Children newly diagnosed with fetal and neonatal alloimmune thrombocytopenia: neurodevelopmental outcome at school age

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Children Newly Diagnosed with Fetal and Neonatal Alloimmune Thrombocytopenia: Neurodevelopmental Outcome at School Age

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Objective To evaluate the neurodevelopmental outcome at school age in children newly diagnosed with fetal and neonatal alloimmune thrombocytopenia (FNAIT).

Study design This observational cohort study included children diagnosed with FNAIT between 2002 and 2014. Children were invited for cognitive and neurological testing. Behavioral questionnaires and school performance results were obtained. A composite outcome of neurodevelopmental impairment (NDI) was used, defined, and subdivided into mild-to-moderate and severe NDI. Primary outcome was severe NDI, defined as IQ <70, cerebral palsy with Gross Motor Functioning Classification System level ≥ III, or severe visual/hearing impairment. Mild-to-moderate NDI was defined as IQ 70-85, minor neurological dysfunction or cerebral palsy with Gross Motor Functioning Classification System level ≤ II, or mild visual/hearing impairment.

Results In total, 44 children were included at a median age of 12 years (range: 6-17 years). Neuroimaging at diagnosis was available in 82% (36/44) of children. High-grade intracranial hemorrhage (ICH) was detected in 14% (5/36). Severe NDI was detected in 7% (3/44); two children had high-grade ICH, and one had low-grade ICH and perinatal asphyxia. Mild-to-moderate NDI was detected in 25% (11/44); one child had high-grade ICH, and eight children were without ICH, yet for two children, neuroimaging was not performed. Adverse outcome (perinatal death or NDI) was 39% (19/49). Four children (9%) attended special needs education, three of whom had severe NDI and one had mild-to-moderate NDI. Total behavioral problems within the clinical range were reported in 12%, which is comparable with 10% in the general Dutch population.

Conclusion Children who are newly diagnosed with FNAIT are at increased risk for long-term neurodevelopmental problems, even those without ICH. *(J Pediatr 2023;258:113385)*.

Trial registration The study was registered at ClinicalTrials.gov (Identifier: NCT04529382).

Fetal and neonatal alloimmune thrombocytopenia (FNAIT), the platelet equivalent of hemolytic disease of the fetus and neonate, can cause severe bleeding in children during pregnancy and shortly after delivery. This risk of bleeding is caused by maternal platelet-directed alloantibodies that are actively transported across the placenta during pregnancy.

These antibodies result in platelet destruction and possibly interfere with endothelial cells[1] in the fetus/neonate, resulting in a risk of bleeding. Intracranial hemorrhage (ICH) occurs in 10%-25% of the cases with severe thrombocytopenia and can be effectively prevented by antenatal treatment.[2,3] However, in the absence of antenatal screening for platelet alloantibodies, FNAIT is often diagnosed postnatally when bleeding symptoms are present, or thrombocytopenia is detected as a finding by chance. Effective antenatal treatment is currently only given in subsequent pregnancies.[3-5]

Knowledge on long-term outcome of children with FNAIT is scarce. Previous studies primarily addressed the neurodevelopment of children after antenatal treatment for FNAIT,[6] mainly focused on cases with ICH,[7-10] or based their conclusions on questionnaire surveys.[11] It is important to evaluate neurodevelopment of children only treated after diagnosis of FNAIT and who did not have

CP	Cerebral palsy	IVIg	Intravenous immunoglobulin
FNAIT	Fetal and neonatal alloimmune thrombocytopenia	MND	Minor neurological dysfunction
GMFCS	Gross Motor Functioning Classification System	NDI	Neurodevelopmental impairment
HPA	Human platelet antigen	SGA	Small for gestational age
ICH	Intracranial hemorrhage	WISC	Wechsler Intelligence Scale for Children
IVH	Intraventricular hemorrhage	LUMC	Leiden University Medical Center

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signs of ICH. This knowledge is crucial to provide adequate follow-up care for children affected by FNAIT and to judge the potential need for an FNAIT screening program.

