Fetal and neonatal alloimmune thrombocytopenia : towards implementation of screening in pregnancy

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CHAPTER 10

LONG-TERM OUTCOME IN CHILDREN BORN WITH INTRACRANIAL HEMORRHAGE DUE TO FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA; OBSERVATIONAL COHORT STUDY

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The Journal of Pediatrics 2017 submitted

ABSTRACT

Objective

To evaluate the long-term outcome in children with intracranial hemorrhage due to fetal and neonatal alloimmune thrombocytopenia (FNAIT).

Study design

All pregnancies with a fetus with intracranial hemorrhage caused by FNAIT between 1993 and 2015 were included in this observational cohort study. Neurological, motor and cognitive development was assessed at a minimum of one year of age. Primary outcome were perinatal death or severe neurodevelopmental impairment (NDI). Severe NDI was defined as any of the following: severe cerebral palsy (Gross Motor Function Classification System ≥ 2), bilateral deafness, blindness, severe motor and/or cognitive development delay (<-2 standard deviation). Moderate NDI was defined as cerebral palsy with gross motor function classification system <2, motor and/or moderate cognitive developmental delay (< -1 standard deviation).

Results

Eighteen pregnancies with a fetus with intracranial hemorrhage due to FNAIT were included in the study. Fetal or neonatal mortality rate was 8/18 (44%). Severe NDI and moderate NDI were diagnosed in 6/10 (60%) and 1/10 (10%) of the surviving children. Only 4/18 (22%) of fetuses survived without severe NDI.

Conclusions

The risk of perinatal death or severe NDI in children with intracranial hemorrhage due to FNAIT is high. Only screening and effective preventive treatment can avoid this burden.

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare but potentially serious condition . The most feared complication of FNAIT is intracranial hemorrhage (ICH) and its associated lifelong risks of handicaps and neurologic sequelae.[1,2] Human Platelet Antigen (HPA) allo-antibodies formed during pregnancy due to incompatibility of maternal and fetal/paternal antigen, can cross the placenta, and lead to fetal or neonatal thrombocytopenia.

Anti-HPA-1a is the platelet-specific antibody most commonly involved in FNAIT and this antibody is also responsible for the most severe cases of FNAIT.[1] It may cause bleeding complications such as ICH leading to brain damage and life-long handicaps or even death. One in 50 pregnancies is at risk for FNAIT. Antibodies are present in 1:350 pregnancies, leading to FNAIT-related perinatal death or ICH in at least 1:11.000 fetuses or newborns, and this is likely an underestimation.[2] Also, ICHs caused by FNAIT have a very high recurrence rate in subsequent pregnancies, up to 79%.[3] Therefore, in the absence of screening programs for FNAIT, current management is mainly focused on reducing the risk of recurrence of ICH in subsequent pregnancies.[4]

In view of implementation of such a screening, as well as in order to perform adequate counselling of parents, it is important to increase our knowledge on the implications of these ICHs. Overall the prognosis of ICH in neonates with FNAIT is often more severe compared to neonatal ICH from other causes, associated with a poor clinical outcome and a high mortality rate.[3,5,6] Unfortunately, due to the presumed underreporting and the relative rarity of the disease, little is known about the long term consequences and clinical outcome of these severe bleeding complications. The only available data on long-term follow-up in neonates with severe ICH due to FNAIT are based on two small case series with respectively three and six survivors.[5,6] All survivors had very poor neurodevelopmental outcome. However, these two studies were small and dated.

We therefore set up a study to evaluate the long-term neurodevelopmental outcome in a larger and more recent cohort of children with ICH due to FNAIT and clearly outline the burden of this disease in survivors in the current era of fetal medicine and neonatal intensive care treatment possibilities.

METHODS

Study population

Leiden University Medical Centre serves as the national centre of expertise for FNAIT in the Netherlands. Therefore women at risk for FNAIT with a history of a severe thrombocytopenic child (platelet count < 50×10^9 /L), a child with bleeding complications (ICH or other), or an intrauterine fetal demise due to FNAIT are referred to our center for counseling and treatment in their consecutive pregnancies. Other referral reasons include

newly diagnosed FNAIT during a current pregnancy, for example in case of fetal ICH. From 1993 onward all cases with ICH, as retrieved from medical files, due to FNAIT were identified and included in our study.

