OBSTETRICS

Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the fetus/newborn: the LOTUS study

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OBJECTIVE: To determine the incidence and risk factors for neurodevelopmental impairment (NDI) in children with hemolytic disease of the fetus/newborn treated with intrauterine transfusion (IUT).

STUDY DESIGN: Neurodevelopmental outcome in children at least 2 years of age was assessed using standardized tests, including the Bayley Scales of Infant Development, the Wechsler Preschool and Primary Scale of Intelligence, and the Wechsler Intelligence Scale for Children, according to the children's age. Primary outcome was the incidence of neurodevelopmental impairment defined as at least one of the following: cerebral palsy, severe developmental delay, bilateral deafness, and/or blindness.

RESULTS: A total of 291 children were evaluated at a median age of 8.2 years (range, 2–17 years). Cerebral palsy was detected in 6 (2.1%) children, severe developmental delay in 9 (3.1%) children, and bilateral deafness in 3 (1.0%) children. The overall incidence of neurodevelopmental impairment was 4.8% (14/291). In a multivariate regression analysis including only preoperative risk factors, severe hydrops was independently associated with neurodevelopmental impairment (odds ratio, 11.2; 95% confidence interval, 1.7–92.7).

CONCLUSION: Incidence of neurodevelopmental impairment in children treated with intrauterine transfusion for fetal alloimmune anemia is low (4.8%). Prevention of fetal hydrops, the strongest preoperative predictor for impaired neurodevelopment, by timely detection, referral and treatment may improve long-term outcome.

Key words: hemolytic disease of the fetus/newborn, intrauterine transfusion, neurodevelopmental outcome, red cell alloimmunization

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Fetal and neonatal hemolytic disease results from maternal alloimmunization to red cell antigens, for which mother and fetus are incompatible. Maternal immunoglobulin gamma (IgG) antibodies pass the placenta into the fetal circulation and cause destruction of fetal red cells. The resulting progressive fetal anemia leads, when untreated, to fetal hydrops and perinatal death.[1]

Before 1970, hemolytic disease because of antibodies against the Rhesus-D antigen was the most important cause of perinatal death.[2] Several interventions have drastically reduced the incidence and severity of the disease, including postnatal and more recently antenatal anti-D prophylaxis programs,[3,4] improved diagnostic management and neonatal treatment.[1,5-7] One of the major advances was the introduction in 1963 of intrauterine blood transfusions (IUTs),[1] first performed by Liley using the intraperitoneal technique.[8] In the 1980s, this technique was replaced by the intravascular IUT.[1] Nowadays, this treatment is the most successful procedure in fetal therapy, with perinatal survival rates exceeding 95% in experienced centers.[1,7] However, one of the concerns of the more widespread and successful use of fetal therapy is that a decrease in perinatal mortality may lead to an increase of children with long-term handicaps. Only a few studies with small patient numbers have reported on long-term neurodevelopmental outcome after IUT, with an incidence of adverse outcome ranging from 4.5 to 12%.[9-16] The aim of our study was to determine

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the incidence and risk factors for adverse neurodevelopmental outcome after IUT treatment in the largest cohort of children worldwide.

MATERIALS AND METHODS

In 2008, we designed a large national cohort study to evaluate the long-term neurodevelopmental outcome in children treated with IUT: the LOTUS study (LOng-Term follow-up after intra-Uterine transfusionS).[17] All mothers with red cell alloimmunization treated with IUT between Jan. 1, 1988, and Jan. 1, 2008, at the Leiden University Medical Center and their children were invited to participate in this large follow-up study. For the purpose of this study, we included all children of 2 to 17 years of age who had complete follow-up, including a cognitive development test. Children with severe congenital anomalies and syndromal disorders were excluded. This study was approved by the ethics committee of the Leiden University Medical Center. Informed consent was obtained from all participating families. A limited outcome evaluation in a small part of our study group (11 children treated between 1991 and 1993) was described before.[9] Primary outcome was a composite outcome termed neurodevelopmental impairment (NDI) defined as at least 1 of the following; cerebral palsy (CP), severe cognitive developmental delay (< -2 standard deviation [SD]), bilateral deafness requiring hearing amplification, and/or bilateral blindness.