The present study evaluates the long-term neurodevelopmental outcome of children newly diagnosed with FNAIT. In addition, behavioral difficulties and school performance reports were assessed.

Methods

Participants

All children newly diagnosed with FNAIT between 2002 and 2014 and referred to the Leiden University Medical Center (LUMC) who survived the neonatal period were eligible for study participation. The LUMC is the national clinical expertise center for FNAIT in the Netherlands. FNAIT was diagnosed based on clinical suspicion with a neonatal platelet level of $<150 \times 10^9$/L and/or bleeding complications, confirmed fetal-maternal human platelet antigen (HPA) incompatibility, and the presence of maternal HPA-specific alloantibodies.[12] Children who died perinatally were excluded. Other exclusion criteria were congenital abnormalities not related to FNAIT and the family having moved abroad. The Medical Ethics Committee of Leiden, Delft, The Hague approved the study (P19.069). Written informed consent from all parents or caregivers was obtained. All children provided assent. If children could not assent, parents were asked for permission, and the study was conducted unless children opposed participation. The study was registered at ClinicalTrials.gov (Identifier: NCT04529382).

When informed consent was obtained, a one-time follow-up examination was planned, consisting of taking the history, a neurological examination, and a standardized intelligence test, either at home or at the outpatient clinic of the LUMC. Parents were asked to complete a questionnaire on their child's behavior and to share school performance results. Three cases were also included and described in a previous study that examined the long-term development of children with FNAIT.[7]

Methods of Measurement

The following maternal, obstetrical, and neonatal characteristics were obtained from the medical records: gravidity, parity, gestational age at birth (weeks plus days), birth weight (grams), neonatal sex, lowest platelet count, HPA alloantibody specificity, reason for suspecting FNAIT, postnatal treatment, bleeding symptoms, neonatal morbidity including perinatal asphyxia (5-minute Apgar score <7 or arterial blood cord pH <7.0) and/or neonatal sepsis (clinical suspicion of infection and positive blood culture), and cerebral imaging report. If the report of the cerebral ultrasound described abnormalities, the images were retrieved and re-evaluated by neonatologists specialized in neonatal cerebral imaging. All scans were scored for ICH, including intraventricular hemorrhage (IVH) and/or parenchymal hemorrhage. IVH was classified as any blood in the ventricular system with a distinction between low grade (small IVH without associated ventricular dilatation) and high grade (large IVH with associated ventricular dilatation or periventricular hemorrhagic infarction). Parenchymal hemorrhage was classified with a distinction between low-grade parenchymal hemorrhage (hemorrhagic lesions in the brain parenchyma/cerebellum ≤4 mm) and high-grade parenchymal hemorrhage (lobar hemorrhages). High-grade ICH was defined as either high-grade IVH or high-grade parenchymal hemorrhage. Low-grade ICH was defined as low-grade IVH or low-grade parenchymal hemorrhage. Organ bleeding that required supportive care was classified as severe organ bleeding.

Cognitive development was assessed with the Wechsler Intelligence Scale for Children, fifth edition (WISC-V-NL).[13] The WISC generates a Full Scale IQ score representing a child's general intellectual ability. The Full Scale IQ is based on a standard score metric with a mean of 100 and a SD of 15. In the Dutch norm population, 13.6% have mild-to-moderate cognitive impairment (IQ: 70-85, [-1 SD]), and 2.2% have severe cognitive impairment (IQ <70, [-2 SD]).[13] In case of problems in language and speech development and communication, the Snijders-Oomen nonverbal intelligence test was performed.[14]

Neurological examination was performed according to the adapted version of the Touwen examination, which aims to detect minor neurological dysfunction (MND) and addresses eight neurological domains.[15] Before puberty, the severity of MND, simple or complex, is based on the number of abnormal domains, whereas after puberty, it is based on specific abnormal domains.[16] The level of cerebral palsy (CP) was classified using the Gross Motor Functioning Classification System (GMFCS)[17] where a score of 2 or higher was categorized as CP. If lower, a child was categorized as having minor neurologic dysfunction.