The study was approved by the institutional review board at the Leiden University Medical Centre (P11.190) and all parents gave written informed consent for the follow-up of their children.

A case was defined as FNAIT if incompatibility between maternal and paternal/fetal HPA type was confirmed and maternal anti-HPA antibodies were detected.

Outcomes

Primary outcome was perinatal death and/or severe neurodevelopmental impairment (NDI). Severe NDI was defined as any of the following: severe cerebral palsy (GMFCS ≥ 2), cognitive and/or motor test score of less than 70 (<-2 SD), bilateral blindness, or bilateral deafness requiring amplification.

Secondary outcome was moderate NDI defined as cerebral palsy with GMFCS <2, motor and/or mild-to-moderate cognitive developmental delay (< -1 SD and > -2 SD).

The following antenatal and neonatal data were recorded: antenatal treatment, gestational age at birth, mode of delivery, birth weight, platelet count at birth, clinical course, cerebral imaging. When available, neuroradiological images were reviewed by an experienced neonatologist (SS) to confirm the presence of ICH and to classify the type of bleeding. When images were obtained in another hospital and not available for review, written reports of the imaging evaluation by other experienced radiologists were obtained from the patient files. Hemorrhage was classified as subdural, subarachnoid, cerebellar, intraventricular or intraparenchymal with a separate notion for unilateral or bilateral occurrence and the extent of lobar involvement (frontal, parietal, occipital or temporal).[7]

Neurological, motor and cognitive development was assessed at a minimum of 1 year of age. Most children underwent neurodevelopmental follow-up and reports of tests were requested at the institution where the neurological examination and assessment of neuromotor and cognitive development had taken place. In cases were neurodevelopmental testing was not performed, children were asked to visit our outpatient clinic for a follow-up examination by our medical psychologist. This included neurological examination and assessment of cognitive and motor development using standardized psychometric tests appropriate for age (BSID-III: Bayley Scales of Infant and Toddler Development third edition, WPPSI-III: Wechsler Preschool Primary Scale of Intelligence third edition, WISC-III: Wechsler Intelligence Scale for Children third edition).[8-10] Bayley-III, WPPSI and WISC scores follow a normal distribution curve with a mean of 100 and a standard deviation (SD) of 15. A cognitive test score that is, a Bayley-III cognitive composite score, WPPSI Total IQ- or WISC Total IQ score below 70 (< -2 SD) indicates severe cognitive delay and scores below 85 (< -1 SD) indicate mild-to-moderate cognitive delay. Children with severe cognitive impairments (with scores below 50) or who were unable to participate in standardized testing due to severe cognitive impairment were assigned a score of 49 in the database.

Cerebral palsy (CP) was defined according to the European CP Network and classified as diplegia, hemiplegia, quadriplegia, dyskinetic, or mixed. Subsequently CP was scaled according the Gross Motor Function Classification System (GMFCS) in level I-V varying from decreased speed, balance and coordination at level I to impaired in all motor functions, cannot sit, stand, walk independently and has physical impairments that restrict voluntary control of movement and the ability to maintain head and neck position against gravity at level V.[11]

Statistical analysis

All data were analyzed with SPSS software (V.18.0 SPSS Inc, Chicago, Illinois, USA), using descriptive statistics. Categorical data are presented as numbers and percentages. Continuous variables are presented as median with Inter Quartile Range (IQR) or mean with standard deviation (SD).

RESULTS

A total of 20 children with severe bleeding complications due to FNAIT were identified. All children were born between 1993 and 2015 in different areas in the Netherlands. Two of these children were excluded because bleeding occurred in another organ, being a pulmonary and gastrointestinal hemorrhage. Of the 18 children with ICH, perinatal death occurred in eight cases (44%). Demise was due to fetal death at 22 weeks (n=1), fetal death during labour after drainage of post-hemorrhagic hydrocephalus (n=1) and neonatal demise within the first days after delivery due to severe ICH (n=6).

