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Severe bleeding complications other than intracranial hemorrhage in neonatal alloimmune thrombocytopenia: a case series and review of the literature

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BACKGROUND: The most feared bleeding complication in fetal and neonatal alloimmune thrombocytopenia (FNAIT) is an intracranial hemorrhage (ICH). However, FNAIT may also lead to other severe bleeding problems. The aim was to analyze this spectrum and evaluate the occurrence of severe hemorrhages other than ICH in fetuses or neonates with FNAIT.

STUDY DESIGN AND METHODS: A retrospective chart analysis of cases of FNAIT presenting with severe bleeding complications other than ICH at our institution from 1990 to 2015 was conducted. Additionally, a review of the literature was performed to identify case reports and case series on FNAIT presenting with extracranial hemorrhage.

RESULTS: Of 25 fetuses or neonates with severe bleeding due to FNAIT, three had isolated severe internal organ hemorrhage other than ICH, two pulmonary hemorrhages and one gastrointestinal hemorrhage. Two of these three neonates died due to this bleeding. Eighteen cases of extracranial bleeding complications as a first presentation of FNAIT were found in the literature, including ocular, gastrointestinal, spinal cord, pulmonary, renal, subgaleal, and genitourinary hemorrhages.

CONCLUSION: Bleeding complications other than ICH may be more extensive, and the presentation of FNAIT may have a greater spectrum than previously described. A high index of suspicion on the possible diagnosis of FNAIT with any bleeding complication in a fetus or neonate may enable adequate diagnostics, adequate treatment, and appropriate follow-up in future pregnancies, as is especially relevant for FNAIT.

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by human platelet antigen (HPA) incompatibility between mother and child. Alloantibodies produced by the mother can cross the placental barrier and lead to destruction of fetal platelets (PLTs) as well as compromised vascular integrity.¹ FNAIT is the main cause of severe thrombocytopenia in term neonates.² Low PLT count in FNAIT correlates with an increased risk of bleeding complications, of which the most feared is an intracranial hemorrhage (ICH). The incidence of FNAIT-related ICH or perinatal death is estimated to be at least 1:11,000 fetuses or neonates; this, however, is likely an underestimation.³ ICH is a devastating complication, which may lead to death or permanent neurologic impairment. Outcomes are often more severe than for neonatal ICH from other causes.⁴ Consequently, most publications and clinical guidelines of FNAIT are focused on the occurrence and prevention of ICH. The same trend can be observed in clinical practice, where the

ABBREVIATIONS: FNAIT = fetal and neonatal alloimmune thrombocytopenia; ICH = intracranial hemorrhage.

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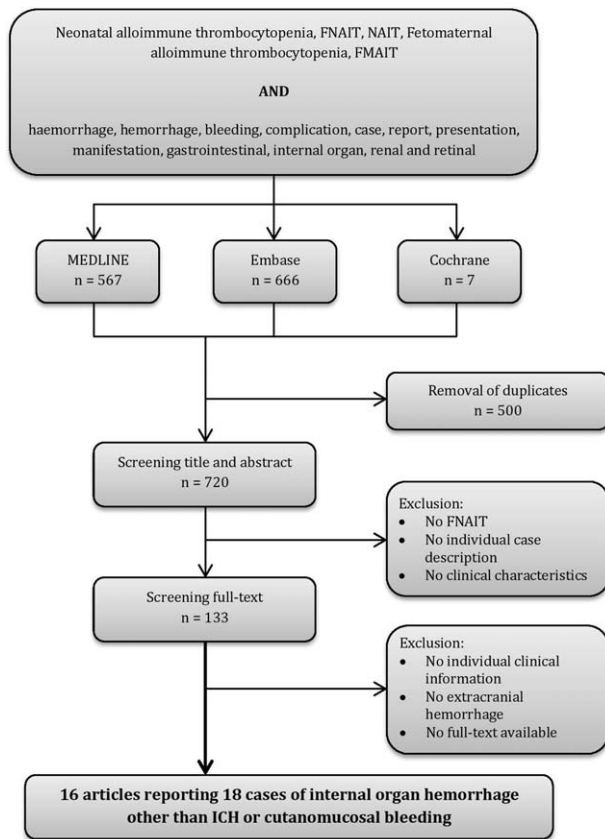


