3 (6%) from normal neurodevelopment at 2 years to severe NDI at 5 years. Of the 18 children with mild-moderate NDI at 2 years, 8 (44%) remained in the mild NDI group, 4 (22%) improved to a normal outcome, and 6 (33%) deteriorated to severe NDI. One child diagnosed with a severe motor developmental delay at age 2 years (Bayley-III-NL motor score of 69) had normal motor development at age 5 years. This was due to the fact that the child could not walk at age 2 years but started walking after that point.

Overall, at a group level, neurodevelopment was normal at both time points in 47% of the children (34 of 73). In 8% (6 of 73), neurodevelopmental outcome at 5 years improved from mild-moderate NDI to normal development in 5% (4 of 73) and from severe to normal development in 1 child. In 34% (25 of 73), neurodevelopment at 5 years deteriorated from normal to mild in 22% (16 of 73), from mild to severe NDI in 8% (6 of 73), and from normal development to severe NDI in 4% (3 of 73). Only 58% of children (42 of 73) remained in the same neurodevelopmental category at both time points.

The 34 children with mild-moderate or severe NDI at age 5 years did not differ from the 39 children without NDI at 5 years with respect to possible risk factors for adverse outcome, including gestational age at birth, donor status, SGA, being a single survivor, severe cerebral injury, and maternal education ($P > .05$) (Table III). Significantly more male survivors had mild or severe NDI at the 5-year assessment ($P = .033$).

Discussion

This study found relatively high rates of mild-moderate (34%) and severe (12%) NDI in school-aged survivors of TTTS that were not detected when the same children were examined as toddlers. Our findings indicate that neurodevelopment examined at age 2 years changed in the following years in 42% of children. Therefore, assessment at age 2 years might not reliably predict neurodevelopmental outcome in the future. In addition, behavioral problems observed at age 2 years can be completely resolved at age 5 years, and new or other problems may occur. Our findings highlight the importance of ongoing follow-up, as early termination could possibly lead to unnecessary delay in detecting neurodevelopmental problems in this high-risk group. At the 5-year reassessment, we observed significantly lower cognitive scores and more children with severe NDI compared with the assessment at age 2 years. Overall, 36% moved from normal neurodevelopment at 2 years to mild-moderate or severe NDI at 5 years. Only 58% of the children were in the same neurodevelopmental outcome category at both time points.

The reported 12% rate of severe NDI at 5 years is comparable to NDI rates reported in other studies, although most studies included survivors of TTTS born at >30 weeks of gestation and with a birth weight appropriate for gestational age.[4] Sananès et al and Mullers et al reported NDI in 13% and 14% of survivors of TTTS at a 43- and 48-month assessment, respectively.[23,24] The mean gestational age at birth in these studies was 33.0 and 29.7 weeks, respectively, and in the first study, SGA was reported in 13% (<5th percentile) of the

			Five-year assessment		
			Normal	Mild impairment	Severe impairment
Two-year assessment	Cognitive		N=47	N=21	N=5
		Normal N=64	46 (72%)	17 (27%)	1 (20%)
		Mild impairment N=8	1 (13%)	3 (38%)	4 (50%)
		Severe impairment N=1	0 (0%)	1 (100%)	0 (0%)
	Motor		N=59	N=4	N=5
		Normal N=60	49 (89%)	2 (4%)	4 (7%)
		Mild impairment N=12	9 (75%)	2 (17%)	1 (8%)
		Severe impairment N=1	1 (100%)	0 (0%)	0 (0%)
	Composite		N=39	N=25	N=9
		Normal N=53	34 (64%)	16 (30%)	3 (6%)
		Mild NDI N=18	4 (22%)	8 (44%)	6 (33%)
		Severe NDI N=2	1 (50%)	1 (50%)	0 (0%)

Figure 2. Change in neurodevelopmental outcome from 2 to 5 years of age.

children. Graeve et al examined survivors of TTTS at 2 years and 6 years and reported severe NDI in 9%.[5] In this group, 23% of the survivors of TTTS were born before 32 weeks of gestation. Concordant with our findings, these authors reported more children with NDI at age 6 years compared with the 2-year assessment (11% [21 of 190] vs 4% [8 of 190]); however, unlike in our study, this difference was not statistically significant.