The median platelet count at birth was 11×10^9/L (IQR: 7.5-24.5$\times 10^9$/L). Maternal characteristics of the infants with ICH are given in table 10.1; clinical outcome characteristics are shown in table 10.2. Neurodevelopmental outcome was assessed in all ten surviving children.

Antenatal treatment

Antenatal treatment was administered in three pregnancies complicated by ICH. One mother (#15) had a previous child with FNAIT without ICH that led to the proposed plan of antenatal treatment with 0.5 g/kg/week intravenous immunoglobulins (IVIG) from 28 weeks of gestation onward in this subsequent pregnancy. Just before the start of treatment a hemorrhage was found during fetal cranial ultrasound. Fetal magnetic resonance imaging (MRI) confirmed parenchymal ICH in the left hemisphere. As planned IVIG was started, only in a higher dose of 1.0 g/kg/week. The second case concerned a dichorionic twin pregnancy (#14) of which one suffered from ICH. Maternal HPA-5b antibodies were found and amniocentesis showed HPA-5b positive status in the unaffected co-twin. IVIG was started to protect the co-twin from bleeding and to prevent worsening of bleeding of the affected fetus. In the third case ICH was diagnosed during routine ultrasound at 20 weeks of gestation, the mother had a previous child with ICH,

Table 10.1 Maternal characteristics of ICH infants

Maternal age in years median (IQR)	30 (28 - 31.5) [1]
Obstetrical history	
sibling with ICH	1
sibling with FNAIT without ICH	2
primigravida	4
firstborn	8
miscarriage	9
HPA type	
HPA 1a	13 [2]
HPA 5b	2
HPA 5a	2
Pregnancy type	
single	17
multiple	1
Antenatal treatment, IVIG 1 gr/kg/week after diagnose ICH	**3**
Delivery	
vaginal	6 [1]
ventouse	3
caesarean section	7

Data in [ ] indicate number of missing data points.

Table 10.2 Clinical outcome characteristics of the ICH infants

Gestational age at delivery, weeks median (IQR)	36 (35 - 38) [2]
Birth weight, grams mean (range)	2407 (1991 - 2942) [6]
Gender female/male (n)	3/11 [4]
Platelet count at birth, $x10^9$/L median (IQR)	11 (7.5- 24.5) [4]
Antenatal treatment, IVIG 1 g/ kg/wk after diagnosis ICH (n)	3

Data in [ ] indicate number of missing data points.

presumed to be caused by birth trauma (case #17 and #18). In this subsequent pregnancy HPA 5a antibodies were detected and FNAIT was diagnosed. Maternal administration with 1.0 g/kg/week IVIG followed from 28 weeks of gestation onward.

In sixteen cases ICH occurred antenatally. In the other two cases this was not reported.

Neuroimaging examinations of intracranial hemorrhage

Type and localization of ICH of the 18 infants with ICH is reported in table 10.3. From five children MRI images were available for review; the other thirteen could be classified using written reports. Seventeen children had intraparenchymal hemorrhage. In five cases there was also intraventricular, and in 1 case subarachnoidal hemorrhage. One child had solely an extensive subarachnoidal hemorrhage. Eight cases had bilateral hemorrhage. Eleven cases were complicated by post-hemorrhagic hydrocephalus, of which 6 developed a porencephalic cyst, resulting in five of these children requiring a ventricular peritoneal shunt.

Long-term neurodevelopmental outcome

In total, ten surviving children with ICH were included for long-term follow-up (table 10.3).

Neurodevelopment was already assessed elsewhere (rehabilitation clinic or pediatric department) in six cases, using developmental tests adapted to their cognitive, motor and/or visual impairments. Two children were evaluated by the medical psychologist at our centre. Two children could not be assessed with psychometric tests due to very severe cognitive and motor impairment and were assigned a score of 49. Children were tested at a median age of 7.5 years (IQR 5-14)

Severe NDI in the studied cohort was found in 6/10 cases (60%). Cerebral palsy was diagnosed in seven cases (70%). One child had moderate NDI due to spastic hemiparesis with a GMFC score of I (moderate NDI).Severe cognitive delay was detected in six children (60%) and severe motor delay in six children (60%). Three children were blind (30%). One child was diagnosed with attention deficit hyperactivity disorder, one child had problems with behavior and attention-regulation but was too young to diagnose ADHD.