Fig. 1. Flowchart of search strategy.

occurrence of ICH in an otherwise healthy infant is immediately associated with FNAIT. This is in contrast to other bleeding problems, where the proper diagnosis might be delayed or even missed, denying these women adequate care in future pregnancies.^{5,6} In this study, we evaluated the occurrence of severe hemorrhage other than ICH in neonates with FNAIT, and present a review of the literature.

MATERIALS AND METHODS

We conducted a retrospective study to evaluate the incidence and clinical course of fetuses and neonates presenting with severe extracranial hemorrhage due to FNAIT. We searched the FNAIT registry of our tertiary center for cases presenting with severe hemorrhage from 1990 to 2015. Clinical and demographic data were retrieved from medical charts. The diagnosis FNAIT had to be confirmed by demonstrating HPA incompatibility together with the presence of maternal alloantibodies. An extracranial hemorrhage was defined as an internal organ hemorrhage other than ICH or cutanomucosal bleeding.

Additionally, we reviewed and summarized the literature for cases of extracranial hemorrhage due to FNAIT. Relevant publications up to August 2015 were identified

by searching MEDLINE, Embase, and the Cochrane Library databases, using a combination of the keywords stated in Fig. 1. No restriction of language or type of publication was applied. Authors were contacted if additional data were needed. We focused on information on initial clinical presentation, immunohematologic evaluation, and treatment provided.

RESULTS

During the study period, from 1990 to 2015, a total of 25 index cases of severe bleeding complications could be extracted from our own FNAIT registry. Of these cases, 22 children suffered from ICH, of which eight died. We identified three neonates with severe extracranial hemorrhage.

Case Report 1

A 29-year-old healthy woman gave birth to her second child after an uneventful pregnancy at 39⁺⁴ weeks' gestation. The first pregnancy and delivery were uneventful as well. A boy was born after an uncomplicated spontaneous delivery, birthweight 3955 g, and Apgar scores of 8 and 9 at 1 and 5 minutes. Two hours after birth the boy developed respiratory distress, for which continuous positive airway pressure treatment was started. Chest X-ray revealed diffuse consolidation of the right hemithorax. Due to persistent respiratory distress, intubation and mechanical ventilation were required. At intubation a massive amount of blood in the nasopharynx and trachea was detected, severely hampering visualization. The infant was transported to our neonatal intensive care unit. On examination, diffuse petechiae were detected on the infant's chest and abdomen. Laboratory evaluation showed a very severe thrombocytopenia (PLT count, $5 \times 10^9/L$). In absence of signs of placental insufficiency, asphyxia, perinatal infection, or maternal autoimmune diseases there was a high suspicion of FNAIT. HPA-1a-negative PLTs were ordered immediately. Meanwhile, a random PLT transfusion was administered, followed directly by matched PLTs. PLT count after these two transfusions was $216 \times 10^9/L$. The mother was found to be HPA-1a negative and the child was HPA-1a positive. Maternal HPA-1a alloantibodies confirmed the diagnosis FNAIT. Besides slightly abnormal brainstem-evoked response audiometry patterns, implicating damage caused by postnatal hypoxia, a full recovery was achieved.

Case Report 2

A healthy 28-year-old woman gave birth at 33⁺⁶ weeks' gestation. Obstetric history revealed a curettage because of a missed abortion at 12 weeks. This second pregnancy was complicated by premature contractions, occurring at 21 weeks, leading to admission and tocolytic treatment. At 33⁺⁵ weeks' gestation, membranes ruptured