The Leiden University Medical Center serves as the single national reference center for the management of red cell alloimmunization in pregnancy in the Netherlands. IUTs are performed when signs of fetal anemia are detected on Doppler ultrasound examinations. Details on our management guidelines for alloimmunized pregnancies were previously described.[18] Because the implementation of the IUT program using the ultrasound-guided intravascular transfusion technique at our center in 1987, all relevant perinatal data have prospectively been collected in a computerized database. Data included are as follows: type of alloimmunization, gestational age at IUT, hemoglobin level, presence and severity of hydrops at the start of the intrauterine treatment, number of IUTs, gestational age at birth, sex, birthweight, and neonatal outcome. Neonatal outcome data included: number of exchange transfusions because of severe hyperbilirubinemia, respiratory distress syndrome, necrotizing enterocolitis (classified according to Bell et al[19]), sepsis (defined as clinical symptoms of infection and a positive bacterial blood culture) and severe cerebral injury detected either on cranial ultrasound, computed tomography scan (CT), or magnetic resonance imaging (MRI). Severe cerebral injury was defined as the presence of intraventricular hemorrhage $\geq$ grade 3 (classified according to Volpe[20]), cystic periventricular leukomalacia $\geq$ grade 2 (classified according to de Vries et al[21]), and/or ventricular dilatation (defined according to Levene[22]). Other major cerebral abnormalities associated with adverse neurologic outcome were also recorded and classified as severe cerebral lesions. We recorded the presence of perinatal asphyxia, defined as 3 or more of the following 5 criteria: nonreassuring cardiotocogram patterns, umbilical cord arterial pH <7.10, Apgar score <5 at 5 minutes after birth, failure of spontaneous breathing at 5 minutes after birth, and onset of multiple organ failure.

Parental education was determined by the level of education of each parent individually. A score of 1 was given if the parent's education was low, a score of 2 for an average educational level, and a score of 3 for higher levels of education. Education scores of both parents were then added (score range from 2 to 6). Ethnicity was recorded as white or nonwhite. Children were considered to be white when 1 or both parent(s) were of white ethnicity.

Follow-up

All participating families visited our outpatients clinic from August 2008 to November 2010. At this visit, a physical and neurologic examination according to Touwen et al[23] and an assessment of cognitive development using standardized tests were performed.[17] All children were assessed by 1 of the 3 investigators specialized in developmental assessment (I.L., V.S., and E.L.).

Presence of CP was assessed according to the criteria of the European CP Network and classified as diplegia, hemiplegia, quadriplegia, dyskinetic, or mixed.[24] Minor neurologic dysfunction (MND) was defined as a moderate abnormality of tone, posture, and movement leading to only minor functional impairment or minor developmental delay.[23]

Cognitive development in children aged 2 to 3 years was assessed according to the Dutch version of the Bayley Scales of Infant Development, 2nd edition (BSID-II).[17] BSID-II scores provide a mental developmental index (MDI). Children between 3 and 7 years of age were tested with the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III-NL).[17] Cognitive development in children between 7 and 17 years of age was assessed with the Dutch version of the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III-NL).[17] Both the WPPSI and the WISC provide a full scale IQ score. BSID-MDI, WPPSI, and WISC scores follow a normal distribution curve with a mean score of 100. A score of 70-84 indicates mild delay (ie, < -1 SD) and a score <70 indicates severe delay (ie, < -2 SD). A trained psychologist (J.K.), blinded to the antenatal course and neonatal outcome, performed the tests in all children.

Risk factors

Potential risk factors for NDI were investigated including severity of fetal anemia (actual hemoglobin level and Z-hemoglobin), presence, and severity of fetal hydrops (classified according to van Kamp et al[25]) at start of the intrauterine treatment, number of IUTs, gestational age at birth (divided into 3 groups: neonates born before 32 weeks' gestation, between 32 and 35 weeks' gestation, and after 35 weeks' gestation), severe neonatal morbidity, and perinatal asphyxia. Standardized Z scores of hemoglobin (Z-hemoglobin) were defined as the number of SDs that an actual value deviated from the normal mean for gestational age. Reference values for hemoglobin were derived from the literature.[26] Se-

vere neonatal morbidity was defined as the presence of 1 or more of the following: respiratory distress syndrome, necrotizing enterocolitis ≥ grade 2, sepsis, and/or severe cerebral injury.

