Fetal and Neonatal Alloimmune Thrombocytopenia: evidence based screening

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Chapter 3

Perinatal outcome and long-term neurodevelopment after intracranial hemorrhage due to fetal/neonatal alloimmune thrombocytopenia

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Abstract

Objectives. To evaluate perinatal and long-term neurodevelopmental outcome in a cohort of children with an intracranial hemorrhage (ICH) due to fetal and neonatal alloimmune thrombocytopenia (FNAIT) and clearly outline the burden of this disease.

Subjects and methods. We performed an observational cohort study and included all consecutive cases of ICH caused by FNAIT from 1993 to 2015 at Leiden University Medical Center. Neurological, motor and cognitive development were assessed at a minimum age of one year. Primary outcome was adverse outcome, defined as perinatal death or severe neurodevelopmental impairment (NDI). Severe NDI was defined as any of the following: cerebral palsy (Gross Motor Function Classification System (GMFCS) ≥ 2), bilateral deafness, blindness, severe motor and/or cognitive developmental delay (< -2 SD).

Results. In total, 21 cases of ICH due to FNAIT were included in the study. Perinatal mortality rate was 10/21 (48%). Long-term outcome was assessed in ten children ($n = 1$, lost-to follow-up). Severe NDI and moderate NDI were diagnosed in 6/10 (60%) and 1/10 (10%) of surviving children. Overall adverse outcome, including perinatal mortality or severe NDI, was 16/20 (80%).

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

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is one of the leading causes of thrombocytopenia in otherwise healthy newborns.[1,2] Maternal alloantibodies are formed after exposure to the incompatible, paternally derived human platelet antigen (HPA) on fetal platelets. In FNAIT, these alloantibodies are predominantly targeted against HPA-1a, in approximately 80% of cases.[3,4] When these antibodies enter the fetal circulation, they can destroy fetal platelets and damage endothelial cells.[5] Hence, FNAIT presents as an (asymptomatic) thrombocytopenia or results in bleeding complications. The most feared complication is an intracranial hemorrhage (ICH), due to its associated risk of lifelong handicaps and neurological sequelae.[6,7] In addition, ICHs caused by FNAIT have a high recurrence rate, in up to 79% of subsequent pregnancies.[8] Therefore, in the absence of population-based screening for FNAIT, current management is focused on preventing the occurrence of bleeding complications and ICHs in subsequent pregnancies through antenatal treatment with intravenous immunoglobulin (IVIg).[9] ICH is estimated to occur in 1 out of 25,000 pregnancies and in 1 out of 10 cases of severe FNAIT.[10]

Despite the fact that ICH caused by FNAIT is often more severe compared to ICH from other causes, leading to a high mortality and handicap rate, no detailed long-term follow-up studies have been published so far. [8,11,12] Long-term follow-up data are necessary for performing adequate evidence-based counseling of parents, and for professionals involved in guiding these children. Even more, in light of potential future implementation of population-based screening, knowledge on the long-term implications of these ICHs is indispensable.

We evaluated the perinatal and long-term neurodevelopmental outcome in a cohort of children with ICH due to FNAIT and clearly outlined the burden of this disease in survivors in the current era of fetal medicine and neonatal intensive care treatment possibilities.

Subjects and methods

Study population
The Leiden University Medical Center serves as the national center of expertise for FNAIT in the Netherlands. From 1993 to 2015 all consecutive cases with ICH due to FNAIT were identified and eligible for inclusion. We identified through women that were counselled, diagnosed, or treated at our center, either in the pregnancy of interest or during a subsequent pregnancy. These cases were cross-checked with Sanquin, the national reference laboratory for FNAIT, where the diagnosis FNAIT was confirmed in case of incompatibility between maternal and paternal/fetal HPA type in combination with the detection of maternal anti-HPA antibodies.

