Long-term neurodevelopmental outcome in children after antenatal intravenous immune globulin treatment in fetal and neonatal alloimmune thrombocytopenia

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OBSTETRICS

Long-term neurodevelopmental outcome in children after antenatal intravenous immune globulin treatment in fetal and neonatal alloimmune thrombocytopenia

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BACKGROUND: Children with fetal and neonatal alloimmune thrombocytopenia face increased risk of intracranial hemorrhage potentially leading to developmental impairment. To prevent intracranial hemorrhage, pregnant women with alloantibodies against fetal platelets are often treated with intravenous immunoglobulin. Intravenous immunoglobulin seems effective in vastly reducing the risk of fetal or neonatal bleeding complications. However, information on long-term neurodevelopment of these children is lacking.

OBJECTIVE: This study aimed to evaluate long-term neurodevelopmental outcome in children with fetal and neonatal alloimmune thrombocytopenia who were treated with intravenous immunoglobulin antenatally.

STUDY DESIGN: An observational cohort study was performed, including children of mothers treated with intravenous immunoglobulin during pregnancy because a previous child was diagnosed with fetal and neonatal alloimmune thrombocytopenia. Children were invited for a follow-up assessment including standardized cognitive and neurologic tests. The parents were asked to complete a behavioral questionnaire and school performance reports. The primary outcome was severe neurodevelopmental impairment, defined as severe cognitive impairment (intelligence quotient <70), cerebral palsy with Gross Motor Function Classification System Level ≥3, bilateral blindness, and/or bilateral deafness (requiring amplification). The secondary outcome was mild to moderate neurodevelopmental impairment, defined as either mild to moderate cognitive impairment (intelligence quotient <85), cerebral palsy with Gross Motor Function Classification System Level ≤2, minor neurologic dysfunction, vision loss, and/or hearing loss.

RESULTS: Between 2003 and 2017, 51 children were live-born after antenatal intravenous immunoglobulin treatment. One family moved abroad and was therefore not eligible for inclusion. In total, 82% (41/50) of the eligible cases were included for neurodevelopmental assessment at a median age of 9 years and 8 months. Severe neurodevelopmental impairment was not detected. The incidence of mild to moderate neurodevelopmental impairment was 14% (6/41; 95% confidence interval, 6%–29%). The children's mean cognitive score, behavioral scores, and academic achievement were not different from those observed in the Dutch norm groups. Neuroimaging was performed in 90% (37/41) of cases. Severe intracranial hemorrhage was diagnosed in 2 cases (5%), one antenatally before the start of intravenous immunoglobulin and the other case 1 day after birth. Both cases had a normal neurodevelopmental outcome.

CONCLUSION: The risk of neurodevelopmental impairment in children whose mothers were treated for fetal and neonatal alloimmune thrombocytopenia with antenatal intravenous immunoglobulin is comparable to that reported in the general population.

Key words: fetal and neonatal alloimmune thrombocytopenia, fetal therapy, intravenous immune globulin, neurodevelopmental outcome

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a disease defined by maternal human platelet antigen (HPA)-directed alloantibodies. The maternal antibodies can induce severe thrombocytopenia and possibly damage the endothelial cell layer with an increased risk of fetal or neonatal intracranial hemorrhage (ICH), potentially leading to irreversible brain damage or perinatal death.[1–3] The recurrence rate of ICH in subsequent HPA-incompatible pregnancies is up to 72%.[4] The mainstay of antenatal treatment of FNAIT to reduce the bleeding risk in the unborn child is weekly administration of intravenous immunoglobulin (IVIg) to the pregnant woman.[5,6] In the absence of a screening program, this treatment is almost exclusively given to women who had a previous pregnancy complicated by FNAIT.[7] The exact mechanism of maternal IVIg treatment is not completely understood. It is hypothesized that IVIg treatment leads to lower pathogenic IgG transport from mother to fetus.[8,9]

Although virtually every guideline worldwide recommends IVIg treatment, the use of IVIg during pregnancy is currently still off-label.[6] The efficacy in the reduction of the risk of ICH seems to be very high,[5] although no placebo-controlled studies have been done. The lack of understanding of the mechanism of action of IVIg raises some concerns about its widespread use and safety in FNAIT. Adverse maternal effects of IVIg include but are not limited to headache, rash, fatigue, hemolytic anemia, renal failure, pancytopenia, and aseptic meningitis.[10,11] Whether IVIg may also have adverse effects in fetuses, including long-term side effects and

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AJOG at a Glance

Why was this study conducted?