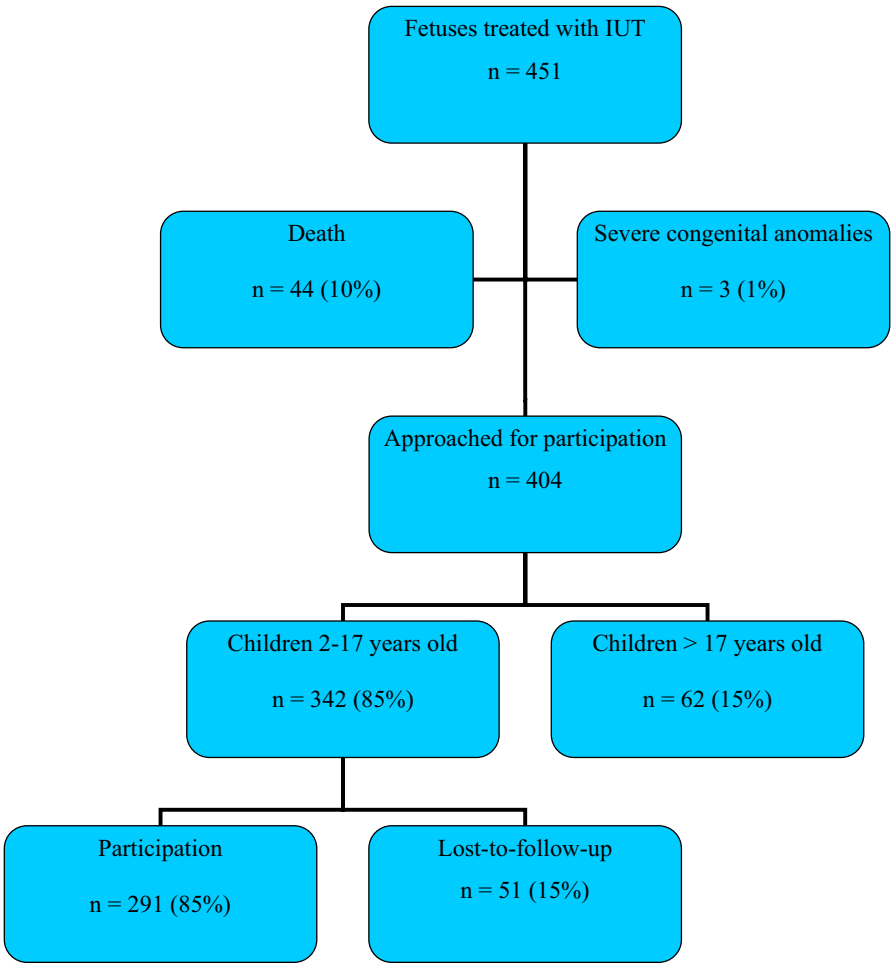
Statistical analyses

We used univariate logistic regressions to test the association between NDI and the potential risk factors. We entered the risk factors into a multivariate logistic regression model and included additional potential confounders, including sex, parental education, and ethnicity. Multiple logistic regression analysis was used to measure the independent effect of the potential risk factors for NDI. Results of logistic regression were considered significant at P values $< .05$. We used the Pearson correlation test to calculate the correlation between hemoglobin at first IUT and IQ score. Analyses were performed using SPSS version 16 (SPSS Inc, Chicago, IL).

RESULTS

During the study period 1284 IUTs were performed in 451 fetuses. Thirty-one fetuses died in utero and 11 in the neonatal period resulting in a perinatal survival rate of 91% (409/451). Two more children died during childhood because of causes unrelated to hemolytic disease of the fetus/newborn (1 accidental infant death occurred because of incorrect construction of the bedframe and 1 infant death was due to acute cardiomyopathy and pulmonary hypertension). Thus, the overall survival rate was 90% (407/451). Three children were diagnosed with congenital anomalies, including Kinsbourne's syndrome, congenital cerebellar hypoplasia, and Phelan-McDermid syndrome and were excluded from further analysis. A total of 342 children were 2 to 17 years of age and thus eligible for the study. Fifty-one (15%) children were lost-to-follow-up because of declined consent (6%, 21/342) or loss of contact address (9%, 30/342). Complete follow-up data were obtained from 291 children by a visit at our outpatient clinic. A flowchart showing the derivation of our study population is shown in Figure 1.

FIGURE 1
Flowchart showing the derivation of our study population



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Perinatal outcome

Detailed information on the baseline perinatal characteristics on 291 long-term survivors is summarized in Table 1. The mean hemoglobin level at first IUT was 5.5 g/dL (± 2.4 SD), and the Z-hemoglobin −7.3 SDs. Both the mean hemoglobin level and Z-hemoglobin in fetuses with hydrops (mild or severe) were significantly lower than in fetuses without hydrops, 3.3 vs 6.3 g/dL ($P < .001$) and −9.1 vs −6.7 ($P < .001$).

