PART II

INTRAUTERINE TRANSFUSION IN FETAL ANEMIA

Chapter 1

Long-term neurodevelopmental outcome after intrauterine transfusion for fetal anemia: A systematic review

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Abstract

The long-term neurodevelopmental outcome of children born after intrauterine blood transfusion (IUT) for red cell alloimmunization is considered favorable. Severe hydrops has been identified as a strong predictor for neurodevelopmental impairment. However, the long-term outcome of survivors of IUT for congenital Parvovirus B19 infection and fetomaternal hemorrhage is not well known. Limitations of the follow-up studies to date are small sample size, lack of controls, unclear criteria for impairment and lack of standardized developmental tests. Future research should take in to account more subtle impairments, since cognitive functioning < - 1 SD, behavioral and learning problems already have a significant impact on care requirements and future socio-economic potential. A better understanding of the effect of IUT and fetal anemia on child development over time will allow more accurate parental counseling and targeted interventions to optimize child development when needed.

Background

Fetal anemia can have either an immune or non-immune cause. Maternal red blood cell alloimmunization is the most common cause of immune fetal anemia. Alloimmunization results from prior contact with an antigen, for which mother and fetus are incompatible, either through fetomaternal transfusion or prior blood transfusion.[1] This triggers the formation of immunoglobulin G antibodies that are able to cross the placenta into the fetal blood circulation, causing hemolysis.

Non-immune fetal anemia has many causes including congenital Parvovirus B19 infection and fetomaternal hemorrhage (FMH). Fetal anemia due to congenital Parvovirus B19 infection results from crossing of the placental barrier of the virus and inhibition of fetal erythropoiesis by infection of erythroid precursor cells.[2] Fetal anemia in FMH results from the passage of (acute or chronic) fetal blood into the maternal circulation, due to placental abnormalities, maternal trauma or invasive obstetrical procedures.[3;4]

When untreated, fetal anemia may result in cardiac failure, hydrops, hypovolemic shock, fetal or neonatal death, neurologic injury or cerebral palsy (CP).[1;3] The mainstay to correct fetal anemia is intrauterine intravascular blood transfusion (IUT). IUT can be considered a safe procedure with a relatively low procedure-related complication rate and a low perinatal loss rate.[5] Perinatal survival rates after IUT nowadays exceed 90%.[5;6] Although advances in techniques allow even moribund and severely anemic fetus to survive, severe anemia or a prolonged hydropic state may lead to neurodevelopmental impairment (NDI).[7;8] Hence, the outcome of antenatal management must be assessed not only by survival but also by long-term neurodevelopmental outcome.[9]

We performed a systematic review of the literature on the long-term neurodevelopmental outcome in children treated with IUT for fetal anemia, secondary to maternal alloimmunization, Parvovirus B19 infection and FMH. The prevalence and nature of favorable and adverse neurodevelopmental outcome in light of methodological strengths and weaknesses of studies will be highlighted. In addition, risk factors for NDI are discussed. The aim of the review was to identify important areas for future research.

Methods of the Review

A systematic literature search was utilized to retrieve the studies and articles for this review. An electronic MEDLINE literature search was performed using the following mesh terms: Fetal Erythroblastosis, Intrauterine, Time, Prognosis, Epidemiologic Studies, Human Development, Neurobehavioral Manifestations and Morbidity. The computer aided search was limited to English, French, Dutch and German language

articles and included the period from 1981 to January 2011, since intrauterine intravascular transfusions are performed since 1981. All reference lists of primary articles and reviews were examined to search for additional references. Then, a manual search of identified articles was conducted. If needed, authors were contacted for further information. The following inclusion criteria were applied: children treated with intrauterine intravascular transfusion for fetal anemia secondary to maternal alloimmunization, congenital Parvovirus B19 infection or fetomaternal hemorrhage, assessment of neurodevelopmental outcome and the conduct of statistical tests. The methodological quality of each selected study was assessed independently by two reviewers (JK and EL). The following exclusion criteria were applied: case reports, dissertations, qualitative studies, book chapters, guidelines and commentaries.