In fetal and neonatal alloimmune thrombocytopenia (FNAIT), administration of intravenous immune globulin (IVIg) to the mother during pregnancy is widely accepted for preventing the occurrence of antenatal or perinatal intracranial hemorrhage (ICH) in the child. However, knowledge about the long-term neurodevelopmental outcomes of these children is lacking.

Key findings

Mild to moderate neurodevelopmental impairment was present in 6 of 41 (14%) children. Two children were diagnosed with severe ICH. Both had normal neurodevelopmental outcomes.

What does this add to what is known?

Neurodevelopmental outcomes of children with FNAIT born after a pregnancy in which their mother was treated with IVIg are comparable to those reported in the general population.

neurodevelopmental impairment, is not well known.

Thus far, only 2 small cohort studies have assessed the long-term neurodevelopmental outcomes of children with FNAIT after antenatal treatment.[12,13] These studies concluded that long-term outcomes of these children were favorable. However, the interpretation of the studies was hampered by methodological limitations: substantial loss to follow-up, remote developmental assessment, and heterogeneous study population.[12,13] Knowledge of long-term outcomes is essential to evaluate and improve the current quality of care and in evidence-based counseling of parents, particularly because children with FNAIT are at risk for ICH and its associated neurologic sequelae. FNAIT survivors have a 70% to 82% risk of lifelong sequelae (eg, delayed development, cerebral palsy, cortical blindness, or seizures) as a result of ICH.[14,15]

This study aimed to assess long-term neurodevelopmental outcomes in children with FNAIT who were treated with IVIg during pregnancy. In addition, we assessed behavioral difficulties and school performance reports.

Materials and Methods

Study population

The Leiden University Medical Center (LUMC) is the national clinical expertise center in the Netherlands for platelet alloimmunization in pregnancy. Children of mothers referred to LUMC between 2003 and 2017 and who were treated with IVIg because of a risk of FNAIT were eligible for this study. FNAIT was diagnosed if there was a clinical suspicion in a previous pregnancy (neonatal platelet count $<150\times10^9$/L and/or [fetal] ICH or organ bleeding), confirmed fetal−maternal HPA incompatibility, and presence of HPA-directed antibodies in the maternal plasma.[16] Exclusion criteria for long-term follow-up examination were severe congenital abnormalities unrelated to FNAIT or the family moving abroad. Weekly maternal IVIg treatment was administered according to the clinical guidelines: 0.5 g/kg/wk from 28 weeks of gestation in standard-risk pregnancies (without history of ICH or organ bleeding) and 1.0 g/kg/wk starting between 16 and 20 weeks of gestation in high-risk pregnancies (with a history of ICH or organ bleeding).[7] Cesarean delivery was not recommended as a standard delivery mode in HPA-immunized pregnancies. For standard-risk pregnancies with a previous vaginal delivery, planned induction of labor was considered to be safe. Between January 2005 and September 2007, treatment was given according to the study protocol of a randomized trial in standard-risk pregnancies comparing low-dose IVIg (0.5 g/kg/wk) with standard-dose IVIg (1.0 g/kg/wk) starting at 28 weeks of gestation.[17]

Ethics

The medical ethical committee of Leiden-Delft-Den Haag provided ethical approval (P19.069). All parents and children (aged ≥12 years) gave written informed consent. This study was registered at ClinicalTrials.gov (identifier: NCT04529382).

Clinical data

The following obstetrical data were obtained from medical records: gravidity, parity, antenatal treatment, mode of delivery, specificity of the HPA alloantibody, and gestational age at delivery. Data on the occurrence of ICH or organ bleeding in previous children were also noted. The following neonatal data were obtained: platelet count nadir, postnatal treatment and bleeding symptoms, birthweight, sex, and neonatal morbidity. Two experienced neonatologists specialized in neonatal neurology (S.S. and L.V.) reviewed cerebral imaging and cerebral imaging reports. Severe ICH was defined as intraventricular hemorrhage (IVH) grade III or IV or ICH with parenchymal involvement visible on cranial ultrasound. Minor ICH was defined as IVH grade I or II.[18] Severe organ bleeding was defined as organ bleeding requiring supportive care (eg, ventilation in case of a pulmonary bleed).