Table III. Characteristics of children with and without NDI

Characteristics	With mild-moderate or severe NDI (N = 34)	Without NDI (N = 39)	*P* value
TTTS stage, n (%)			
1	9 (23)	5 (15)	—
2	13 (33)	14 (41)	.69
3	14 (36)	14 (41)	.34
4	3 (8)	1 (3)	.37
Gestational age at birth, wk, median (min-max)	30.0 (25.6-35.3)	29.7 (25.9-36.4)	.74
Donor, n (%)	17 (50)	21 (54)	.74
Female sex, n (%)	**19 (56)**	**31 (79)**	**.030**
SGA, n (%)	14 (41)	10 (26)	.16
Single survivor, n (%)	1 (3)	4 (10)	.22
Severe cerebral injury, n (%)	5 (15)	2 (5)	.24
Maternal educational level; higher vocational education, university, n (%)	11 (32)	21 (54)	.07

Significant values are in bold type.

The rate of mild-moderate NDI (34%) at the 5-year assessment in our study is higher than the rates reported in other studies, which ranged from 0 to 26% based on a variety of definitions and in most cases measured at age 2 years.[4-11] McIntosh et al reported "borderline cognitive impairment," defined as a WPPSI full-scale IQ score of 70-79, in 18% of survivors of TTTS born at a mean gestational age of 32 weeks, with 39% born SGA.[8] In our study, a substantially wider spectrum of criteria was used to classify mild-moderate NDI, that is, WPPSI-III-NL verbal, performance, and/or full-scale IQ of 70-84, M-ABC-II-NL scores between the 5th and 15th percentiles, CP GMFCS grade 1, and/or minor visual/hearing impairment. We also tested the children at a mean age of 5 years and 9 months, whereas the children in the study of McIntosh et al were tested at age 4 years.

A comparable course of neurodevelopment is reported in studies of preterm-born children without TTTS. A follow-up study from Sweden assessed 91 children born before

32 weeks of gestation at age 2.5 years and 6.5 years, using the Bayley-III, WPPSI-III, and Wechsler Intelligence Scale for Children, 4th edition.[25] They reported cognitive impairments at the 6.5-year assessment in 22% of children (19 of 88) with normal results on the Bayley at the 2.5-year assessment. A German study in 2-, 5-, and 10-year-old preterm-born children, born before 28 weeks of gestation, reported similar large variations in neurodevelopment between 2 and 5 years, respectively, and 9% and 25% of the children scored in a lower category on cognitive and motor development, respectively, at age 5 years.[26] Variations between age 5 and 10 years were smaller. In addition, a similar shift in individual behavioral outcomes was described as in our study. Between age 5 and 10 years, 43% of children had a change in behavioral category; 15% went from borderline and clinical range to normal behavior scores, and 21% changed from normal behavior scores to scores in the borderline to clinical range. A previous study by our center reported a similar rate of behavioral problems in survivors of TTTS as in the normal population.[27] The rate of behavioral problems in this study is consistent with these results.

At a younger age, impairment can potentially remain concealed due to low test sensitivity (ie, Bayley scales vs Wechsler scales). The previously mentioned study from Sweden reported the sensitivity and specificity of Bayley-III cognitive scores in predicting scores on Wechsler scales.[25] The specificity of Bayley scores below 2 SD in predicting WPPSI scores below 2 SD was high (99%), although sensitivity was low (20%). Only 44% with scores below −1 SD at age 2.5 years still scored below −1 SD. At 6.5 years, 22% of the children with scores below −1 SD had average scores at 2.5 years. Another possible explanation is that some problems may only arise as children age with increasing demands on the child's functioning, especially their academic, cognitive, and social-emotional functioning. In that case, children do not "deteriorate" but instead "grow into" seemingly new deficits as they fail to make age-appropriate developmental gains.[28]

The scientific literature contains only a few studies on neurodevelopment beyond age 2 years in survivors of TTTS treated with laser therapy, and most studies did not use a validated neurodevelopmental test in all their subjects. One of the strengths of this study is the follow-up of patients until age 5 years using internationally accepted and validated tests.

