Follow-up studies in prenatal medicine

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CHAPTER 7

Long-term outcome after fetal transfusion for hydrops associated with parvovirus B19 infection

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Abstract

Objective To evaluate neurodevelopmental status of children treated with intrauterine red blood cell and platelet transfusion for fetal hydrops caused by parvovirus B19.

Methods Maternal and neonatal records of all intrauterine transfusions for congenital parvovirus B19 infection in our center between 1997 – 2005 were reviewed. Congenital B19 virus infection was confirmed by the presence of parvovirus B19-specific IgM or parvovirus B19 DNA in fetal blood samples. All children underwent a general pediatric and neurological examination. Primary outcome measure was neurodevelopment status (developmental index by Bayley Scales of Infant Development or Snijders-Oomen test). Secondary outcome measure was general health status of surviving children.

Results A total of 25 IUT sessions were performed in 24 hydropic fetuses. Median fetal hemoglobin concentration, platelet count, and blood pH before intrauterine transfusions were 4.5 g/dL (range 2.4- 11.4 g/dL), 79 x 10^9/L (range 37-238 x 10^9/L) and 7.36 (range 7.31-7.51), respectively. Sixteen survivors aged 6 months to 8 years were included in the follow-up study. Eleven children (68%) were normal and 5 children (32%) demonstrated a delayed psychomotor development with a suboptimal neurological examination (mild delay n=3, severe delay n=2). Neurodevelopmental status did not correlate with pre-intrauterine transfusion hemoglobin, platelet, or blood pH values. Growth and general health status were normal in all. Two children had minor congenital defects.

Conclusion Neurodevelopmental status was abnormal in 5 of 16 survivors and was not related to the severity of fetal anemia and acidemia. We hypothesize that fetal parvovirus B19 infection may induce central nervous system damage.

Introduction

The incidence of parvovirus B19 (B19V) infection among seronegative pregnant women is around 2.4%.[1] Vertical transmission occurs in 33-51% of cases of maternal infection.[2,3] Fetal infection is fatal in 9% of the cases.[4] Fetal death occurs in more than half of the B19V cases with severe fetal anemia and hydrops.[3,5-11] Management of B19V infection with intrauterine red blood cell and platelet transfusions significantly reduces the mortality and morbidity of B19V infection.[12-16] However, severe fetal anemia or a prolonged hydropic state may also lead to delayed neurodevelopment in surviving children.[17,18] B19V has also been associated with cases of prenatal stroke, leading to significant neurodevelopmental delay in surviving patients.[19-21]

Few data are available concerning long-term neurodevelopmental outcome of patients surviving hydrops treated with intrauterine transfusions. Four groups studied the outcome in survivors of severe anemia due to red cell alloimmunization treated with intrauterine transfusions. The percentage of children with disabilities ranged from 4.5% to 10.5%.[14,15,22,23] However, fetal hemolytic disease may not be fully compared to B19V-induced fetal hydrops.

Dembinski *et al.* reported normal neurodevelopmental outcome in 20 survivors after B19V-induced fetal hydrops treated with intrauterine transfusions.[24] However, 11 other children in their series were lost to follow-up. Three children who received intrauterine transfusions for B19V described in two reports also had normal developmental outcome.[8,10]

The main objective of our study was to evaluate the neurodevelopmental status of children who survived fetal hydrops caused by B19V and treated with intrauterine transfusions. Primary outcome measure was the neurodevelopmental status of surviving children. We also studied the correlation between neurodevelopmental outcome and the severity of fetal anemia, thrombocytopenia and acidemia. Secondary outcome measure was the general health status of surviving children.