Results

We found no other review article or meta-analysis focusing solely on the long-term neurodevelopmental outcome in children treated with IUT for anemia due to maternal red cell alloimmunization, congenital Parvovirus B19 infection and FMH. In over 30 years, we identified only 11 studies that met our inclusion criteria (9 on maternal alloimmunization and 2 on congenital Parvovirus B19 infection). Beyond case reports, research on long-term neurodevelopmental outcome following FMH is limited to 3 small series (31, 26 and 15 children).[10;11] Since no IUTs were performed to correct anemia, these series were not included for review. Our selected studies are summarized, in chronological order, in Tables 1 (red cell alloimmunization) and 2 (Parvo B 19 infection).

Table 1 Long-term neurodevelopmental outcome in children treated with IUT for maternal red cell alloimmunization.

Author, year	Outcome measure	CP	NDI	Methodological comments
Doyle, 1993[12]	Bayley Scales	2.6% (1/38)	7.9% (3/38)	Controls not contemporaneous, transfusion group better SES
Stewart, 1994[9]	Cattel Test	no (0/8)	no (0/8)	Insufficient information on patients and methods, insufficient power
Janssens, 1997[13]	Van Wieghen, POPS, Gesell Schedules, Denver Screening Test	4% (3/69)	10.1% (7/69)	Wide age range of the children
Hudon, 1998[14]	Gesell Schedules, McCarthy Scales	4.5% (1/22)	n.a.	No controls, high lost to follow-up rate, no formal criteria NDI, insufficient power
Grab, 1999[15]	School Performance	no (0/35)	n.a	No controls, no neurodevelopmental tests
Farrant, 2001[16]	Neurodevelopmental questionnaire	3.3% (1/30)	n.a	No controls, insufficient information patients and methods, no neurodevelopmental tests
Harper, 2006[17]	Differential Ability Scales, Wide Range Assessment, Gordon Diagnostic System	6.2% (1/16)	12.5% (2/16)	Insufficient power
Weisz, 2009[18]	Neurodevelopmental questionnaire	no (0/40)	n.a	No controls, no neurodevelopmental tests, no formal criteria NDI
Lindenburg, 2011[19]	Touwen, Bayley Scales, Wechsler Scales	2.1% (6/291)	4.8% (14/291)	No controls, wide age range of the children
Total		**2.4% (13/549)**	**4.9% (27/549)**	

Table 2 Long-term neurodevelopmental outcome in children treated with IUT for parvovirus B19 infection.

Author, year	Outcome measure	CP	NDI	Methodological comments
Dembinski, 2002[20]	Griffiths Test, Snijders Oomen Intelligence Test, Kaufman Battery	no (0/20)	no (0/20)	No controls, high lost to follow up rate
Nagel, 2007[8]	Bayley Scales, Snijders Oomen Intelligence Test	6.25% (1/16)	12.5% (2/16)	No controls, insufficient power
Total		**2.7% (1/36)**	**5.5% (2/36)**	

CP is Cerebral Palsy; NDI is Neuro Developmental Impairment which is defined as CP, cognitive functioning or developmental delay (< 2SD), blindness or deafness; n.a. is not available; POPS is Project on Preterm and Small for Gestational Age Infants in the Netherlands 1983.

Methodological Issues

The overall quality of the 11 selected studies is suboptimal. All studies concern small single center follow-up studies, including between 8 and 69 children, except for a recent study including 291 children for follow-up.[19] Only 4 studies included controls, to validate their outcome against healthy children, children with similar neonatal problems, or children diagnosed with fetal anemia who did not receive IUTs. Both interval and timing of follow-up range considerably between studies that is, from 1984-1990 to 1988-2008 and the children are tested as young as one month old to 16 years of age. All studies are cross sectional in design and, therefore, do not allow for observation of development over time. In 3 follow-up studies the children were not individually investigated with formal psychological testing. Criteria for NDI were not consequently described and neither was the way impairment was 'measured'. In general, the outcome measures were able to identify major neurological deficits, but the more subtle abnormalities like behavioral problems or learning difficulties, which have a significant impact on care requirements, were likely overlooked.[21] Abovementioned methodological issues and heterogeneity make the selected studies difficult to compare and, as a consequence, knowledge on the neurodevelopmental outcome of these children remains limited. Knowledge on the long-term development of children after IUT over time is however necessary. The main findings of each follow-up study are listed below, in chronological order.