Follow-up assessment of all treated survivors of TTTS at age 2 years is standard of care in our center since 2015. Before 2015, not all children treated with fetal therapy were included in long-term follow-up, only those born premature or SGA. The group of children included in this study likely represents a more at-risk group compared with survivors of TTTS in general, because our study group was born more premature or SGA, which is associated with a higher rate of neonatal and long-term morbidity. This might have led to overestimation of the overall rate of NDI. However, the 34 survivors of TTTS with mild-moderate or severe NDI at age 5 years did not differ from the 39 children without NDI at 5 years with respect to important risk factors for long-term NDI, including severe cerebral injury, gestational age at birth, and birth weight.

Only female sex was associated with better neurodevelopmental results at 5 years; however, this study was not designed to distinguish outcomes by sex, owing to the unequal distribution of females (69%) and males (31%) in our follow-up group. The study was not powered to demonstrate associations with known risk factors for NDI, such as prematurity and birth weight. In addition, the design of this study was not suited to distinguish between the influence of TTTS and prematurity on the trajectories. The discrepancies in NDI at age 2 years and 5 years could be due to TTTS, prematurity, or a combination.

In this study, we observed 34% mild and 12% severe NDI in 5-year-old survivors of TTTS who were born premature (<30 weeks) and/or SGA (<1500 g). Between the 2 time points, we observed a change in neurodevelopmental outcome, particularly concerning cognitive and behavioral scores. We conclude that in the future, predictions of neurodevelopmental outcome should not be based solely on the examination at age 2 years. Follow-up of survivors ofTTTS at 5 years and preferably also at 8 years and during adolescence with standardized developmental tests can provide more insight into the neurodevelopmental trajectory of survivors of TTTS. Accurate and timely detection of NDI is important to offer appropriate developmental support and to help caregivers in the counseling of future parents and survivors of TTTS. ■

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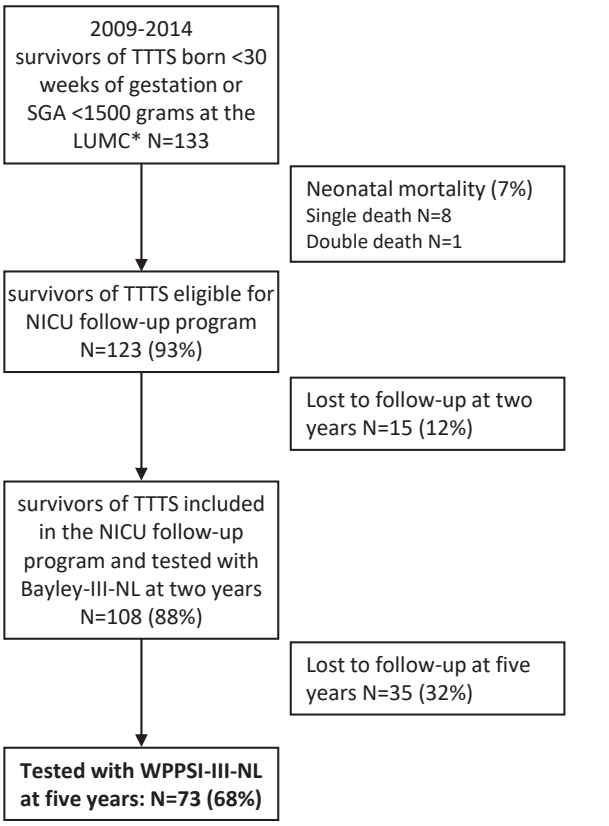

Figure 1. Flowchart of the study population. *Fetal demise N = 36 (16 double and 4 single demise). *LUMC,* Leiden University Medical Center.