Outcomes

The primary outcome was perinatal death and/or severe neurodevelopmental impairment (NDI). Severe NDI was defined as any of the following: severe cerebral palsy (Gross Motor Function Classification System [GMFCS] score ≥ 2), a cognitive and/or motor test score <70 (< -2 SD), bilateral blindness, or bilateral deafness requiring amplification. The secondary outcome was moderate NDI defined as cerebral palsy GMFCS < 2 or mild-to-moderate motor and/or cognitive developmental delay (< -1 SD and > -2 SD).

The following ante- and neonatal data were retrieved from the medical files: antenatal treatment, gestational age at birth, mode of delivery, birth weight, platelet count at birth, clinical course and cerebral imaging. When available, neuroradiological images were reviewed by an experienced neonatologist (S.J.S.) to confirm the presence of ICH and to classify the type of bleeding. When original images from another hospital were unavailable for review, written reports by other experienced radiologists were obtained. Hemorrhages were 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).[13] Cases with no imaging or no classification of imaging performed elsewhere available were excluded.

Neurological, motor and cognitive development was assessed at a minimum of 1 year of age. The following standardized psychometric tests, appropriate for age, were used: the Bayley Scales of Infant and Toddler Development third edition (Bayley-III), the Wechsler Preschool Primary Scale of Intelligence third edition (WPPSI-III), and the Wechsler Intelligence Scale for Children third edition (WISC-III).[14-16] Bayley-III, WPPSI-III, and WISC-III scores follow a normal distribution curve with a mean of 100 and a standard deviation of 15. A cognitive test score, i.e., a Bayley-III cognitive composite score, WPPSI-III or WISC-III total IQ score < 70 (< -2 SD) indicates severe cognitive delay. Scores < 85 (< -1 SD) indicate mild-to-moderate cognitive delay. Children with severe cognitive impairments (with scores < 50) or who were unable to participate in standardized testing due to severe cognitive impairment were assigned a score of 49 in the database. Testing was either performed by our specialized medical psychologist at our outpatient clinic or results were requested at their institution of care.

Cerebral palsy was defined according to the European Cerebral Palsy Network and classified as diplegia, hemiplegia, quadriplegia, dyskinetic, or mixed. Subsequently, cerebral palsy 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.[17]

Statistical analysis

All data were analyzed with SPSS software (version 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 range or mean with standard deviation.

Results

Study population

Between 1993 and 2015 a total of 31 cases with an ICH due to FNAIT were identified (Figure 3.1). Of these, 7 (23%) were excluded because there were no clinical data available on either short- or long-term outcome. Three additional cases were excluded because there were no images or reports of the ICH available. The remaining 21 children with ICH were included and assessed for short-term outcome. Perinatal death was reported in 10 (48%) cases because of fetal demise at 19-22 weeks gestation ($n = 3$), death during labor after drainage of post-hemorrhagic hydrocephalus ($n = 1$) and neonatal death related to severe ICH ($n = 6$).

Obstetric history revealed a previous miscarriage in 10 (48%) cases (Table 3.1). HPA-1a was the predominantly involved alloantibody, in 18 (86%) cases. In 5 (24%) cases the ICH occurred in the first pregnancy and in 12 cases the ICH affected the first-born child. The lowest platelet count in all cases not treated antenatally with IVIg was below 30×10^9/L, with a median of 11×10^9/L.