Neonatal morbidity was defined as the presence of 1 of the following conditions: perinatal asphyxia (5-min Apgar score <7 or arterial cord blood pH <7.0), neonatal sepsis (clinical suspicion of infection and positive blood culture), or necrotizing enterocolitis.[19] Small for gestational age (SGA) was defined as birthweight below the 10th percentile.[20]

Maternal education levels were obtained from a demographic questionnaire and categorized according to the Dutch Social and Cultural Planning Office (in Dutch: Sociaal en Cultureel Planbureau).[21] All data were collected in a secure online database.[22]

Procedures

We first sent introduction letters to the parents, explaining the purpose of the study, followed by a phone call. If informed consent was obtained, an appointment for follow-up assessment either at home or at our outpatient clinic was made. Neurodevelopmental assessment consisted of a standardized cognitive test and neurologic examination. Parents were requested to complete a questionnaire on their child's behavior and to obtain school performance scores from their child's teachers.

Cognitive development in children aged 3 to 6 years was assessed using the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition (WPPSI-IV-NL).[23] Cognitive development in children aged between 7 and 17 years was assessed using the Dutch version of the Wechsler Intelligence Scale for Children—Fifth Edition (WISC-V-NL).[24]

Neurologic functioning was examined with the adapted version of the Touwen examination for evaluating minor neurologic dysfunction (MND).[25] This examination is divided into the following domains: posture, reflexes, involuntary movements, coordination, fine manipulative ability, associated movements, sensory deficits, and cranial nerve function. With 1 dysfunctional domain, the outcome is classified as simple MND. If ≥2 clusters are dysfunctional, the outcome is classified as complex MND. The presence and grade of cerebral palsy (CP) was determined using the Gross Motor Function Classification System (GMFCS).[26]

To investigate behavioral problems, parents completed the Child Behavior Checklist for 1.5 to 5 years or 6 to 18 years.[27] Standard T scores were created using a Dutch normative sample. These scores compare the raw score with what would be "normal" responses for children of the same age and sex. The T scores of the normative sample are scaled with a mean of 50 and a standard deviation (SD) of 10. Higher scores indicate a greater severity of problems. For each broadband scale of internalizing, externalizing, and total behavior problems, T scores can be interpreted as on the borderline (T=60−63, 84th−90th percentile) or in the clinical range (T≥64, ≥91st percentile).

For children aged >6 years, school performance reports were obtained from the Dutch National Pupil Monitoring System (Cito, Arnhem, the Netherlands) for the following categories: reading comprehension, spelling, and arithmetic/mathematics.[28] Individual scores were compared with age-matched peers and categorized into levels I to V, with level I being the top 20% scoring children and level V being the lowest 20% scoring children.

Outcomes

The primary outcome was the incidence of severe neurodevelopmental impairment (NDI). NDI is a composite outcome consisting of 4 different domains: cognitive functioning, vision, hearing, and neurologic functioning. Severe NDI was defined as the presence of 1 of the following criteria: severe cognitive impairment (intelligence quotient [IQ] <70 [−2 SD]), CP GMFCS level ≥3, bilateral blindness, and/or bilateral deafness (requiring amplification).[26] The secondary outcome was mild to moderate NDI, defined as the presence of 1 of the following criteria: mild to moderate cognitive impairment (IQ <85 [−1 SD]), CP GMFCS level 1 or 2, MND, vision loss, or hearing loss.[26] Other outcomes were cognitive test scores (IQ) compared with Dutch norm scores and overall adverse outcomes including severe NDI and/or perinatal mortality. In addition, we report the incidence of simple and complex MND, borderline and clinical behavior problems, and school performance scores.