Neurodevelopmental Outcome after Maternal Red Cell Alloimmunization

The first report on long-term neurodevelopment was published in 1993 by Doyle et al.[12] With formal psychological testing and clearly described criteria for NDI, Doyle found no impairment at 2 years of age in 92% (3/38) of children transfused in utero. The transfusion group compared favorably with both high risk survivors of very low birth weight (VLBW) and low risk children of normal birth weight. However, the low risk group was not contemporaneous with the transfusion group.

With little information on their patients and methods, Stewart et al. reported no difference in neurodevelopment at 18-24 months between 8 children with Rhesus disease treated with IUT and 8 children with Rhesus disease not treated with IUT.[9] Neither group was different in terms of neurodevelopmental outcome from the general population. Such a small sample size evidently lacks statistical power to find differences. Furthermore, age range of follow up was 18-24 months, which is often too early for accurate assessment of CP or severe developmental delay.

Janssens et al. found normal neurodevelopment in 89.9% (62/69) of children after IUT (range 6 months to 6 years of age).[13] With well-defined criteria for NDI, the 69 children compared favorably with children of very low birth weight and/or small for gestational

age, 10.1% versus 18% respectively. In contrast to the findings by Doyle et al.[12], the transfusion group compared less favorably with healthy controls, 10.1% versus 6% respectively. Unfortunately, no p-values were reported. The discrepancy between Doyle et al. and Janssens et al. is probably to the much larger sample size in the latter.

Hudon et al. reported neurodevelopmental scores within average at 9-62 months in 33 children, with no differences in children with or without a history of hydrops ($P = .72$).[14] One child presented with CP (1/22) and one child with bilateral deafness (1/21). One of the major limitations of this study was the relatively large loss-to follow-up (82.5%, 33/40). This may have biased results, as chances for adverse outcome are generally higher in the group that is initially lost to follow up.[22]

Grab et al. found no moderate or severe neurologic impairment at 6 years of age in 35 children, including 7 cases with fetal hydrops at initial transfusion.[15] Fetuses with hydrops at initial transfusion tended to have a higher perinatal mortality and had a significant higher rate of preterm delivery ($P = .03$). At follow-up, survivors were not individually investigated nor tested for neurodevelopment. Conclusions were solely based on questionnaires that were completed by the child's primary care providers, a method known for underreporting of affected children.[17]

Farrant et al. performed a follow-up study in 36 children treated with IUT.[16] One child was born prematurely following death of a co-twin from twin-twin-transfusion syndrome and had CP and developmental delay, with an abnormal cranial ultrasound. Although 2 other children had an abnormal cranial ultrasound, no other child had neurodevelopmental impairment. Again, no child was individually investigated and tested for neurodevelopment. Of note, little information on the patients and methods was reported e.g., the age of assessment of the children was not recorded.

In 16 children with a history of hydrops, Harper et al. reported major neurological morbidity in 12.5% (2/16) of children.[17] The neuropsychological assessment represented a balance of tasks to identify general and, even, subtle neuropsychological deficits. Except for a measure of attention, neurologic and neuropsychological outcome was similar to their unaffected siblings. According to the authors the significant difference was not verified by clinical and classroom behavioral observations that were required for confirmation of the diagnosis of attention deficit hyperactivity disorder. Six of the sixteen survivors (37.5%) had a minor physical or neurologic finding. However, like previous studies, this study was underpowered.