Short-term outcome

Antenatal treatment

In 11 (52%) cases, the ICH was already detected antenatally, and in 4 of these pregnancies antenatal treatment was administered. One mother (#17) had a previous child with FNAIT without ICH, which led to the proposed plan of antenatal treatment with IVIg from 28 weeks of gestation. Just before the start of treatment a hemorrhage was detected during fetal cranial ultrasound. IVIg was started as planned. The second case concerned a dichorionic twin pregnancy (#16) of which one suffered from ICH. Maternal HPA-5b antibodies were found and IVIg was started to protect the co-twin from bleeding and to prevent worsening of bleeding of the affected fetus. In the other 2 cases, ICH was detected during routine ultrasound at 20 weeks of gestation. In one of these cases the mother had a previous child with ICH, presumed to be caused by birth trauma. In this subsequent pregnancy HPA-5a antibodies were detected and FNAIT was diagnosed. In 19 (90%) cases, it was clear that the ICH occurred antenatally. In the other two cases the exact timing of the ICH was not reported.
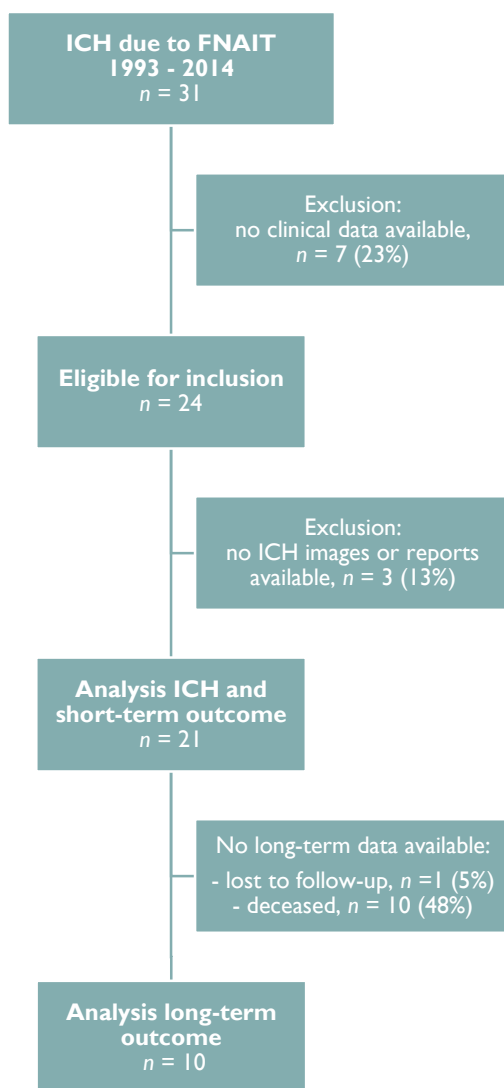
Figure 3.1 – Flow chart study population

Neuroimaging examinations of ICH

Type and localization of ICH of the 21 children with ICH are reported in table 3.2. From 8 (38%) children MRI images were available for review; the other 13 (62%) could be classified using written reports. Nineteen (91%) children had intraparenchymal hemorrhage. In 8 cases there was also intraventricular bleeding and in 2 cases subarachnoidal bleeding. Eight cases had bilateral hemorrhage. Eleven cases were complicated by posthemorrhagic hydrocephalus, of whom 6 developed a porencephalic cyst, resulting in 5 of these children requiring a ventricular peritoneal shunt.

Table 3.1 – Demographic characteristics of study population

Maternal age (years)	30 (21-41)
Obstetrical history	
Sibling with ICH	1 (5)
Sibling with FNAIT	2 (10)
Miscarriage	10 (48)
HPA type	
HPA 1a	18 (86)
HPA 5b	2 (10)
HPA 5a	1 (5)
Obstetrical characteristics	
Singleton pregnancy	20 (95)
First pregnancy	5 (24)
First born child	12 (57)
Antenatal treatment,	4 (19)
IVIg 1 gr/kg/week after antenatal detection ICH	
Gestational age at delivery*, weeks^{+days}	36^{+0} (30^{+0} – 41^{+6})
Delivery*	
Vaginal	6 (33)
Ventouse	3 (17)
Caesarean section	9 (50)
Neonatal characteristics	
Male sex	13 (62)
Birth weight, gram*	2408 (1178-4080)
Platelet count, $\times 10^9$/L *	
without antenatal IVIg	158 (133-164)
with antenatal IVIg	11 (6-29)

Data are presented as *n* (%), mean (SD) or median (IQR). FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen; ICH, intracranial hemorrhage; IVIg, intravenous immunoglobulin.