Methods

The Department of Obstetrics of the Leiden University Medical Center is the national referral center for intravascular fetal transfusion in the Netherlands. We searched our database for all intrauterine transfusions performed between December 1997 and December 2005 for cases of fetal hydrops and B19V infection. Fetal hydrops was defined as excess fluid in two or more cavities of the fetal body. Diagnosis was confirmed by the presence of B19V-specific IgM or B19V DNA in fetal blood samples. Fetal blood samples were assessed for hemoglobin

concentration (g/dL), platelet counts (x 10^9/L) and pH before and after intrauterine red blood cell and platelet transfusion. In all cases, blood samples were drawn to exclude chromosomal abnormalities. The amount of transfused blood necessary to correct for fetal anemia was calculated on the basis of the initial hematocrit and the estimated fetal weight according to the protocol by Rodeck *et al.*.[20] Results are depicted as percentages of the estimated fetal blood volume (120 mL/kg estimated fetal weight) in **Table 1.**

Table 1. Maternal, fetal and neonatal characteristics of the study population.

	Normal development at investigation (n=11)	Abnormal development at investigation (n=5)
Maternal age at intrauterine transfusions (y)	28 (19-36)	28 (24-32)
Gravidity	3 (1-4)	2 (1-3)
Parity	2 (0-3)	1 (0-2)
Maternal symptoms		
Fever	3	1
Skin rash	2	1
Arthralgia	3	4
Fetal movements		
Normal	3	2
Reduced	8	3
Gestational age at infection (wk)	17 (14–25)	14 (10-23)
Gestational age at intrauterine transfusions (wk)	22 (20–27)	20 (18-28)
Hemoglobin before intrauterine transfusions (g/dL)	5.4 (2.4-11.0)	4.4 (2.4-4.9)
Hemoglobin after intrauterine transfusions (g/dL)	12 (9.7–13.9)	11.8 (9.7-18.7)
pH before intrauterine transfusion	7.3 (7.3-7.4)	7.4 (7.3-7.5)
pH after intrauterine transfusion	7.3 (7.2-7.4)	7.3 (7.2-7.4)
Platelets before intrauterine transfusion (x 10^9)	54 (37-238)	102 (79-137)
Transfused volume of fetal blood volume (%)	27 (6 - 42)	20 (17-87)
Birth weight (g)	3145 (2145-4160)	3170 (2890-3340)
Gestational age at birth (wk)	39 (32 - 41)	40 (37-41)
Current age (y)	4 (0.5 - 8.0)	4 (0.4-8.0)
Intelligence quotient scores	104 (86-132)	76 (26-84)

Data are presented as median (range) or n.

The Institutional Review Board of the Leiden University Medical Center approved the follow-up study and all parents gave written informed consent for their children. A trained examiner assessed neurodevelopmental outcome using tests validated for each age category. The Bayley Scales of Infant Development (Second Edition-Dutch version :BSID-II-NL) was used for infants 1 to 42 months of age.[25,26] It is made up of three separate scales (mental scale, motor scale, and behavioral rating). Mental and motor scale scores are converted to a mental developmental index and a psychomotor developmental index with a mean of 100 and a standard deviation (SD) of 15. Normal limits are defined as mental developmental index and psychomotor developmental index values between 85 and 114. A score of 70-84 indicates a mild and a score <70 a severe delay. For children at 2.5 to 7 years of age, the revised Snijders-Oomen Non-Verbal Intelligence Test–Revised (2.5-7) was used.[27] This test consists of six basic subtests (Categories, Mosaic, Puzzles, Patterns, Situations and Analogies). Scores are calculated as performance scale and reasoning scale. Raw subtest scores are standardized with population and age-specific scores with a mean value of 100 and a SD of 15. The Snijders-Oomen Non-Verbal Intelligence Test-Revised has been validated for Dutch and Belgian children.

Data on parental ethnicity, education and socio-economic status were recorded. A pediatrician performed a standardized general examination, including weight, height and head circumference to evaluate growth using age-specific percentiles, and a standardized neurological examination.[28,29] A recent medical history was taken from the parents or caretakers.

Statistical analysis was performed by SPSS statistics (version 12 SPSS inc., Chicago, Illinois, USA). A P-value of < .05 was considered to indicate statistical significance. Results are depicted as median value and range. The correlation between neurodevelopmental status and fetal hemoglobin values, blood pH, and platelet counts was explored using separate linear regression analyses.