Behavioral functioning was assessed using the Child Behavior Checklist for 6-18 years.[18] In the present study, internalizing problems score (anxious and depressive symptoms, social withdrawal, and somatic complaints), externalizing problems score (rule-breaking and aggressive behavior), and total problems score were assessed. The Child Behavior Checklist scoring system creates a T score based on a Dutch normative sample with a mean of 50 and SD of 10, which was interpreted as within the normal (T <60, <84th percentile), borderline (T = 60-63; 84th–90th percentile), or clinical range (T ≥64; ≥91st percentile).

School performance results were obtained for reading comprehension, spelling, and arithmetic/mathematics according to the Dutch National Pupil Monitoring System (CITO).[19] These results were compared with peers and graded as I through V. Grade I represents the 20% highest scoring children, and grade V represents the 20% lowest scoring children. Additionally, the proportion of children that needed special education was reported.

Outcomes

The primary outcome measure was the prevalence of severe neurodevelopmental impairment (NDI), defined as at least one of the following: severe cognitive impairment (IQ <70, [-2 SD]), CP GMFCS level ≥ III, bilateral blindness, and/or bilateral deafness requiring amplification. Secondary outcome measures were mild-to-moderate NDI, total behavioral problem score, school performance, and the overall adverse outcome defined as NDI or perinatal mortality. In addition, we compared the risk of severe NDI between cases with and without ICH. Mild-to-moderate NDI was defined as the presence of one of the following criteria: mild-to-moderate cognitive impairment (IQ: 70-85, [-1 SD]), CP GMFCS level I or II, MND, vision loss, and/or hearing loss.

Data Analyses

Data are presented as frequencies and percentages for categorical variables and as means with SD or medians with IQR for continuous variables. The mean IQ score was compared with Dutch norm data using a one-sample *T* test. The mean IQ score was compared between children with and without ICH using a two-sample *T* test. The proportion of cases with cognitive impairment, behavior problems, and levels of school performance scores were compared with the Dutch norm data using a binominal test. The risk of severe NDI in cases with severe ICH was compared with the risk of severe NDI in cases without severe ICH using the Fisher exact test. Clinical characteristics and risk factors for NDI (neonatal morbidity, small for gestational age [SGA], gestational age at delivery, and/or maternal educational level) were reported for cases with NDI and without NDI. Data were analyzed using IBM SPSS Statistics 26.0. Clinical characteristics of the included children and the children who did not undergo neurodevelopmental assessment were compared to assess selection bias.

Results

Study Sample

Between 2002 and 2014, 67 cases with newly diagnosed FNAIT were referred to the LUMC. Perinatal mortality occurred in 5 (7%) children: one termination of pregnancy after the diagnosis of severe ICH and hydrocephalus, two children died in utero after ICH, and two children died in the neonatal period due to severe ICH. An additional 6 subjects were excluded due to concomitant medical conditions or because the family had moved abroad, and 12 families did not provide consent for a variety of reasons (**Figure 1**). In total, 44 of 56 (79%) children were included for long-term neurodevelopmental assessment.

Clinical Characteristics and Neonatal Outcome

Table I shows the clinical characteristics of the 44 school-aged children included for long-term follow-up. The majority (84%) had anti-HPA-1a alloantibodies (35 with anti-HPA-1a only, one with both anti-HPA-1a and anti-HPA-3a, and one with both anti-HPA-1a and anti-HPA-5b). Children were born at a median gestational age of 38^{+5} (IQR: 37^{+3}-40^{+5}) weeks with a median birth weight of 3135 (IQR: 2610-3649) grams. In total, 35 (80%) children were males. Neonatal morbidity occurred in four (9%) children: one child had early neonatal sepsis and three had perinatal asphyxia. The median nadir platelet count was 14×10^9/L (minimum 2×10^9/L and maximum 158×10^9/L), and 31 (71%) children had a platelet count below 25×10^9/L. Characteristics of the included cases were comparable to the cases who did not undergo neurodevelopmental assessment (**Table II**).