* Terminations of pregnancy excluded ($n = 3$).

Long-term neurodevelopmental outcome

In total, 10 surviving children with ICH were included for long-term follow-up (Table 3.3). Long-term outcome could not be assessed in 1 child (5%) due to loss of contact information.

Neurodevelopment was already assessed elsewhere (rehabilitation clinic or pediatric department) in 6 cases, using developmental tests adapted to their cognitive, motor and/or visual impairments (i.e. Snijders Oomen Nonverbal Intelligence Test and Kent Infant Development Scale). Two children were evaluated by the medical psychologist at our center. 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 (range 1 – 23). Overall adverse outcome, including perinatal mortality or NDI, was 16/20 (80%).

Table 3.2 – Intracranial hemorrhage characteristics and short-term outcome

Child #	GA at birth	IVIg antenatal	Location ICH
1	33+4	No	extensive subarachnoid and unilateral parenchymal frontal/temporal/occipital
2	35+0	No	unilateral intraventricular and parenchymal and parenchymal
3	31+5	No	bilateral parenchymal
4	36+5	No	extensive bilateral parenchymal.
5	38+1	No	extensive bilateral parenchymal
6	22+0	No	bilateral parenchymal
7	32+2	No	extensive subarachnoidal
8	30+0	No	bilateral intraventricular and parenchymal
9	19+0	No*	extensive bilateral parenchymal
10	19+4	No	unilateral parenchymal and intraventricular
11	38+1	No	unilateral parenchymal, occipital
12	36+0	No	unilateral parenchymal, temporal
13	35+0	No	bilateral parenchymal, temporal
14	36+1	No	bilateral parenchymal, temporal and occipital
15	35+3	Yes, from 30 weeks	extensive bilateral intraventricular, parenchymal and cerebellar hemorrhage
16	36+0	Yes, from 28 weeks*	unilateral parenchymal, occipital and cerebellar
17	40+6	No	bilateral parenchymal, parietal, temporal and occipital
18	41+3	No	unilateral parenchymal, fronto-temporal
19	37+6	Yes, from 20 weeks	unilateral parenchymal, intraventricular and bilateral cerebellar
20	41+5	No	bilateral frontal parenchymal and intraventricular
21	37+0	No	extensive bilateral intraventricular

APLA, abortus provocatus lege artis; GA, gestational age; ICH, intracranial heamorrhage; IVIg, intravenous immunoglobulins; TOP, termination of pregnancy; VPD, ventriculoperitoneal drain.

Associated lesions	Mortality	Obstetric history mother	
-	Yes, neonatal	G1P0	
hydrocephalus	Yes, neonatal	G2P1	healthy child
-	Yes, neonatal	G1P0	
	Yes, neonatal	G3P1	healthy child, miscarriage
hydrocephalus	Yes, fetal during labor	G2P0	miscarriage
hydrocephalus	Yes, TOP	G2P0	miscarriage
	Yes, neonatal	G2P1	child with trisomy 21
hydrocephalus	Yes, neonatal	G3P0	miscarriage, one abortion
-	Yes, TOP	G4P3	two healthy children, one child with FNAIT
-	Yes, TOP	G3P1	healthy child, miscarriage
-	No	G3P0	two miscarriages
hydrocephalus, VPD	No	G1P0	
porencephalic cyst hydrocephalus, VPD	No	G2P0	miscarriage
porencephalic cyst hydrocephalus, VPD	No	G2P0	miscarriage
bilateral porencephalic cyst, cerebel-lar destruction hydrocephalus, VPD	No	G2P1	healthy child
-	No	G4P1	two miscarriages, one child with FNAIT
bilateral porencephalic cyst hydrocephalus, VPD	No	G1P0	
-	No	G1P0	
hydrocephalus, unilateral porencephalic cyst	No	G4P2	immature delivery at 17 weeks, child ICH, abortion
hydrocephalus, bilateral porencephalic cysts	No	G2P0	molar pregnancy
-	No	G2P1	healthy child