TABLE 1. Reports of extracranial hemorrhage caused by FNAIT

First author, year	Hemorrhage	Skin manifestations	Lowest PLT count ($\times 10^9/L$)	HPA	Treatment
Baber, 2015	Postcircumcision	No	5	Unknown	IVIG, PTx
Jerónimo, 2014	Intraocular	No	27	HPA-1a	IVIG, PTx
Cook, 2012	Scrotal	Yes	7	HPA-1a	PTx
Borensztajn, 2010	Subgaleal	Yes	13	HPA-1b	RBC transfusion, PTx
Nomura, 2010	Retinal	Yes	42	HPA-5b	Expectative
Ghevaert, 2007	Pulmonary	No	23	HPA-5b	Unknown
Paladini, 2007	Renal	NA	NA	HPA-5b	Termination of pregnancy
Rousseau, 2004	Gastrointestinal	Unknown	Unknown	HPA-1a, HPA-5b	Unknown
Abel, 2003	Cervical spinal cord	Yes	2	HPA-1a	IVIG, PTx
Davoren, 2002	Retinal	Unknown	Unknown	HPA-1a	IVIG, PTx
	Subgaleal	No	14	HPA-1a	Steroids, RBC transfusion, PTx
Tomicic, 2001	Gastrointestinal	Yes	29	HPA-1a	Steroids
Kankirawatana, 2001	Gastrointestinal	Yes	15	NAK	IVIG, steroids, PTx
Mokhtari, 1997	Gastrointestinal	Yes	8	HPA-3a	Exchange transfusion, PTx, IVIG, steroids
Allen, 1992	Gastrointestinal	Yes	36	HPA-5b	None
Puig, 1993	Gastrointestinal	Yes	9	HPA-4b	PTx
Kaplan, 1991	Gastrointestinal	Yes	10	HPA-5b	RBC transfusion, PTx
	Pulmonary	Yes	80	HPA-5b	IVIG, steroids

PTx = platelet transfusion; NA = not applicable.

spontaneously, followed by contractions and preterm birth. The girl had a birthweight of 1630 g. There were no signs of perinatal asphyxia or a neonatal infection. Shortly after delivery the clinical condition worsened progressively and a massive lung bleeding was discovered. Resuscitation was to no avail and the infant died a couple of hours after birth. Because of a severe thrombocytopenia (PLT count, $40 \times 10^9/L$), immunohematologic investigation was performed and showed a HPA-1a mismatch mother and father together with maternal HPA-1a alloantibodies. In retrospect the diagnosis FNAIT was stated as the most likely cause of this pulmonary hemorrhage and neonatal death.

Case Report 3

A healthy 36-year-old woman, G2P0, gave birth at 39⁺³ weeks' gestation. Obstetric history included a miscarriage at 10 weeks. After an uneventful pregnancy, delivery occurred at home and was uncomplicated, with a birthweight of 2810 g and Apgar scores of 10 and 10 at 1 and 5 minutes. A couple of hours after delivery the infant was brought to the hospital because of petechiae and hematomas. Laboratory examination revealed a very severe thrombocytopenia (PLT count, $2 \times 10^9/L$), which did not improve after emergency transfusion with random PLTs. The evaluation presented no evidence for neonatal infection. The clinical situation worsened, demonstrated by the occurrence of a large amount of bloody stool and acute abdominal distension. A laparotomy was performed, which demonstrated extensive gastrointestinal and intra-abdominal hemorrhage. After surgery the clinical condition remained unstable with hypotension, metabolic

acidosis, and progressive abdominal distension, leading to a second-look surgery involving extensive lavage and abdominal drain placement. Eventually, at 4 days of age, an irreversible shock resulted in neonatal death. Immunohematologic evaluation confirmed the presumed diagnosis of FNAIT caused by HPA-1a and HPA-5b alloantibodies.

Review of literature

Our initial search yielded a total of 1240 publications. Figure 1 shows a flowchart of the complete search strategy. After full-text screening, 16 articles containing 18 cases of neonates or fetuses with isolated severe extracranial bleeding complication caused by FNAIT, in absence of ICH, were identified (Table 1).