Perinatal cerebral imaging was performed in 36 of 44 children (82%). ICH was reported in eight children (22%). Two were classified as high-grade IVH, three as high-grade parenchymal hemorrhage, one as low-grade IVH, and two as low-grade parenchymal hemorrhage. In two of these children, high-grade ICH was detected antenatally upon routine ultrasound examination (at 23 weeks and 30 weeks of gestational age). In both cases, antenatal intravenous immunoglobulin (IVIg) treatment was started after HPA antibodies were diagnosed.

Long-Term Neurodevelopmental Outcome

Long-term neurodevelopment was assessed at a median age of 12 years (minimum 6 years and 5 months and maximum 17 years and 4 months (**Table III**). Overall, NDI was present in 14 (32%) children of which 3 had severe NDI (7%, 3/44, 95% CI: −0.8 to 14%), and 11 had mild-to-moderate NDI (25%, 11/44, 95% CI: 12-38%). The overall incidence of adverse outcome, either NDI or perinatal death, was 39% (19/49, 95% CI: 25-54%).Cognitive assessment with the WISC-V was performed in 41 of 44 children. The mean IQ score was 100 (SD: 14). Due to severe problems in speech and language development, two children were assessed with the Snijders-Oomen nonverbal intelligence test. IQ scores of these two children were 49 and 60. For one child, the parents did not consent to cognitive testing. Overall, the mean IQ score (98 ± 17) was not different from the general Dutch population norm (100 ± 15; $P = .420$). Mild-to-moderate cognitive impairment was present in 16% (7/43, 95% CI: 5.0-28%) and severe cognitive impairment in 5% (2/43, 95% CI: −1.8 to 11%).

Neurological testing was completed in 41 children (93%). MND was detected in eight children, four with simple MND (10%, 95% CI: 0.5-19%) and four with complex MND (10%, 95% CI: 0.5-19%). CP was observed in two children (5%, 2/41, 95% CI: −1.9 to 12%), one with spastic diplegia and one with spastic tetraplegia, both classified as GMFCS level IV. One child (2%) was diagnosed with bilateral deafness requiring hearing amplification, related to perinatal asphyxia. The cause of perinatal asphyxia in this child remained unclear.

Table IV presents the details of the children with NDI. Of the three children with severe NDI, one was diagnosed with high-grade IVH and one with high-grade parenchymal hemorrhage. The third child with severe NDI was diagnosed with bilateral deafness; postnatal magnetic