The percentage of neonates born < 32 weeks', between 32 and 35 weeks', and ≥35 weeks' gestation was 2% (6/291), 15.5% (45/291), and 82.5% (240/291).

Exchange transfusions during the neonatal period were performed in 58% (168/291) of children. The following severe neonatal morbidities were recorded: respiratory distress syndrome (2.4%, 7/291), necrotizing enterocolitis (1.0%, 3/291), sepsis (5.8%, 17/291), perinatal asphyxia (3.8%, 11/291), and severe cerebral injury (1.7%, 5/291). Severe cerebral injury detected on cranial ultrasound included ventricular dilatation (n = 2), hemorrhagic periventricular leukomalacia (n = 1), cystic periventricular leukomalacia (n = 1), and extensive cerebral abscess (n = 1). In both children with ventricular dilatation, cerebral abnormalities were already detected antenatally. The incidence of severe neonatal morbidity was significantly higher in the group neonates born before 32 weeks' gestation (odds ratio [OR], 32.1; 95% confidence interval [CI], 5.4–190.8; $P < .001$). No significant differences in antenatal and neo-

TABLE 1
Baseline characteristics

Characteristic	Value
Rhesus D alloimmunization, n (%)	233 (80)
Kell, n (%)	36 (12)
Rhesus c, n (%)	15 (5)
Other, n (%)	6 (2)
Gestational age at first IUT, wks[a]	26 ± 4.2 (16–35)
Number of IUTs per fetus[a]	3 ± 1.1 (1–6)
Hemoglobin at first IUT, g/dL[a]	5.5 ± 2.4 (1.1–13.2)
Hydrops, n/N (%)	75/291 (26)
Mild hydrops, n/N (%)	54/75 (72)
Severe hydrops, n/N (%)	21/75 (28)
Gestational age at birth, wks[b]	36 (35–37)
Birthweight, g[b]	2812 (2520–3159)
Neonates requiring an exchange transfusion, n (%)	168 (58)

[a] Values are given in mean ± 1 SD (range); [b] Value given in median and interquartile range.

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natal characteristics were found between the follow-up (n = 291) and lost-to-follow-up group (n = 51).

Long-term neurodevelopmental outcome

The median age at follow-up was 8.2 years (range, 2–17 years). The incidence of CP was 2.1% (6/291) (spastic quadriplegia: n = 3, spastic diplegia: n = 2, dyskinetic: n = 1). MND was recorded in 11.0% (32/291). None of the children had kernicterus. Nineteen children were evaluated using BSID-II tests, the average MDI score was 93 ± 14. A total of 89 children were tested using the WPPSI and 183 were tested using the WISC. The average full scale IQ in the WPPSI-group and WISC-group was 100 ± 14.8 and 101 ± 13.5, respectively. We found no correlation between hemoglobin level at first IUT and full scale IQ score (r = 0.1, $P = .1$) (Figure 2). Severe developmental delay (< −2 SD) was detected in 3.1% (9/291) of children. Moderate developmental delay (< −1 SD) was detected in 14.4% (42/291) of children. Bilateral deafness was present in 3 children (1.0%). None of the children had bilateral blindness. Table 2 summarizes the long-term neurodevelopmental outcome.

Overall, the incidence of NDI (CP, severe developmental delay, deafness, and/or blindness) was 4.8% (14/291). Details on the combinations of abnormal findings in the children with adverse outcome are presented in Table 3. One infant with CP (no. 14 in Table 3) had no cranial ultrasound examination in the neonatal period, but a MRI performed at 2 years of age showed signs of cerebral atrophia, suggestive for periventricular leukomalacia. One infant with severe cerebral injury detected on ultrasound and MRI (hemorrhagic periventricular leukomalacia) in the neonatal period had a favorable outcome. Another infant with extensive bacillus cereus cerebral abscess had also a favorable outcome and was previously reported.[27]

The incidence of NDI was significantly higher in children with a history of mild and severe hydrops. Mild hydrops was present in 36% (5/14) of children with NDI compared with 18% (49/277) of children without NDI (OR, 4.3; 95% CI, 1.2–15.3; $P = .025$). Severe hydrops was present in 29% (4/14) of children with NDI compared with 6% (17/277) of children without NDI (OR, 9.9; 95% CI, 2.4–40.5; $P = .001$).