Table 3.3 – Intracranial hemorrhage and long-term outcome

Child #	Associated lesions	Age at evaluation	Cerebral palsy
11	None	8 year	-
12	Hydrocephalus, VPD	2, 8 and 14 years	spastic tetraplegia GMFCS V
13	Porencephalic cyst hydrocephalus, VPD	20 year	spastic tetraplegia GMFCS V
14	Porencephalic cyst hydrocephalus, VPD	23 year	spastic tetraplegia GMFCS V
15	Bilateral porencephalic cyst, cerebellar destruction hydrocephalus, VPD	3 year	spastic diplegia GMFCS IV
16	None	5 year	-
17	Bilateral porencephalic cyst hydrocephalus, VPD	1 year	spastic hemiplegia GMFCS IV
18	None	7 year	
19	Hydrocephalus, unilateral porencephalic cyst	5 year	spastic hemiplegia GMFCS I
20	Hydrocephalus, bilateral porencephalic cysts	8 year	spastic diplegia GMFCS II
21	None	None	*Loss of contact information, no long-term follow-up available*

ADHD, attention deficit hyperactivity disorder; Bayley-III, Bayley Scales of Infant and Toddler Development third edition; GMFCS, Gross Motor Function Classification System; KID-N, Kent Infant Development Scale; NDI, neurodevelopmental impairment; SON, Snijders-Oomen Nonverbal Intelligence Test; VPD, ventriculoperitoneal drain; WISC-III, Wechsler Intelligence Scale for Children third edition; WPPSI-III, Wechsler Preschool Primary Scale of Intelligence third edition.

Severe NDI in the studied cohort was found in 6/10 cases (60%). Cerebral palsy was diagnosed in 7 cases (70%). One child had moderate NDI due to spastic hemiparesis with a GMFCS score of I. Severe cognitive delay was detected in 6 children (60%) and severe motor delay in 6 children (60%). Three children were blind (30%) and 1 child was diagnosed with severe visual impairment. Epilepsy was reported in 4 (40%) children. One child was diagnosed with attention deficit hyperactivity disorder; 1 child had problems with behavior and attention regulation, but was too young to be already diagnosed with attention deficit hyperactivity disorder.

Developmental test	Total IQ	Long-term outcome	Severe NDI
WISC	86	ADHD	no
Bayley/BSID;Reynell-Zinkin;KID-N	49	bilateral blindness, severe cognitive and motor delay, epilepsy	yes
not tested due to severe impairment	49	bilateral blindness, severe cognitive and motor delay, epilepsy	yes
not tested due to severe impairment	49	bilateral blindness, hearing impairment, severe cognitive and motor delay	yes
SON	60	severe cognitive and motor delay	yes
WPPSI	110		no
KID-N	49	visual impairment, severe cognitive and motor delay, epilepsy	yes
WISC	112		no
WPPSI	85	problems with behaviour and attention-regulation	no
SON	50	severe cognitive and motor delay, epilepsy	yes

Discussion

This study shows that ICH caused by FNAIT is associated with a high risk of perinatal death and lifelong neurological sequelae in survivors. Of the 10 surviving infants, 6 had severe NDI and 2 had moderate NDI. Therefore, only 2 of the 10 survivors were completely free of long-term neurodevelopmental sequelae. Cerebral palsy was diagnosed in 70% and severe cognitive delay in 60%. In addition, 40% of the children had severe visual impairment and 40% was diagnosed with epilepsy. Our findings stress the severity and implications of major and permanent life-long impairments associated with FNAIT, particularly in case of ICH.