Results

We retrospectively evaluated the occurrence of maternal symptoms of B19V infection in the 16 mothers of children tested at 0.5 to 8 years of age. Symptoms occurred at a median gestation of 17 weeks (range 10- 25 weeks). In one case the timing of symptoms could not be determined. All women experienced general malaise, 4 (25%) had fever for 2-3 days, 7 (43%) noted generalized arthralgia, and 3 (18%) had a skin rash. Three women (18%) reported two or more symptoms. Seven women (43%) experienced no symptoms at all and were referred because of a suspected B19V contact during pregnancy.

Fourteen women became infected through contact with children who had fifth disease, either their own children or children at school or a daycare center.

In two cases, the source of infection could not be identified. Eleven women (68%) reported reduced fetal movements during clinical infection. Treatment by intrauterine transfusions invariably resulted in an immediate and persistent increase of fetal movements.

During the study period, 690 intrauterine transfusion procedures were performed at our center. Twenty-five intrauterine transfusion procedures (3.5%) were performed in 24 fetuses to correct B19V-induced hydrops and anemia. One fetus received two intrauterine transfusions. One fetus died during the intrauterine transfusion session, six died in utero after intrauterine transfusion sessions, and one infant died at birth (mortality rate: 33%). Sixteen of the 24 fetuses survived and all children were available for investigation at follow-up.

Maternal, fetal, and neonatal characteristics are depicted in **Table 1**. In two cases, hemoglobin concentrations after intrauterine transfusion could not be determined due to needle displacement. Fetal blood pH measurements were obtained in 12 cases. All available blood pH values were within the normal range before and after intrauterine transfusions.

One infant was born at 32 weeks of gestation by spontaneous preterm delivery. There were no signs of acute intrauterine infection and antenatal fetal heart rate monitoring was normal. He was ventilated for respiratory distress syndrome and recovered clinically with normal development at follow-up. All other infants were delivered at 37 or more weeks of gestation. One infant was small for gestational age with a birthweight of 2,340 grams at 37 weeks of gestation, the other infants had a normal birthweight. Fifteen infants had a 5-minute Apgar score higher than 7. One infant had a 5-minute Apgar score of 4, but neurodevelopment was normal at follow-up.

Physical examination demonstrated a cardiac murmur in one child with a clinically insignificant mitral valve insufficiency and a corrected hypospadia in another child. No other signs of dysmorphology were detected in these children. All other children were normal on examination. Weight, length, and head circumference were all within normal limits for age.

Tests for neurodevelopment were performed in the outpatient clinic (n=13). One child was tested in the home situation because of inability to travel. Two children had recently been evaluated extensively elsewhere because of possible neurodevelopmental delay. Parents consented to retrieval of all clinical data, but declined visiting our clinic for repeat investigation.

Seven children were tested with the Snijders-Oomen Non-Verbal Intelligence Test–Revised and nine with the BSID-II-NL test. Snijders-Oomen Non-Verbal Intelligence Test–Revised IQ scores and BSID-II-NL mental scores were within the normal range in 11 children (68%). These children all had a normal neurological examination. The medical history of one child suggested a delayed motor development, but neurological examination and developmental testing revealed

no abnormalities. He was later diagnosed with the Buschke-Ollendorff syndrome, an autosomal dominant disease consisting of osteopoikilosis and disseminated connective tissue nevi of elastic type, not associated with congenital B19 infection.