DISCUSSION

FNAIT is a potentially hazardous disease associated with fetal thrombocytopenia and severe bleeding complications in the fetus and neonate. The most feared complication of FNAIT is ICH and its associated risk of lifelong handicap and neurologic sequelae.[12-14] This study shows that the risk of death or severe neurodevelopmental impairment in children with ICH due to FNAIT is high (14/18, 78%). Adverse outcome was due to perinatal mortality in 8/18 (44%) of cases and severe NDI in 6 of 10 survivors (60%). In two of four survivors without severe NDI, moderate abnormalities were detected including spastic hemiplegia (GMFC score I) and attention deficit disorders (ADHD), therefore only two of the ten survivors were free of neurodevelopmental sequelae. Remarkably 40% of the children had visual impairment. Our findings stress the severity and implications of major and permanent life-long handicaps associated with FNAIT, particularly in case of ICH.

Table 10.3 Long-term outcome of all infants with ICH

Child	Location ICH	Associated lesions	Age at evaluation	Cerebral palsy	Developmental test	Total IQ	Outcome Long term outcome	Severe NDI
1	extensive subarachnoidal and unilateral parenchymal frontal/temporal/occipital						neonatal death	
2	unilateral intraventricular and parenchymal	hydrocephalus					neonatal death	
3	bilateral parenchymal						neonatal death	
4	extensive bilateral parenchymal.						neonatal death	
5	extensive bilateral parenchymal	hydrocephalus					fetal death during labour	
6	bilateral parenchymal	hydrocephalus					fetal death at 22 wks	
7	extensive subarachnoidal						neonatal death	
8	bilateral intraventricular and parenchymal	hydrocephalus					neonatal death	
9	unilateral parenchymal, occipital		8 year	-	WISC	86	ADHD	no
10	unilateral parenchymal, temporal	hydrocephalus, VPD	2, 8 and 14 years	spastic tetraplegia GMFCS V	Bayley/BSID;Reynell-Zinkin;KID-N	49	bilateral blindness, severe cognitive and motor delay, epilepsy	yes
11	bilateral parenchymal, temporal	porencephalic cyst hydrocephalus, VPD	20 year	spastic tetraplegia GMFCS V	not tested due to severe impairment	49	bilateral blindness, severe cognitive and motor delay, epilepsy	yes
12	bilateral parenchymal, temporal and occipital	porencephalic cyst hydrocephalus, VPD	23 year	spastic tetraplegia GMFCS V	not tested due to severe impairment	49	bilateral blindness, hearing impairment, severe cognitive and motor delay	yes
13	extensive bilateral intraventricular, parenchymal and cerebellar haemorrhage	bilateral porencephalic cyst, cerebellar destruction hydrocephalus, VPD	3 year	spastic diplegia GMFCS IV	SON	60	severe cognitive and motor delay	yes
14	unilateral parenchymal, occipital and cerebellar		5 year	-	WPPSI	110		no
15	bilateral parenchymal, parietal, temporal and occipital	bilateral porencephalic cyst hydrocephalus, VPD	1 year	spastic hemiplegia GMFCS IV	KID-N	49	visual impairment, severe cognitive and motor delay, epilepsy	yes
16	unilateral parenchymal, fronto-temporal		7 year		WISC	112		no
17	unilateral parenchymal, intraventricular and bilateral cerebellar	unilateral porencephalic cyst	5 year	spastic hemiplegia GMFCS I	WPPSI	85	problems with behaviour and attention-regulation	no
18	bilateral frontal parenchymal and intraventricular	bilateral porencephalic cysts	8 year	spastic diplegia GMFCS II	SON	50	severe cognitive and motor delay, epilepsy	yes

Tests: WISC Wechsler intelligence scale for children, WPPSI: Wechsler Preschool and Primary Scale of Intelligence, BSID: Bayley Scales of Infant and Toddler Development Reynel Zinkin: Developmental Scales for Young Visually Handicapped 2 months – 4/5 years, KID-N: Kent Infant Development Scale, dutch version 0- 15 months/8 years, SON: Snijders-Oomen Non verbal Intelligence test

Most cases of ICH seem to occur antenatally, with the majority before the 28th week of gestation.[15] Which is in line with the results from our study. All ICHs occurred antenatal and were mostly parenchymal hemorrhages, with the majority complicated by hydrocephalus and/or porencephalic cysts.