Statistical analyses

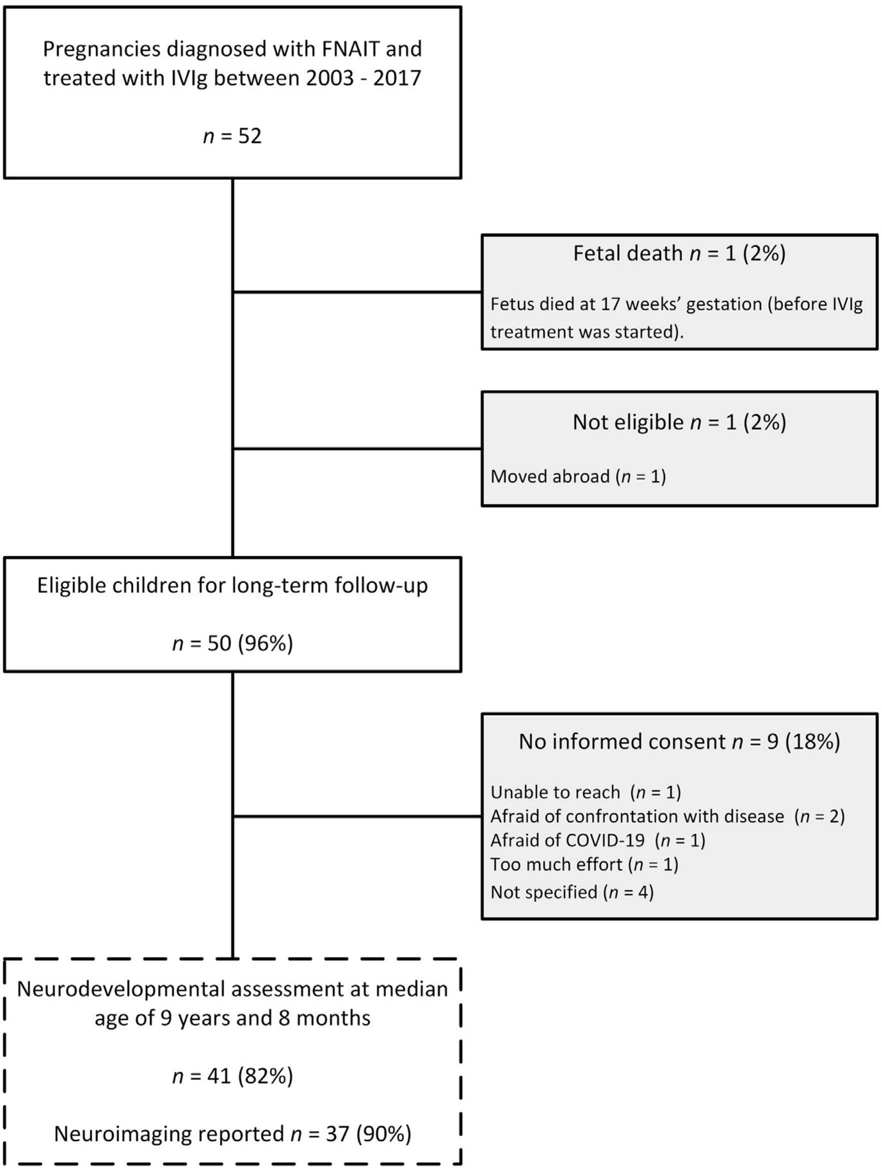
Descriptive results are presented as the number of cases with percentages, mean with SD, or median with interquartile range, depending on the data type and distribution. Proportions of outcomes are presented with 95% confidence intervals (CIs). The mean IQ scores were compared with Dutch norm data with a 1-sample *t* test. The presence of behavioral problems and school performance scores were compared with the Dutch norm data using binomial tests. Data were analyzed using IBM SPSS Statistics software, version 26.0 (IBM, Armonk, NY). Images were created with Microsoft Visio (Microsoft Corporation, Redmond, WA). To examine selection bias, we compared the clinical characteristics of the included cases and the cases that were lost to follow-up.