The vast majority (90%) of the ICHs occurred antenatally, which is in line with a previously published report on the short-term outcome of 43 ICHs due to FNAIT.[7,18] Like in this previously reported series, most ICHs were parenchymal hemorrhages, with the majority complicated by hydrocephalus and/or porencephalic cysts. In our cohort, cases with hydrocephalus and porencephalic cysts were more likely to result in severe NDI (6/7 and 5/6, respectively). Due to the relative small sample size, no correlation could be identified between localization (frontal/temporal/occipital or parenchymal, intraventricular, cerebellar) or extent (uni-/bilateral) and long-term outcome.

Obviously, our study does not match the true prevalence of ICH in our country, whereas it is a single center study and there is a considerable amount of cases with missing clinical information (7/31, 23%). This might have resulted in an overrepresentation of the more severe cases of ICH. For example, we report a rate of perinatal death of 48% (10/21), which is somewhat higher than the previously reported rate of 35% (15/43).[7] Also, because many women were identified because they were treated or counselled at our center in subsequent pregnancies, we might have found a higher rate of primigravid women and first-born children. Furthermore, 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. However, cases were not selected because of behavioral or developmental problems, so it is not likely that cases with better developmental outcome were missed. Undoubtedly, 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. This severity limited our ability to perform standardized psychometric testing in all children.

Despite these limitations, this is an unique study that focuses on long-term outcome of ICH due to FNAIT, clearly outlining the burden of this disease in survivors. One of the strengths of this study is that we used standardized psychochometric tests. Moreover, we were able to do long-term follow-up at a median age of 7.5 years. Previously, follow-up at one year was analyzed in newly detected FNAIT cases, with various clinical presentations, by Knight and colleagues.[19] They reported death or disability in 9 out of 88 cases, 2 infants died, 2 infants had severe global developmental delay, 4 infants had motor and visual impairment and 1 infant had only visual problems. However, no standardized tests were reported and classification of impairment was not further specified.[19] Lastly, we were able to focus on a clear and homogenous group consisting of children with ICH solely due to FNAIT. Earlier, cohorts of ICHs have been described, of which the largest series of intraventricular hemorrhage (IVH) in full term newborns was reported by Mao and colleagues.[11] They analyzed a total of 36 newborns and found a low mortality rate and, generally, a favorable outcome, with 63% of

all cases having no or only mild impairment. In contrast, they found FNAIT to be the single most important cause of adverse outcome. Out of 9 cases, 3 children died and 6 were severely impaired. Jocelyn and Casiro studied a cohort of 15 intraventricular hemorrhage cases in full term newborns, of which three were caused by FNAIT.[12] Of these 3 patients, 2 survived and were both severely impaired. 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 intraventricular hemorrhage, there might be an underrepresentation of (minor) ICHs caused by FNAIT.

In the absence of screening programs for FNAIT, the disease is almost always detected after birth of an affected child, and preventive measures with antenatal IVIg can only be taken in the following pregnancies. Implementation of routine HPA-typing, primarily for HPA-1a, and consequent antibody screening in the near future would strongly reduce the burden associated with this disease. However, before such screening can be implemented, costs and potential benefits should be weighed carefully. So far, several attempts to estimate cost-effectiveness reached the same conclusion, namely that such programs are likely to be cost-effective.[10,20,21] This study, as it is the first one to provide detailed long-term follow-up data of children that suffered ICH due to FNAIT, provides essential knowledge for this debate. In addition, prospective studies including general screening for FNAIT and long-term 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. Furthermore, whereas only a proportion of alloimmunized pregnancies will result in devastating ICH as described in this study, research is needed to establish diagnostic tools to identify pregnancies that are at high risk for these bleeding complications and that would benefit from antenatal intervention and treatment.

Conclusion

This is the first study focusing and reporting on the long-term neurodevelopmental outcome of children suffering from ICH caused by FNAIT, using standardized psychometric measures. 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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