The risk of NDI was significantly increased in the group of neonates born prematurely (gestational age at birth <32 weeks) (OR, 12.8; 95% CI, 2.1–79.5; $P = .006$) (Table 4), but was not increased in the group of neonates born between 32 and 35 weeks (OR, 1.8; 95% CI, 0.5–7.0; $P = .38$) and ≥35 weeks' gestation (OR, 0.4; 95% CI, 0.1–1.3; $P = .08$).

Univariate analysis of potential risk factors for NDI was performed (Table 4). Several risk factors were found to be associated with NDI, including fetal hydrops, hemoglobin level, number of IUTs, prematurity, and severe neonatal morbidity.

We found no difference between the groups with and without NDI for sex 57% (8/14 male) vs 55% (151/277 male) ($P = .85$) and ethnicity (white) 14% (2/14) vs 6% (18/277) ($P = .24$). Mean parental education was significantly lower in the NDI group compared with the no-NDI group 3.2 ± 1.1 vs 4.2 ± 1.4, respectively ($P = .016$). Post hoc analysis showed no difference in the incidence of exchange transfusion between the group with (57%, 8/14) and without NDI (58%, 160/277) ($P = .96$).

Potential risk factors and the possible confounder parental education were entered in a multivariate logistic regression model to assess the independent association with NDI (Table 4). We excluded hemoglobin at first IUT from this multivariate analysis model, as this variable is strongly associated with the presence of hydrops and could possibly bias our results. In a multivariate regression analysis, including prenatal and postnatal factors, the following risk factors were independently associated with NDI: number of performed IUTs (OR, 2.3 per IUT; 95% CI, 1.1–4.6; $P = .02$), severe neonatal morbidity (OR, 85.6; 95% CI, 9.7–755.3; $P < .001$), and parental education (OR, 8.4; 95% CI, 2.2–31.5; $P = .002$).

To determine the predictive role of prenatal risk factors, we entered the following factors in a separate multivariate regression model by using only the following prenatal factors: mild hydrops, severe hydrops, level of hemoglobin at first IUT, and number of IUTs. We found that only severe hydrops (OR, 11.2; 95% CI, 1.7–92.7; $P = .011$) was significantly independent associated with NDI.

Comment

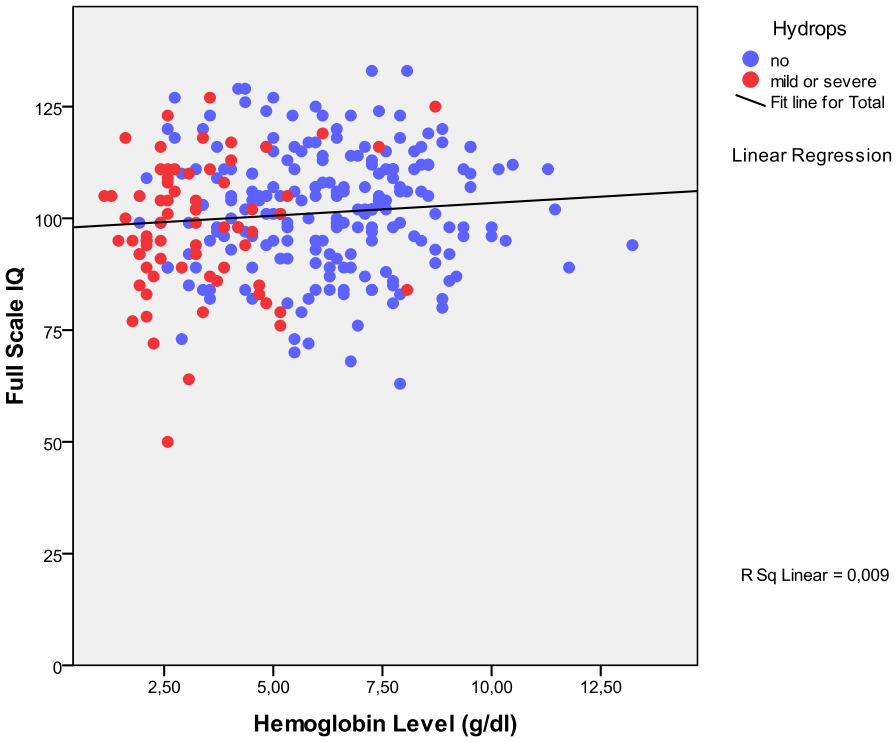
This is the largest study to date on long-term neurodevelopmental outcome in children surviving a high-risk pregnancy thanks to invasive fetal therapy. The vast majority (over 95%) of children treated with IUT for severe fetal anemia had a normal neurodevelopmental outcome. The incidence of severe developmental delay (3.1%) was in line with the Dutch normative population (2.3%).[28] In addition, the incidence of bilateral deafness in the general population was similar to what we found in our cohort.[29] However, the rate of CP (2.1%) in our study was higher compared with the general population (0.7% at 32 to 36 weeks' gestation[30] and 0.2% at 37 weeks' gestation[31]).