Results

Study population

The Figure shows the study population. One pregnancy complicated by HPA antibodies ended in fetal demise unrelated to FNAIT at 17 weeks of gestation. Autopsy revealed no signs of bleeding. Informed consent was obtained in 82% (41/50) of the eligible cases. Table 1 shows the characteristics of the included children (41 cases). In 12% (5/41) of cases, there was a history of severe ICH or organ bleeding in a previous pregnancy-three siblings were diagnosed with severe ICH, one with pulmonary bleeding and one with severe gastrointestinal bleeding. Clinical characteristics at birth of the included cases were comparable to those of children that were lost to follow-up (Supplemental Table). In 75% (30/40) of cases, the pregnant woman received standard-dose IVIg (0.5 g/kg/wk), and in 25% (10/40) of the cases high-dose IVIg (1 g/kg/wk); in 1 case, the dose was not reported. None of the pregnant women were treated with corticosteroids. Fetal blood sampling was not performed. In total, 34% (14/41) of the children were delivered by cesarean delivery, in 1 case because of suspected placental abruption at 31 weeks of gestation. The median gestational age at delivery was 37 weeks and 5 days, with median birthweight of 3280 g. No neonatal morbidities occurred. The median platelet count nadir at birth was 65×10^9/L (minimum 6×10^9/L; maximum 382×10^9/L). In 14 (34%) cases, the nadir was $<25\times10^9$/L, and in 18 (43%) cases, the nadir was $<50\times10^9$/L.

FIGURE
Study population



Flowchart of the study population.

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Neuroimaging

Postnatal neuroimaging was performed in 90% (37/41) of the cases. Cranial ultrasound was performed in 92% (34/37) of these cases, and 8% (3/37) underwent both cranial ultrasound and magnetic resonance imaging (MRI). Two infants (3%, 2/37) were diagnosed with severe ICH. In 1 such infant, parenchymal bleeding was detected on fetal ultrasound 1 week before the planned start of IVIg treatment at 27 weeks of gestation. Antenatal treatment (high-dose) was started directly and the bleeding remained stable on ultrasound. At 36 weeks of gestation, a cesarean delivery was performed. Postnatally, the bleeding was classified as severe ICH. In the second case with severe ICH, a round intraparenchymal lesion in the left frontal lobe was detected on neonatal ultrasound. This lesion was suspected to be intraparenchymal hemorrhage and therefore classified as severe ICH. The postnatal platelet count of this infant was 382×10^9/L. Neonatal MRI was not performed. A previous child in this family had severe gastrointestinal bleeding because of FNAIT. Besides this family in which the mother delivered an infant with ICH after the previous child had a severe gastrointestinal bleeding, severe bleeding did not reoccur in other pregnancies. In addition to the 2 cases of severe ICH, minor ICH was diagnosed in 1 child (3%, 1/37); IVH grade II was suspected on cranial ultrasound and confirmed with MRI.

Long-term neurodevelopmental outcomes

Table 2 shows the long-term neurodevelopmental outcomes of 41 children at a median age of 9 years and 8 months (minimum: 4 years and 5 months; maximum 16 years and 2 months). Of the 40 children who underwent cognitive assessment, 6 (15%) were tested using the WPPSI-IV-NL (mean IQ score, 106 [SD, 6]) and 34 (85%) using the WISC-V-NL (mean IQ score, 103 [SD, 11]). The mean full IQ score of the total cohort was 104 (SD, 11), higher than that of their Dutch peers (P=.042; mean difference, 3.6). Three children had mild to moderate cognitive impairment (IQ score, 70–85). The neurologic examination of the children showed that simple MND was present in 10% (4/40) of the children. Severe NDI was not detected, nor was perinatal mortality. The incidence of mild to moderate NDI was 14% (6/41; 95% CI, 5.6%–29%). Table 3 shows the details of the cases with mild to moderate NDI. All 3 cases with ICH (2 severe and 1 mild) had normal neurodevelopment.