Weisz et al. concluded that 85% of 40 children treated with IUT for fetal anemia reached satisfactory motor milestones according to age.[18] Abnormal motor development by the age of 1 year was observed in 15% (6/40) and abnormal cognitive development in children aged ≥ 1 year in 13.5% (5/37), with no differences in children with a history of mild, moderate or severe anemia. However, the authors did not specify what they

considered 'abnormal' and, like Grab[15] and Farrant[16], obtained their data not from the children individually with formal psychological testing but from their parents using a computerized questionnaire.
Recently, Lindenburg et al. performed a large long-term follow up study of 291 children treated with IUT secondary to maternal alloimmunization between 1992 and 2008.[19] The primary objective was to assess the incidence of NDI, a composite outcome defined as the presence of at least one of the following: abnormal neurological outcome (CP), cognitive developmental test score < -2 SD, bilateral blindness or bilateral deafness requiring amplification. All children were tested at a median age of 8.2 years. Severe developmental delay was detected in 3.1% (9/291) of children, with a 4.8% incidence of NDI (14/291). Despite the notable large sample size, it concerns a single centre study with a considerable large follow-up interval. Moderate developmental delay (< -1 SD) was detected in 14.4% (42/291) of children.
Overall, when the results of the above mentioned follow-up studies are pooled together, the rate of CP and NDI is 2.4% (13/549) and 4.9% (27/549), respectively.

Neurodevelopmental Outcome after Parvovirus B19 infection
Dembinski et al. found neurodevelopmental scores within 2 SD of a normal population in 20 children at 13 months to 9 years of age transfused for Parvovirus B19 induced anemia and fetal hydrops.[20] Although children with neurodevelopmental scores of < -1 SD fall within 2 SD of a normal population, these children are at risk for difficulties in school functioning. Nevertheless, the number and characteristics of these children were not further addressed. As only 20 out of 31 children (65%) were seen for testing, the study was limited by a high loss to follow-up rate.[5]
Nagel and colleagues described 16 survivors at a median age of 4 years of which 5 children (32%) demonstrated neurodevelopmental delay on formal psychological tests (mild delay n=3, severe delay n=2).[8] Two children had minor congenital defects. Five children were <18 months at the time of testing and thus too young for reliable assessment. In this study, adverse outcome was not related to severity of anemia and acidemia, and the authors suggest congenital Parvovirus B19 infection itself might cause CNS damage.[5] This hypothesis needs further study. Once more, low statistical power was the main limitation of this study.
Overall, when the results of the 2 follow-up studies are pooled together, the rate of CP and NDI is 2.7 (1/36) and 5.5% (2/36), respectively.

Risk Factors for Neurodevelopmental Impairment
Lindenburg et al. showed severe hydrops to be a strong pre-operative predictor of NDI[19], while the majority of studies could not confirm such a relationship.[12-15] Other risk factors concerned the number of IUTs received, severe neonatal morbidity and parental

education[19], again in contrast to the majority of studies.[8;12-15;20] According to Janssens et al. the probability that neurologic abnormalities would occur was significantly greater when perinatal asphyxia had been present ($P < 0.05$) and with a lower cord hemoglobin level at birth ($P = .03$).[13] The discrepancy in outcome is due to the considerable difference in sample size between the studies. Sample sizes were often too small to detect a significant effect of risk factors on the outcome measures.
On the whole, risk factors were not clearly defined or registered in all studies and were recorded at different points in time, which make comparison difficult. Furthermore, the risk factors were studied in light of not so subtle outcome measures e.g., CP and cognitive functioning < -2 SD. Risk factors for an adverse outcome might become more apparent with more sensitive outcome measures such as cognitive functioning < -1 SD, which already has a large impact on care and educational requirements of children.