A few small studies on the long-term neurodevelopmental outcome in children treated with IUT have been reported.[9-16] The 2 largest studies to date reveal higher incidences of NDI when compared with our results, 10% (7/69) and 8% (3/38), respectively.[9,10] Differences in long-term outcome may be explained by methodologic differences and heterogeneity between the studies.

Apart from the reassuring results valuable for counseling pregnant women with red cell alloimmunization, the importance of our analysis lies in the identification of potentially avoidable risk factors for adverse outcome. The current study shows a clear association with long-term impairment and the presence of hydrops and number of IUTs performed. Severe fetal hydrops was already known to be associated with increased perinatal mortality.[25] The underlying mechanism causing cerebral damage and long-term NDI in hydropic and severely anemic fetuses is not yet known. Cerebral lesions may result from hypoxic injury related to severe anemia. Because short- and long-term outcome appears to be better in nonhydropic fetuses, clinicians should try to prevent or reduce the development of hydrops in fetuses at risk for fetal anemia. Interestingly, the actual hemoglobin concentration was more strongly associated with NDI than the hemoglobin z-score. This concurs with the concept that tissue oxygenation depends more closely to the number of circulating red cells than on deviation of the hemoglobin level from the mean for gestational age. Whether more timely detection and treatment of fetal anemia, and prevention of hydrops improves outcome, and what degree of anemia actually requires transfusion needs further study.

Another risk factor for NDI was severe neonatal morbidity. As shown in our results, both the incidence of severe neonatal morbidity and the incidence of NDI were associated with the severity of prematurity. Severe prematurity is a well-known risk factor for neonatal morbidity, cerebral injury, and long-term adverse outcome.[32,33] We did not find a relation between NDI

FIGURE 2
Relation between hemoglobin levels



At first IUT and full scale IQ score, in children with (*red dots*) and without (*blue dots*) fetal hydrops.

IQ, intelligence quotient; *IUT*, intrauterine blood transfusions.

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TABLE 2
Long-term neurodevelopmental outcome in 291 long-term survivors after intrauterine transfusions

Variable	
Age at follow-up, y[a]	8.2 (2-17)
Isolated severe development delay, n (%)	5 (1.7)
Isolated cerebral palsy, n (%)	2 (0.7)
Isolated bilateral deafness, n (%)	3 (1.0)
Cerebral palsy and severe developmental delay, n (%)	4 (1.4)
Neurodevelopmental impairment,[a] n (%)	14 (4.8)

[a] Neurodevelopmental impairment is defined as at least one of the following: cerebral palsy, severe development delay (< −2 SD), bilateral deafness, or blindness.

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TABLE 3
Data of 14 long-term survivors after intrauterine transfusions for fetal alloimmune anemia with neurodevelopmental impairment

Case	Hydrops	Hemoglobin, g/dL (GA at IUT-wk)	Number of IUT	GA at birth, wk	Birthweight, g	Severe neonatal morbidity	Age at follow-up, y	Bilateral deafness	Cerebral palsy	Severe developmental delay
1	none	5.3 (33)	1	35	2580	sepsis, asphyxia	8	No	diplegia	No
2	none	7.9 (26)	2	29	1460	PVL II, NEC III B	12.5	No	quadriplegia	Yes
3	mild	3.9 (28)	3	33	3100	None	10	Yes	no	No
4	mild	3.2 (24)	3	30	1700	RDS	8	Yes	no	No
5	none	5.6 (22)	4	35	3020	None	2	No	no	Yes
6	none	5.5 (24)	4	36	2750	None	8	No	no	Yes
7	severe	3.1 (26)	4	35	2526	None	15	No	no	Yes
8	severe	2.4 (26)	4	35	2835	ventricular dilatation	13.5	No	diplegia	No
9	severe	4.2 (22)	4	35	2460	ventricular dilatation	9.5	No	quadriplegia	Yes
10	mild	4.7 (26)	4	34	3200	sepsis	10	Yes	no	No
11	mild	1.5 (19)	5	37	3310	none	5	No	no	Yes
12	mild	2.6 (21)	5	34	1915	none	2	No	dyskinetic	Yes
13	none	6.8 (21)	5	38	2800	none	4.5	No	no	Yes
14	severe	1.9 (18)	5	36	3035	none	14	No	quadriplegia	Yes