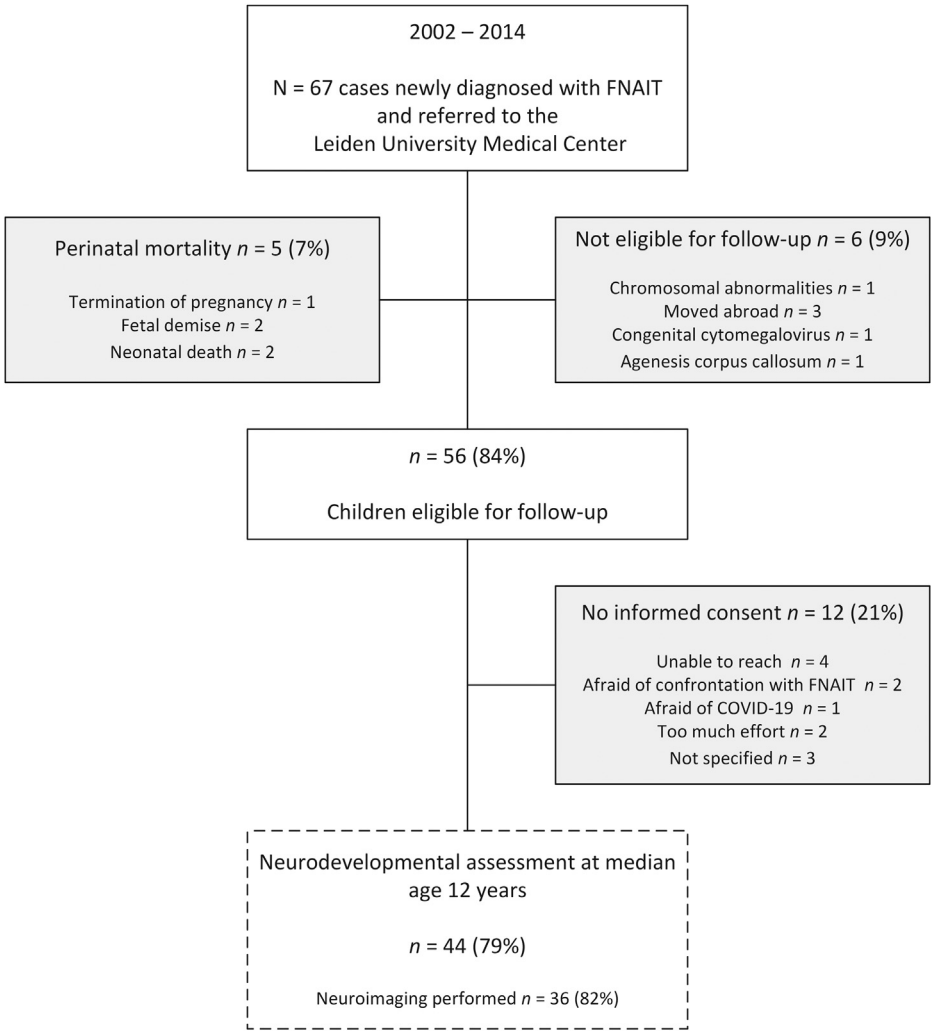

Figure 1. Study population flowchart of the study population. Two (3%) children were excluded from analysis because of unrelated comorbidity affecting the neurodevelopmental outcome: one due to congenital cytomegalovirus infection and the other due to agenesis of the corpus callosum with asymmetric colpocephaly.

resonance imaging showed cerebral edema related to perinatal asphyxia and low-grade parenchymal hemorrhage. Of the 11 children with mild-to-moderate NDI, one was diagnosed with high-grade IVH, eight children did not have cerebral hemorrhage, and in two children, no brain imaging was reported. Two cases with high-grade ICH had a normal neurodevelopmental outcome. Both cases who had no NDI despite high-grade ICH had an unilobular parenchymal hemorrhage (one frontal lobe, one parietal lobe), whereas in the group of children that had NDI and high-grade ICH, two had periventricular hemorrhagic infarction, and one had a multilobular parenchymal hemorrhage. An overview of the neurodevelopmental outcome of the 44 FNAIT cases is shown in **Figure 2**.

Children with high-grade ICH had significantly lower cognitive scores than the children without high-grade ICH (median IQ: 65 (range: 49-106) vs 99 (range: 76-129) respectively, $P = .027$). In total, 40% (2/5) of cases with high-grade ICH had severe NDI vs 3% (1/38) of cases without high-grade ICH (relative risk: 15.6, 95% CI: 1.7-142.6, $P = .030$). In 50% (7/14) of the cases with NDI, other risk factors for NDI were present compared with 20% (6/30) of the cases without NDI. Clinical characteristics of the cases with and without NDI are shown in **Table V**. Within the group of cases who had NDI, the majority (71%, 10/14) were affected by anti-HPA-1a. Of the four children affected by other HPA-specific antibodies, two had high-grade ICH, one was affected by perinatal asphyxia, and one was born SGA.