Genitourinary hemorrhage

Baber and colleagues⁷ described a case of postcircumcision bleeding at 2 days of age. After a neonatal circumcision uncontrolled bleeding occurred. PLT count was $5 \times 10^9/L$ and the diagnosis FNAIT was made. After treatment with intravenous immunoglobulins (IVIG) and PLT transfusions the bleeding stopped on Day 2. The infant made a complete recovery. As part of a retrospective cohort study, describing 20 cases of FNAIT, Cook and colleagues⁸ reported a case of scrotal bleeding caused by HPA-1a alloimmunization. The infant's PLT count was $7 \times 10^9/L$. Unfortunately despite PLT transfusion the hemorrhage led to the loss of a testicle.

Subgaleal hemorrhage

Two cases of subgaleal hemorrhages in neonates with FNAIT have been published.^{9,10} Borensztajn and

coworkers⁹ reported a 2-day-old infant with petechiae and a subgaleal bleeding after vacuum extraction. Only after an unfavorable response to a random PLT transfusion (PLT count, $13 \times 10^9/\text{L}$) was FNAIT suspected. After transfusion with HPA-1a-negative PLTs there was a full recovery. Davoren and coworkers¹⁰ described a neonate with subgaleal bleeding as part of a case-control study of 27 FNAIT cases. In this case, severe hypotensive shock occurred, requiring cardiorespiratory resuscitation. Eventually, a complete recovery was achieved.

Ocular hemorrhage

Ocular bleeding sites were illustrated by Davoren and colleagues¹⁰ as well as Jeronimo and Nomura and colleagues.¹² The first described a retinal bleeding occurring at the first day of life. After treatment with IVIG and a PLT transfusion, the infant made a complete recovery.¹⁰ Jeronimo and coworkers¹¹ described a premature neonate, born at 29 weeks' gestation, with proptosis and hyphema, along with a retinal bleeding (PLT count, $27 \times 10^9/\text{L}$). A random PLT transfusion was administered with a favorable response. However, PLTs decreased again after 5 days, resulting in suspicion of FNAIT. HPA-1a alloimmunization was discovered, and after two additional HPA-1a-negative PLT transfusions and a single dose of IVIG, PLT count increased and the intraocular hemorrhage decreased.

Intra-abdominal hemorrhage

Eight cases of severe intra-abdominal hemorrhage were described as a presentation of FNAIT, of which seven were gastrointestinal bleedings.¹³⁻²⁰ For the gastrointestinal hemorrhages a variety in accountable alloantibody as well in treatment was observed (Table 1). A relatively mild case was reported by Allen;¹⁷ after an uneventful pregnancy and delivery, the infant showed rectal bleeding at 2 days of age and the infant's PLT count was $41 \times 10^9/\text{L}$. A diagnosis of FNAIT due to HPA-5b alloimmunization was stated and without any treatment the hemorrhage ceased and PLT count increased. In contrast, Mokhtari and coworkers¹⁵ describe a more severe case of HPA-3a alloimmunization in which extensive treatment was necessary, eventually, resulting in a normal PLT count after 5 days. The other intra-abdominal hemorrhage was described by Paladini and coworkers,²⁰ a case of severe bilateral renal hemorrhage discovered on ultrasound in a fetus at 22 weeks' gestation. A broad panel of blood tests revealed HPA-5b alloimmunization. After extensive counseling the patient decided to terminate the pregnancy.

Pulmonary hemorrhage

Two pulmonary hemorrhages were reported, both part of larger cohort studies.^{18,21} Ghevaert and coworkers²¹ identified 123 new cases of FNAIT in their prospective cohort, including three cases of internal organ hemorrhages: gas-

trointestinal, retinal, and pulmonary. Only the pulmonary hemorrhage, caused by HPA-5b alloimmunization, occurred in absence of ICH. Kaplan and coworkers¹⁸ present the second case of pulmonary hemorrhage, part of a retrospective cohort of 39 HPA-5b alloimmunizations, occurring in a premature infant (delivered at 33 weeks' gestation). The outcome was favorable after treatment with red blood cell (RBC) and PLT transfusion together with IVIG and corticosteroids.