GA, gestational age; *IUT*, intrauterine transfusion; *NEC*, necrotizing enterocolitis; *PVL*, periventricular leukomalacia; *RDS*, respiratory distress syndrome.

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and exchange transfusions, which we interpret as confirmation of our relatively aggressive neonatal management protocol aimed at reducing the rate of severe hyperbilirubinemia. None of the children had kernicterus.

Finally, parental education was independently associated with NDI. Socioeconomic status (SES) and parental educational level are well known determinants of child cognitive development.[28,34-37] Both factors may influence child cognitive functioning for a variety of reasons, including reduced access to essential material resources (such as cognitively stimulating materials) and/or nonmaterial resources (such as education, information, and skills). Moreover,

TABLE 4
Analysis of potential risk factors for neurodevelopmental impairment (NDI)

Variable	NDI (n = 14)	No NDI (n = 277)	*P* value univariate analysis	OR (95% CI) univariate analysis	*P* value multivariate analysis[a]	OR (95% CI) multivariate analysis[a]
Hydrops, n (%)	9 (64)	66 (24)	.002	5.8 (1.9–17.8)	.11	3.3 (0.76–14.5)
Hemoglobin at first IUT,[b] g/dL	4.2 ± 1.9	5.6 ± 2.4	.032	1.3 per g/dL decrease (1.0–1.7)	—	—
Z hemoglobin (SDs)	−8.1	−7.3	.13	1.3 per SD decrease (0.6–1.1)	—	—
Number of IUTs[c]	4 (1–5)	3 (1–6)	.018	1.7 per IUT (1.1–2.5)	.02	2.3 per IUT (1.1–4.6)
GA at birth <32 wks, n (%)	2 (14)	4 (1)	.006	12.8 (2.1–79.5)	.54	2.3 (0.17–31.1)
Perinatal asphyxia, n (%)	1 (7)	10 (4)	.51	2.0 (0.2–17.1)	.19	5.8 (0.4–81.3)
Severe neonatal morbidity,[d] n (%)	6 (43)	16 (6)	< .001	13.1 (4.0–42.4)	< .001	85.6 (9.7–755.3)

GA, gestational age; *IUT*, intrauterine transfusion; *OR*, odds ratio; *SD*, standard deviation.

[a] Including parental education as a possible confounder; [b] Value given as mean ±SD; [c] Value given as median (range); [d] Severe neonatal morbidity is defined as at least 1 of the following: respiratory distress syndrome, intraventricular hemorrhage ≥ grade 3, periventricular leukomalacia ≥ grade 2, necrotizing enterocolitis ≥ grade 2, and sepsis.

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genetic conditions may account for up to 72% of the variance in intelligence.[38]

The 2 most important limitations of our study were the relatively incomplete follow-up and the lack of a control group. We were not able to trace 9% of children, mainly because of the long time-lap since IUT treatment. In addition, 6% of families declined to participate to the study. The risk for an adverse outcome has been shown to be higher in the lost-to-follow group as children at increased risk for severe neurodevelopmental compromise may not return for evaluation.[39] Nevertheless, comparisons of antenatal and perinatal characteristics between the study group and the lost-to-follow-up showed no significant differences, suggesting that this type of bias was limited.

Conclusions

The high rate of intact survival in this high-risk group of severely anemic fetuses confirms the success of this antenatal treatment. Although hemolytic disease of the fetus/newborn was the main cause of perinatal death for many years, the chance of successful recovery with adequate antenatal management can nowadays be considered as excellent. However, several factors were associated with increased risk for NDI, including fetal hydrops, number of IUTs, and severe neonatal morbidity. Future studies to reduce the incidence of these risk factors in children treated with IUT may help decrease the rate of adverse long-term outcome. ■

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