Behavioral functioning and school performance

The internalizing, externalizing, and total behavior scores of the included children were comparable to Dutch norm data. School performance scores were available for 85% (35/41) of the children; 6 children were aged <6 years. One child with mild-to-moderate NDI in our study population required

TABLE 1
Clinical and demographic characteristics of the fetal and neonatal alloimmune thrombocytopenia cases

Characteristics	Variable	n=41
Diagnostics	HPA specificity, n (%)	
	HPA-1a	33 (80)
	HPA-5b	4 (10)
	Other	4 (10)
Pregnancy	First pregnancy, n (%)	0
	Severe hemorrhage in previous pregnancy, n (%)	5 (12)
	Signs of fetal bleeding on ultrasound, n (%)	1 (2)
	Maternal IVIg treatment, n (%)	41 (100)
Neonatal	Gestational age at delivery, wk^{+d}, median (IQR)	37^{+5} (37^{+2}–38^{+3})
	Female sex, n (%)	21 (51)
	Birthweight, gram, median (IQR)	3210 (2838–3427)
	SGA (birthweight <10th percentile), n (%)	2 (5)
	Skin bleeding, n (%)	10 (24)
	Intracranial hemorrhage, n/N (%)[a]	3/37 (8)
	Minor: IVH grade I – II	1/37 (3)
	Severe: parenchymal	2/37 (5)
	Platelet count nadir $\times 10^9$/L, median (IQR)	65 (20–161)
	Platelet count $<25\times10^9$/L, n (%)	14 (34)
	Postnatal treatment given, n (%)	14 (34)
Demographics	Maternal education, n (%)	
	Primary and secondary school	3 (7)
	Intermediate vocational education	13 (32)
	High vocational education or university	25 (61)

FNAIT, fetal and neonatal alloimmune thrombocytopenia; *HPA*, human platelet antigen; *IQR*, interquartile range; *IVH*, intraventricular hemorrhage; *IVIg*, intravenous immune globulin; *SGA*, small for gestational age.

[a] Neuroimaging was not performed in 4 of 41 (10%) of the cases.

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special-needs education. Compared with the Dutch norm population, fewer children scored in our cohort in the lowest (level V) range for reading comprehension (6% [2/35] vs 20%; P=.019) and mathematics (3% [1/35] vs 20%; P<.001). Nine percent (3/35) of the children scored in the lowest range (level V) for spelling.

Comment

Principal findings

This is the first study to use standardized psychometric tests to assess the long-term neurodevelopmental outcomes of children whose alloimmunized mothers were treated with IVIg for FNAIT. Of the 41 children included, none had severe NDI. Mild to moderate NDI was diagnosed in 3 cases (7%) because of mild to moderate cognitive impairment. Simple MND was detected in 10% of the cases. All cases with ICH had normal neurodevelopmental outcomes. Behavior problem scores were within the normal range. Compared with Dutch norm scores for academic achievement, fewer children in our cohort scored at the lowest level for mathematics and reading comprehension.

Results in the context of what is known

To date, only 2 cohort studies reported the long-term neurodevelopmental outcomes of children born after antenatal FNAIT treatment. Ward et al[13] suggested better neurodevelopmental outcomes in 71 children who received antenatal treatment than in 71 untreated siblings. However, the investigators performed telephone surveys only, and their conclusions were hampered by a substantial (37%) loss-to-follow-up rate. Another study evaluated the neurodevelopmental outcomes after antenatal treatment of 37 children born with FNAIT and found them to be similar to those observed in the normal population.[12] An important limitation of this study was the large heterogeneity in fetal management strategies, including intrauterine platelet transfusion, IVIg treatment, or both. Our loss-to-follow-up rate was low, and we avoided the important limitations of these 2 studies by studying a cohort that received similar antenatal treatment, and by performing standardized neurodevelopmental tests in all participants. Compared with the general Dutch population, our study cohort had higher cognitive test scores. However, the mean difference of 3.6 IQ points is not clinically relevant because this difference is <+0.5 SD (7 IQ points) compared with the national average.[16] The relatively high proportion of mothers with a high education level (61% vs 41% in the Dutch general population) could explain the slightly higher IQ scores in our cohort.[13] The rate of simple MND (4/40; 10%) was comparable to the rates observed in a healthy population, with 10% at preschool age and up to 15% at school age (9-years-old).[26,29]

An intriguing finding, in contrast to literature,[21] was the absence of NDI in the 3 children who were diagnosed with ICH as fetuses or neonates. The most severe ICH occurred before IVIg treatment was started, at 27 weeks of gestation. In our current protocol, the standard-risk pregnancies start treatment with IVIg at 24 weeks. The other 2 children had milder forms of