Discussion

Despite the use of intrauterine transfusion for fetal anemia for 3 decades, knowledge on the long-term neurodevelopment of children treated with IUT is limited. The long-term neurodevelopmental outcome of children born after IUT for red cell alloimmunization is considered to be favorable. Severe hydrops has been identified as a strong predictor for NDI. However, the long-term outcome of survivors of IUT for congenital Parvovirus B19 infection and fetomaternal hemorrhage is not well known.
Few follow-up studies have been performed, commonly with sample sizes lacking the power to detect adverse neurological outcome. Since follow-up studies are restricted by the relative rarity of the disease and treatment, multicenter efforts are of utmost importance to increase sample size. However, with a large enough sample size any effect can be found statistically significant. Therefore, an equal emphasis should be placed on the clinical relevance of outcome: whether or not a child perceives impairment at an individual level and when to intervene as a clinician according to that individual perception.
In order to facilitate communication, replication and collaboration between research groups it is necessary to be transparent, specific and uniform with respect to study design and outcome. Uniform ante-, peri- and neonatal characteristics should be recorded, at fixed time points. Imaging of the brain of the fetus as well as the neonate and child should be performed. It is important to continuously assess neurodevelopment of the children, at fixed points in time, with formal psychological testing and standardized measures of well documented psychometric quality, for instance at 4 years, 8 years, 12 years and at 16 years of age. Table 3 represents a proposition for future research.

Table 3 A proposition for future research: Assessment according to age in years.

Fetus	Neonate	2	5	8	10	12	14	16 years
Brain development: cerebral imaging								
		Senses: hearing test, vision test **Cognitive functioning**: Bayley scales/ Ages and Stages Questionnaire, Wechsler scales						
			Physical functioning: Touwen Neurological Examination, CP (Gross Motor Function Classification System) **School functioning**: special education, number of grades below age-appropriate level					
				Neuropsychological functioning: learning, language, executive functioning, attention, visual spatial abilities, memory, fine motor development **Psychosocial functioning and behavior**: internalizing and externalizing behavior, Quality of Life, Achenbach System, Vineland Adaptive Behavioral Scales **Developmental problems**: Attention deficit, hyperactivity, autism spectrum			

CP is Cerebral Palsy.

Wechsler scales are reliable and valid measures of cognitive functioning in (young) children.[23;24] Beyond a full scale intelligence quotient, one can take into account the abilities that make up a full scale score, such as verbal skills, visual spatial skills and processing speed. For example, a certain child has an average full scale IQ score of 91, with a high-average verbal IQ score of 109, but a performance IQ score of 75. If we just look at the average full scale score, the child's difficulties with visual spatial tasks will be overlooked. The child will not be scored as 'impaired' in the research to date, but in practice the child will encounter considerable difficulties at school or in daily life which are not recognized with the current criteria for an adverse outcome.

To enable valid comparisons between follow-up studies, uniform criteria for an adverse outcome are indispensable. However, the outcome measures to date are not able to identify subtle abnormalities and should therefore be supplemented with a more sensitive definition of impairment: cognitive functioning test score < -1 SD, the presence of a learning problem, mild or moderate motor problems, symptoms of pervasive developmental disorder, attention deficit and/ or behavioral problems. These 'subtle abnormalities' already have a significant impact on care and educational requirements and affect the future socioeconomic potential of a child.[21] Since subtle abnormalities might also include increased behavior or social emotional problems, questionnaires that cover psychosocial and behavioral functioning should be included to obtain a full image of the child at different ages and stages. Up till now, these measures are lacking in the long-term follow-up of children treated with IUT for fetal anemia.

A better understanding of the impact of IUT on child development over time, based on standardized outcome measures, will allow more accurate counseling of parents and targeted interventions to optimize development in these children when needed.

Key Guidelines:

- Long-term neurodevelopmental outcome after IUT for maternal red cell alloimmunization is considered favorable.
- Severe hydrops is a risk factor for an adverse outcome after IUT for maternal red cell alloimmunization, as well as neonatal morbidity, the number of IUTs received and parental education.
- Neurodevelopmental outcome after IUT in congenital Parvo B19 infection and FMT is not well known.

Research Directions:

- Long-term follow-up studies after IUT in congenital Parvo B19 infection and FMT are urgently needed.
- To enable valid comparisons between follow-up studies, uniform and well described criteria for an adverse outcome are indispensable.
- Future research should take in to account more subtle abnormalities, since cognitive functioning < -1SD, behavioral problems and learning difficulties already have a significant impact on care requirements and the child's future socio-economic potential.

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