Interestingly the proportion of males was much higher (11 male versus 3 female) An association between sex and ICH due to FNAIT was also found in previous publications. How the sex of the offspring is involved in FNAIT remains to be explored[16,17].

This study has some limitations. Cases could have been missed because only cases referred to our center were included. Furthermore the retrospective nature of this cohort study makes it susceptible to confounding and information bias and may have led to the inclusion of more severe ICH cases and therefore possibly cases with poorer outcome. However, it is not likely that cases with better developmental outcome were missed because the cases in this study were selected by ICH from all FNAIT cases referred to our own center and not by developmental problems. In addition due to this retrospective design, no conclusions on the prevalence of these ICHs compared to the total cases of FNAIT detected can be drawn. Cultural differences or legal restrictions in administration of intensive neonatal care may have influenced the outcome in this cohort. It is plausible that withholding or withdrawing neonatal intensive care treatment in cases with poor prognosis, may have led to a higher perinatal mortality and therefore to a lower number of survivors with poor neurodevelopmental outcome. Lastly, there is heterogeneity in developmental testing performed, adapted to the age as well as to the severity of impairment of the children included for follow-up. Importantly, standardized psychometric testing was not feasible in all children due to severe motor, cognitive and neurosensory impairments.

Nevertheless, despite these limitations, this is the first study that focuses on long-term outcome of ICH due to FNAIT and the largest study to describe actual long-term follow-up. Our findings show that FNAIT-related ICH is associated with severe developmental delay.

In absence of cohort studies assessing the long term outcome of ICH caused specifically and solely by FNAIT, data originate from cohort studies of ICH in term neonates with a variety of other causes (mainly birth trauma, asphyxia).[5,6,12-14]

The largest case series of intraventricular hemorrhage (IVH) in full term newborns is described by Mao et al.[5] They analyzed a total of 36 newborns and found a low mortality rate and generally favorable outcome, with 63% of all cases having no or only mild handicaps. In contrast, they found FNAIT to be the single most important cause of poor outcome. Out of nine cases three infants died and six were severely handicapped. Jocelyn et al studied a cohort of 15 IVH cases in full term newborns, of which three were caused by FNAIT.[6] Of these three, two survived and were both severely impairment. Both studies are limited by the small number of patients as well as by their selection of cases. Whereas both studies selected newborns with diagnosis of IVH, there might be an underrepresentation of (minor) intracranial hemorrhages that have been caused by FNAIT.

In the absence of screening programs for FNAIT the disease is mostly always detected after birth of an affected child and preventive measures with antenatal IVIG can only be taken in next pregnancies. Implementation of routine HPA-typing and antibody screening in the near future would strongly reduce the burden associated with this disease. Several groups have published calculations of costs and potential benefits of screening and intervention, all reaching the same conclusion that such programs are likely to be cost-effective.[2,18,19] The main reason for this cost-effectiveness, despite large-scale testing and, in case of IVIG, expensive treatment, are the disease burden and excessive costs for a child with life-long severe neurological sequelae.

As long as screening for FNAIT is not implemented in standard care, reliable information about the incidence of ICH among FNAIT cases cannot be given. Furthermore, prospective studies including general screening for FNAIT and follow-up are needed to learn more about the pathophysiology of this disease, including establishing if there is also a milder phenotype of ICH with discrete symptoms and better outcome.

CONCLUSION

This is the first study focusing and reporting on long-term neurodevelopmental outcome of children suffering from ICH caused by FNAIT. In the vast majority of cases, ICH leads to either perinatal death or, in survivors, severe impairment. These long-term sequelae can only be avoided by screening and effective preventive treatment.

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