Behavioral Functioning and School Performance

Five out of 41 children (12%) scored in the clinical range (T score ≥91st percentile) on the total problem score of the behavioral questionnaire (**Table VI**). School performance scores were available for 43 of 44 (98%) children (**Table VI**). The prevalence of the children scoring the lowest level V range did not differ significantly from the

Table I. Clinical characteristics and neonatal outcome

Category	Variables	n = 44
Diagnostics	HPA specificity, *n* (%)	
	HPA-1a	35 (80)
	HPA-5a	2 (5)
	HPA-5b	5 (11)
	HPA-1a and HPA-3a	1 (2)
	HPA-1a and HPA-5b	1 (2)
	Reason for FNAIT suspicion, *n* (%)	
	Skin bleeding	24 (54)
	Organ bleeding	2 (5)
	Hematological examination without clinical signs of thrombocytopenia	16 (36)
	Antenatal ICH	2 (5)
Pregnancy	First pregnancy, *n* (%)	23 (52)
	Signs of fetal bleeding on ultrasound, *n* (%)	2 (5)
	Maternal IVIg treatment, *n* (%)*	2 (5)
Neonatal	Gestational age at delivery, weeks $^{+\ days}$, median (IQR)	38^{+5} (37^{+3} – 40^{+5})
	Female sex, *n* (%)	9 (20)
	Birth weight, gram, median (IQR)	3135 (2610 – 3649)
	SGA (birth weight <10th percentile), *n* (%)	9 (20)
	Apgar score, 5 minutes after birth, median (IQR)	10 (9 – 10)
	Skin bleeding (hematoma or petechiae), *n* (%)	29 (66)
	ICH, *n*/N (%)†	8/36 (22)
	Low-grade ICH	3/36 (8)
	High-grade ICH	5/36 (14)
	Organ bleeding, *n* (%)‡	5 (11)
	Of which severe	2 (5)
	Platelet count nadir × 10^9/L, median (IQR)	14 (7 – 30)
	Platelet count <25 × 10^9/L, *n* (%)	31 (71)
	Postnatal treatment given, *n* (%)	26 (59)

HPA, human platelet antigen; *FNAIT*, fetal neonatal alloimmune thrombocytopenia; *ICH*, intracranial hemorrhage; *IVIg*, intravenous immunoglobulin; *IQR*, interquartile range; *SGA*, small for gestational age; *L*, liter.
*In two children, ICH was observed during pregnancy after which FNAIT was diagnosed and IVIg treatment was started, in one case at 23 weeks' gestation and in the other child at 30 weeks' gestation (for details see **Table IV**).
†Neuroimaging was not performed in 8 of 44 (18%) of the children. In 29 of 44 children (66%), cerebral ultrasound was performed, and in 7 of 44 children (16%), both cerebral ultrasound and magnetic resonance imaging were performed.
‡One case with lung bleeding (severe), one case with gastro-intestinal bleeding (severe), two cases with retinal bleeding (mild), and one case with scrotal hematoma (mild).

Table II. Comparison of characteristics of children undergoing and excluded from neurodevelopmental testing

Variables	Included children n = 44	No neurodevelopmental assessment n = 12
Gestational age at delivery, weeks$^{+\ days}$, median (IQR)	38^{+5} (37^{+3} – 40^{+5})	37^{+6} (36^{+5} – 38^{+3})
First pregnancy, *n* (%)	23 (52)	4 (33)
Female sex, *n* (%)	9 (21)	3 (25)
Birth weight, gram, median (IQR)	3135 (2610 – 3649)	2953 (2288 – 3266)
SGA, (birth weight <10th percentile), *n* (%)	9 (21)	2 (17)
Platelet count nadir, median (IQR)	14 (7 – 30)	29 (19 – 54)
Skin bleeding, *n* (%)	29 (66)	6 (50)
ICH, *n*/N (%)*	7/36 (19)	0
Postnatal treatment given, *n*/*N* (%)†	26/44 (59)	4/9 (44)

IQR, interquartile range; *SGA*, small for gestational age; *ICH*, intracranial hemorrhage.
Characteristics of the children included in the study were compared with the surviving FNAIT children who did not undergo neurodevelopmental assessment. Analysis was performed using the Mann-Whitney *U* test (gestational age, birth weight, and platelet count) or with the Fisher exact test (categorical variables). No statistically significant differences were found.
*Data available for 36 of 44 (82%) children. For the children who did not undergo neurodevelopmental assessment, it was not known whether neuroimaging was performed or not.
†Data available for 9 of 12 (75%) children.