TABLE 2
Neurodevelopmental outcome of antenatally treated fetal and neonatal alloimmune thrombocytopenia cases

Outcome	Variable	n=41
	Age, y mo, median (IQR)	9 y 8 mo (7 y 5 mo–11 y 8 mo)
Cognitive	Full IQ scale, mean (±SD)[a]	104 (11)
	Verbal comprehension	106 (14)
	Visual spatial score	103 (12)
	Fluid reasoning scale	102 (12)
	Working memory score	99 (12)
	Processing speed	103 (16)
	Normal range (TIQ >85), n (%)[b]	38 (93)
	Mild-moderate impairment (TIQ, 85–70)	3 (7)
	Severe cognitive impairment (TIQ <70)	0
Neurologic	MND, n/N (%)[c]	
	Simple MND	4/40 (10)
	Complex MND	0
	Abnormal domain, n/N (%)	
	Posture	1/40 (3)
	Reflexes	2/40 (5)
	Involuntary movements	2/40 (5)
	Coordination	2/40 (5)
	Fine manipulative ability	0
	Associated movements	1/40 (3)
	Sensory deficits	1/40 (3)
	Cranial nerve function	1/40 (3)
	Cerebral palsy, n (%) Bilateral blindness or deafness	0 0
Behavior	Total behavior problems (borderline to clinical), n (%)	2 (2)
	Internalizing behavior problems (borderline to clinical), n (%)	3 (7)
	Externalizing behavior problems (borderline to clinical), n (%)	2 (5)
NDI	Neurodevelopmental impairment (NDI), n (%)	
	Normal	35 (85)
	Mild-moderate NDI	6 (15)
	Severe NDI	0

FNAIT, fetal and neonatal alloimmune thrombocytopenia; *IQR*, interquatile range; *MND*, minor neurologic dysfunction; *NDI*, neurodevelopmental impairment; *SD*, standard deviation; *TIQ*, total intelligence quotient.

[a] Cognitive test was not done in 1 of 41 (2%) anticipated FNAIT cases; [b] On the basis of the information of the school results and questionnaires that were completed by the caregivers, cases with missing cognitive test scores were normal; [c] Neurologic test was not completed in 1 of 41 (2%) anticipated FNAIT cases.

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bleeding, possibly even unrelated to FNAIT. Whether the IVIg may have had a protective effect on the vascular endothelium, as suggested by some recent studies, cannot be concluded from our data.[1–3]

Despite weekly IVIg infusion, approximately 40% of the children were born with a platelet count $<50\times10^9$/L. This was in line with previous retrospective studies that reported that up to 67% of neonates had a platelet count $<50\times10^9$/L after IVIg-treated pregnancies.[5] These cases with severe thrombocytopenia despite antenatal IVIg treatment are sometimes referred to as "nonresponders," whereas some colleagues suggest that this occurs because the dose of IVIg was too low in these cases.[30] The current study was not designed to provide explanations for this phenomenon.

Clinical implications

This study used standardized tests to address the long-term neurodevelopmental outcomes of children treated antenatally for FNAIT, demonstrating that the risk of severe NDI in this population is low. An earlier cohort study[14,15] performed by our group reported severe and mild to moderate NDI in 60% and 10% of survivors with severe ICH because of untreated FNAIT, respectively.[21] These findings are in line with another study reporting neurologic sequelae in 82% of surviving FNAIT cases with ICH.[27] Both studies underline the importance of preventing ICH in pregnancies complicated by FNAIT. Currently, FNAIT is predominantly diagnosed in cases with thrombocytopenia as a chance finding or in cases with unexpected fetal or neonatal bleeding. In subsequent pregnancies, antenatal IVIg therapy seems to work exceptionally well, although adequate placebo-controlled studies are lacking. To prevent all ICH and its associated neurodevelopmental injury, it would be necessary to timely start IVIg treatment in pregnancies at risk for FNAIT with a high risk of severe neonatal outcome. Perhaps this would be possible with a long-debated population-based screening program. However, the efficacy of IVIg in such a cohort of first immunizations has not been studied; this would require setting up a screening program first. In addition to evaluating the long-term outcomes of

TABLE 3
Characteristics of cases with mild to moderate neurodevelopmental impairment