Spinal cord hemorrhage

Finally, a cervical spinal cord hemorrhage caused by FNAIT was described by Abel and colleagues²² in a full-term infant, born after cesarean section because of a non-reassuring fetal heart rate pattern with vacuum assistance for delivering the head. A PLT count of $2 \times 10^9/\text{L}$ together with skin manifestations implied FNAIT. Because of hypotonic upper extremities and severe head lag, magnetic resonance imaging was performed, revealing a hemorrhage in the medulla extending inferiorly into the spinal cord. After PLT transfusion and IVIG, PLT count increased. Unfortunately, at 6 weeks' follow-up, the infant continued to have upper-extremity weakness and hypotonia.

DISCUSSION

Although ICH is the most feared and well-known bleeding complication, FNAIT can have a wide variety of presentations. Symptoms can differ from isolated minor skin manifestations such as petechiae or purpura to massive and possible life-threatening organ hemorrhages. The most reported severe bleeding complication is ICH; hence the brain seems to be the most susceptible organ. Although the pathogenic mechanism is not fully understood, recently published data suggest that impairment of angiogenesis rather than thrombocytopenia causes these ICHs, possibly explaining the vulnerability of the fetal brain.²³ Although seldomly described in guidelines or review articles on FNAIT, the site of bleeding can conceptually be in all kinds of organs.

To our knowledge, we present the first case series and review of literature of severe internal organ hemorrhages other than ICH caused by FNAIT. A total of 21 cases, including three cases from our center, were identified. The overall incidence of extracranial hemorrhages per 100,000 live births cannot be calculated based on these numbers, retrospectively acquired from a selected population. The relative frequency of extracranial hemorrhage in relation to ICH found in this study is 0.12 (3/25). Therefore, either the proportion of bleedings in the brain in FNAIT is much larger than at other sites in the body or the bleeding in other organs is underreported. Our series shows that the consequences of bleeding in other organs than the brain can lead to severe morbidity and even mortality. Obviously, our study design does not permit any conclusion on

prevalence. Underestimation, in terms of both numbers and severity, seems to be likely. To gain more insight into incidence numbers and severity of bleeding complications in FNAIT a nationwide prospective cohort study is being set up by our center.

Clinicians need to be aware that FNAIT can also present as an extracranial hemorrhage in fetuses and neonates. Not only will this lead to a quicker diagnosis and targeted treatment, it will also lead to the ability of preventing FNAIT and bleeding complications in a possible subsequent pregnancy. This rationale is underlined by Fontão-Wendel and colleagues⁵ as well as Madani and coworkers.⁶ The latter reported a delayed or missed diagnosis in 15% of first affected children, retrospectively, in 26 FNAIT cases that were treated during a subsequent pregnancy. Fontão-Wendel and coworkers⁵ described a case of a firstborn with petechiae and a PLT count of $8 \times 10^9/L$, discharged without a diagnosis. A year later, pre-conceptional advice yielded immunohematologic evaluation, which showed a HPA-1a mismatch between mother and father, leading to adequate monitoring and treatment in the subsequent pregnancy.

Knowledge of a history with confirmed FNAIT not only provides the opportunity to apply additional diagnostics during the subsequent pregnancy, for example, determining fetal HPA genotype in case of paternal heterozygosity and monitoring the pregnancy and fetal brain by ultrasound. It also presents the ability to administer adequate treatment during pregnancy, to prevent the development of ICH and likely other bleeding. This is even more relevant now that the antenatal treatment strategy over the past years has changed from invasive to a safe and effective noninvasive weekly administration of IVIG.²⁴

In conclusion, FNAIT is the most common cause of thrombocytopenia in term neonates. The most feared and well-known bleeding complication is an ICH. However, this is not the only possible presentation of this disease. We have described the first case series strengthened by an extensive review of the literature of severe bleeding complications other than ICH as a first presentation of FNAIT. A wider scope when dealing with bleeding problems in full-term newborns and adequate diagnostics will result in adequate treatment and appropriate follow-up as well as antenatal treatment with IVIG, when applicable, in future pregnancies.

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and revised the manuscript; LK, JZ, and DO critically reviewed the manuscript; and EL conceptualized and designed the study and reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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