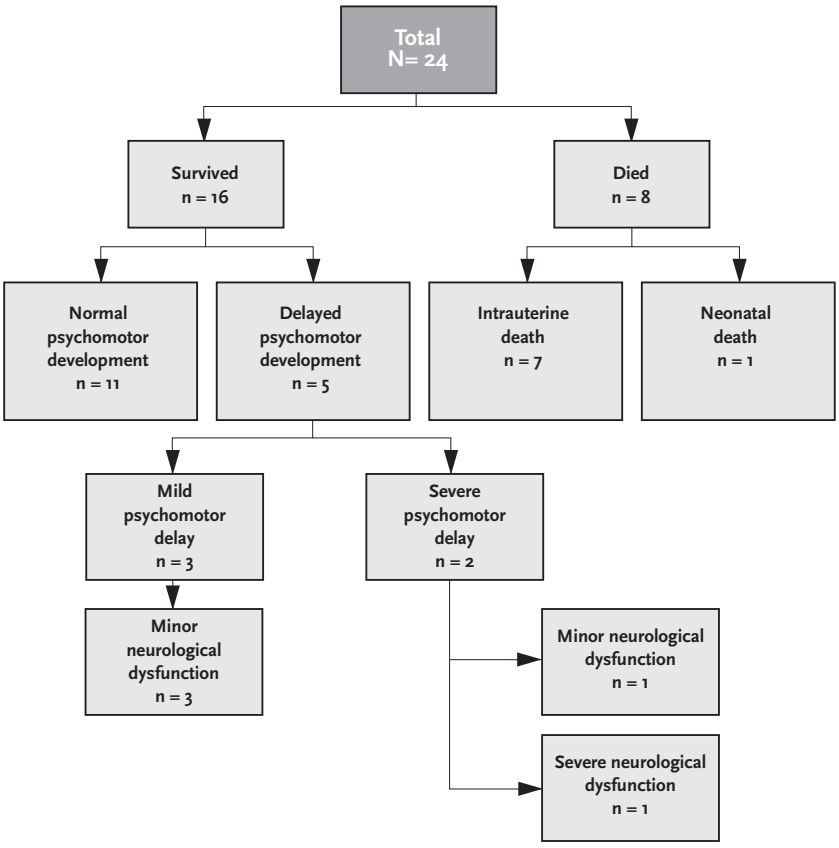
Table 2. Details of the 5 children with mild to severe neurodevelopmental delay.

Child	Current Age (y)	Sex	Gestational Age at Intrauterine Transfusion (wk)	Pre-Intrauterine Transfusion Hemoglobin (g/dL)	Pre-Intrauterine Transfusion Platelets (x 10^9/L)	Pre-Intrauterine Transfusion pH	Transfused Volume of Fetal Blood Volume (%)	Gestational Age at birth (wk)	Birth Weight (g)	DQ/IQ score (95% Confidence Interval)
1	1.5	Female	18	4.0	128	7.41	19	41	3,155	PDI:84 (87-97)
2	3.2	Male	20	5.0	87	7.35	17	40	3,175	MDI:76 (75-87)
3	7	Male	22	8.3	76	7.36	6	37	2,340	IQ:80 (107-117)
4	0.5	Female	23	4.5	79	7.51	24	40	3,170	MDI:55 (55-78)
5	7.5	Male	28	5.0	137	7.32	87	37	3,340	IQ:26 (107-117)

DQ: developmental quotient; IQ: intelligence quotient; MDI: mental developmental index; PDI: psychomotor developmental index.

Five children (32 %) had a developmental score indicating delay. Three children had a mild delay (children 1-3 in **Table 2**). Two children had a severe developmental delay (children 4 and 5 in **Table 2**). All five children demonstrated signs of a neurological deficit on examination. One child had marked hypotonia of the lower extremities, two children experienced delayed development of fine motor coordination, and one child suffered from marked hypertonia and hyperreflexia of the upper extremities suspect of developing diplegia. One of the two children with severe developmental delay (child 5) had strabismus convergens, ataxia and generalized hypotonia. Additional laboratory and metabolic investigations were unremarkable, but a cerebral magnetic resonance imagining (MRI) scan demonstrated atrophy of the cerebellar vermis.

Figure 1. Psychomotor and neurological outcome in the study group.