Sex	GA at birth (wk)	SGA	Platelet count <25×10^9/L	Neuroimaging (cranial ultrasound)	HPA	Age at evaluation (y)	TIQ	Neurologic examination; abnormal domain	Behavior total problem score (CBCL)	School
Male	34	Yes	Yes	No abnormalities	HPA-1a	9	73	Simple MND; sensory	Normal	Special-needs education
Female	37	No	No	No abnormalities	HPA-1a	10	78	Normal	Normal	Regular education
Female	37	No	No	No abnormalities	HPA-1a	9	84	Normal	Normal	Regular education
Male	38	No	No	Not available	HPA-1a	8	89	Simple MND; coordination	Normal	Regular education
Male	38	No	No	No abnormalities	HPA-1a	9	112	Simple MND; coordination	Normal	Regular education
Female	37	No	No	No abnormalities	HPA-15a	10	112	Simple MND; posture	Normal	Regular education

CBCL, Child Behavioral Checklist; *GA*, gestational age; *HPA*, human platelet antigen; *MND*, minor neurologic dysfunction; *SGA*, small for gestational age; *TIQ*, total intelligence quotient.

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children that were treated with IVIg, it would be interesting to assess the outcomes of children newly diagnosed with FNAIT. A study from our research group on the long-term outcomes of children with newly diagnosed FNAIT both with and without ICH is in preparation.

In addition to being indicated for FNAIT, antenatal IVIg treatment is also indicated for several other diseases, such as hemolytic disease of the fetus and neonate, gestational alloimmune liver disease, antiphospholipid syndrome, and immune thrombocytopenia.[31] Because of major differences in pathophysiology between FNAIT and these other diseases, it is not possible to generalize the favorable long-term outcomes of our study population to pregnancies with these conditions. However, the results from our study indicate that administration of IVIg during pregnancy did not have a negative impact on the cognitive, neurologic, and behavioral development of the children studied.

Strengths and limitations

The major strength of our study is that all children underwent standardized assessment of cognitive, neurologic, and behavioral development, including school performance scores, which provides an integrated view of these children's neurodevelopmental outcomes. This cohort is the largest FNAIT cohort with antenatal IVIg treatment that has been assessed using standardized tests.

One limitation of this study is that we were unable to include all children in our follow-up (18% of the cases were lost to follow-up). However, our analysis showed that the clinical characteristics of the lost-to-follow-up group were similar to those of the children included in our study.

Conclusions

Normal distribution in cognitive, neurologic, and behavioral development and school performance can be expected in children whose mothers have been treated with IVIg for FNAIT during pregnancy. ■

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SUPPLEMENTAL TABLE

Comparison of the characteristics of cases that were included with those of cases that were lost to follow-up

Characteristics	Anticipated cases: Included cases n=41	Anticipated cases: Lost to follow-up n=9
HPA specificity, n (%)		
HPA-1a	33 (80)	6 (67)
HPA-5b	4 (10)	1 (11)
Other	4 (10)	2 (22)
Gestational age at delivery, median (IQR)[a]	37^{+5} (37^{+2}—38^{+3})	38^{+0} (37^{+1}—39^{+2})
First pregnancy, n (%)	0	0
Female sex, n (%)	21 (51)	6 (87)
Birthweight, g, median (IQR)[a]	3210 (2838—3427)	3116 (2645—3385)
SGA, n/N (%)[a]	2/41 (5)	1/7 (14)
Platelet count nadir, median (IQR)[a]	65 (20—164)	88 (50—247)
Skin bleeding, n/N (%)[a]	10/41 (24)	0/7 (0)
Severe ICH, n (%)	2/41 (5)	0
Postnatal therapy, n (%)[a]	14/41 (34)	1/7 (14)

Characteristics of the included cases were compared with those of the cases that were lost to follow-up. Analysis was performed using the Mann—Whitney *U* test (gestational age, birthweight, and platelet count) or the Fisher exact test (categorical variables). No statistically significant differences ($P<.05$) were found.

HPA, human platelet antigen; *ICH*, intracranial hemorrhage; *IQR*, interquartile range; *SGA*, small for gestational age.

[a] Data available for 7 of 9 (78%) of the cases that were lost to follow-up.

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