Dutch norm population. Four children (9%, 4/44) attended special needs education, of which three had high-grade ICH.

Discussion

This study shows that children newly diagnosed with FNAIT and who survived the neonatal period have a high risk of long-term NDI. Severe NDI was present in 7% and mild-to-moderate NDI in 25%, thus combined nearly one-third of the children had long-term neurodevelopmental problems. The overall adverse outcome, perinatal mortality or NDI, was 39%. Of note, while neuroimaging revealed the presence of ICH in all children with severe NDI, the vast majority of children with mild-to-moderate NDI had no radiographic evidence for ICH.

The risk of severe NDI in children with newly diagnosed FNAIT is especially high among those with high-grade ICH. In our cohort, severe NDI was observed in two children with high-grade ICH and one child with low-grade ICH and cerebral injury related to perinatal asphyxia. This is in line with a previous study from our group that reported on the neurodevelopmental outcome after ICH due to FNAIT. In this study, severe and mild-to-moderate NDI was diagnosed in 60% (6/10) and 10% (1/10) of the FNAIT survivors with ICH, respectively.[7] In an international cohort study of 43 children with FNAIT-related ICH, 82% of the children who survived had severe neurological disabilities.[10] In our cohort, two cases with high-grade ICH had normal neurodevelopmental outcome; this finding fits in with previous literature in which children can have normal neurodevelopment despite severe brain hemorrhage.[20]

We hypothesized that the neurodevelopmental outcome of newly diagnosed children would be worse than the general population, independent of the presence of ICH. This expectation was based on increasing evidence that the maternal alloantibodies in FNAIT not only cause platelet destruction but possibly interfere with endothelial cells.[1,21] This might result in small cerebral bleeding and/or impaired (cerebral) angiogenesis that remains clinically undetectable directly after birth but, in the long term, affects brain development, leading to developmental delay.[22] Alternatively, it could be that fetal thrombocytopenia itself, irrespective of the presence of anti-HPA-1aantibodies, influences brain development.

Within our study, we found mild-to-moderate NDI in 25% of the children of whom only one was diagnosed with high-grade ICH. This percentage was higher than one would expect in the normal population. Half of the children who

Table III. Neurodevelopmental outcome

Category	Variables	n = 44	Dutch norm scores
Age	Age, years and months, median (IQR)	12y0m (9y9m - 14y11 m)	
Cognitive	Full Scale IQ, mean (SD)*	98 (17)	100 (15)
	Verbal comprehension	104 (13)	
	Visual spatial score	99 (16)	
	Fluid reasoning scale	101 (13)	
	Working memory score	97 (14)	
	Processing speed	98 (13)	
	Normal range (IQ >85), *n* (%)†	35 (80)	
	Mild-to-moderate cognitive impairment (IQ: 70 – 85)	7 (16)	13.6%
	Severe cognitive impairment (IQ <70)	2 (5)	2.2%
Neurological	MND, *n*/N (%)‡		
	Simple MND	4/41 (10)	15%
	Complex MND	4/41 (10)	6%
	Abnormal domain, n/N (%)		
	Posture	4/41 (10)	
	Reflexes	0	
	Involuntary movements	1/41 (2)	
	Coordination	6/41 (15)	
	Fine manipulative ability	2/41 (5)	
	Associated movements	0	
	Sensory defects	1/41 (2)	
	Cranial nerve function	1/41 (2)	
	CP, *n* (%)§	2 (5)	0.4%
	Bilateral deafness requiring hearing amplification, *n* (%)	1 (2)	
	Bilateral blindness, *n* (%)	0	
Demographics	Maternal education level, *n*/N (%)		
	Low	4/42 (10)	
	Intermediate	17/42 (40)	
	High	21/42 (50)	
NDI	NDI, *n* (%)¶		
	Normal NDI	30 (68)	
	Mild-to-moderate NDI	11 (25)	
	Severe NDI	3 (7)	