Neurodevelopmental outcome data are depicted in **Figure 1**, details are presented in **Table 2**. Using repeated linear regression analysis, no statistically significant correlations were found between neurodevelopmental status and fetal pre-intrauterine transfusion hemoglobin levels (r 0.059; 95% confidence interval [CI] -8.0 to +9.8, P=.834), intrauterine pH (per 0.1 unit: r 0.209; 95% CI -47.5 to +26.5; P=.537), or pre-intrauterine transfusion platelet counts (r 0.184; 95% CI -0.450 to +0.082; P=.159).

Discussion

The objective of this study was to evaluate long-term neurodevelopmental outcome and general health status of children who experienced fetal hydrops due to

intrauterine B19V infection. All children had been treated by intrauterine transfusions. Neurodevelopmental status was abnormal in one-third of the survivors of B19V infection. This is in contrast to the findings of the only other published large series of long-term follow-up in these patients. Dembinski and colleagues reported a good clinical outcome after intrauterine transfusions for B19V-induced hydrops.[24] However, they had a high loss to follow-up as only 20 out of 31 children (65%) were seen for testing. We agree with Wolke *et al.* that the chances for adverse outcome are generally much higher in the group that is initially lost to follow-up.[30] Miller *et al.* described long-term outcome after parvovirus B19 infection in 427 pregnancies with 367 surviving infants, of whom 129 were followed up at 7- 10 years of age by sending questionnaires to obstetricians and general practitioners.[8] Only seven fetuses in this series developed fetal hydrops, and only 3 of them survived, of whom 2 underwent an intrauterine transfusion. These 2 survivors had a good neurodevelopmental outcome. Rodis *et al.* investigated 108 children with congenital B19V infection and 97 controls at a median age of 4 years.[10] Significant delays in motor, speech, or language development or significant attention deficits requiring special education were observed in 7.4% of the children in the study group versus 7.2% in the controls, cerebral palsy was detected in one patient of the study group.[10] However, this study included only one hydropic fetus and outcome was assessed by sending a questionnaire to the caretakers.[10] We consider it a strength of our study that all children were individually investigated and tested for neurodevelopmental status.

Our findings on the association of B19V with congenital anomalies are similar to those of previous reports. Miller *et al.* described a case of ventricular septum defect and an earlier cohort study reported hypospadias.[8,4] We detected a case of mitral valve insufficiency and a case of hypospadias. Although some case reports suggest a possible teratogenic effect of B19V, a clear association of maternal B19V infection with congenital defects has not been proven.[31-33] This is further supported by normal growth and general health status in our study population. Dembinski *et al.* reported a higher incidence of preterm births (9 out of 20 children) compared to our report (1 of 16 births) and an average number of 4 intrauterine transfusions.[24] In contrast, all fetuses in our study received one intrauterine transfusion, except for one who received 2 intrauterine transfusions. The higher frequency of intrauterine transfusions in the group of Dembinski *et al.* may explain the increase in the number of preterm deliveries.[24] Average duration of gestation and hemoglobin levels at intrauterine transfusion were similar in both reports. We did not find any correlation between fetal hemoglobin levels, fetal blood pH, or pre-intrauterine transfusion platelet counts and neurodevelopmental status, but this may be due the limited sample size. The wide confidence intervals in the regression analyses confirm that the small number of study subjects is a limiting factor in this study.

One of our patients with a severe developmental delay had an abnormal MRI scan with atrophy of the cerebellar vermis. This is an interesting finding as two experimental studies on fetal B19V infection report cerebellar hypoplasia and ataxia as principal adverse outcomes.[34,35] Clinical studies have confirmed the presence of cerebellar lesions on MRI scans after congenital B19V infection and support the possibility of prenatal stroke in these infants.[19,36,37] We were not able to perform imaging studies in the other children as this was beyond the scope of this study. Future investigations should focus on the possibility of central nervous system damage after congenital B19V infection, especially in the presence of clinical symptoms or developmental delay.

Conclusion

Severe fetal hydrops may be prevented by timely referral and treatment of B19V infection during gestation. Because neurodevelopmental outcome is not clearly related to the severity of fetal anemia and acidemia, we speculate that fetal B19V infection may induce central nervous system damage.

Acknowledgements

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