IQR, Interquartile range; *IQ*, intelligence quotient; *SD*, standard deviation; *MND*, minor neurological dysfunction; *CP*, cerebral palsy; *NDI*, neurodevelopmental impairment.
*IQ was not available in 1 of 44 (2%) children. Verbal comprehension, visuospatial score, fluid reasoning scale, and working memory score were not available in 4 of 44 (9%) children. Processing speed was not available in 3 of 44 (7%) children.
†Based on the information of the school results and questionnaires that were completed by the parents or caregivers, we categorized the missing cognitive test scores as normal.
‡Neurological test was not performed in 3 of 44 (7%) children due to no permission.
§Both children with CP were classified as a Gross Motor Functioning Classification System level IV. One child had spastic diplegia, and the other had spastic tetraplegia.
¶Based on the information of the school results and questionnaires that were completed by the caregivers, we categorized the missing scores needed for NDI as normal.

were classified as mild-to-moderate NDI were diagnosed with MND. In general, the proportion of complex MND (10%) in our study group was slightly higher than that of the 6% in Dutch school-aged children.[15] Possibly, the high proportion of children with MND is related to subclinical cerebral damage that remained undiagnosed for a short time after delivery but led to mild and/or multiple neurodevelopmental problems in the long term. Alternatively, the higher proportion of children with MND could be explained by the unequal sex distribution in our study group. In accordance with previous cohort studies on FNAIT,[23,24] we observed an overrepresentation of boys in our cohort. However, these previous studies found a more balanced gender distribution than our cohort. Both simple and complex MND are diagnosed two times more often in male children than in female children. Possibly the high rate of NDI could be related to the relative higher risk of MND in male infants; 13 of the 14 children with NDI were males. Besides the overrepresentation of male sex, we observed that in 50% of the cases with NDI, other risk factors for NDI were present, whereas in the cases without NDI, other risk factors were present in only 20%. Unfortunately, an independent risk factor analysis to identify these factors was not possible due to our limited sample size. In addition, SGA, neonatal morbidity, and low maternal education level are closely intertwined. HPA-1a immunization was reported to be associated with reduced birth weight in other cohort studies.[24,25]

Previous studies have described the neurodevelopmental outcome of newly diagnosed children with FNAIT. Ward et al[11] concluded that newly diagnosed children had a worse long-term outcome than their IVIg-treated siblings, but this was based on a behavioral questionnaire taken over the phone with a loss to follow-up of 32%. Knight et al.[26] conducted a study based on obstetric and pediatric surveillance data in the United Kingdom on children with FNAIT. In this study, 8% of the children newly diagnosed with FNAIT had a disability. However, this study was limited by a follow-up to only 1 year of age. The percentage of 8% disability seems lower than in our study, yet it was based on national surveillance data and not on standardized individual assessments, and the definition of disability was not clearly described.

Table IV. Characteristics of the children with neurodevelopmental impairment

Case	Sex	GA birth (wks)	Other risk factor for NDI*	PC < 25 × 10^9/L	ICH	Neuroimaging†	Other bleeding symptoms	Age at test HPA	Age at test (y)	IQ	Neurological examination; abnormal domain	Behavior total problem score	School performance; reading comprehension, spelling, arithmetic‡	NDI
1	F	40	Perinatal asphyxia, SGA	No	Low-grade parenchymal hemorrhage	MRI: white matter: cerebral edema (related to perinatal asphyxia). Parenchymal hemorrhage left parietal, ⌀ 2 mm	None	5b	16	85	Simple MND, bilateral deafness	ADHD	V, III, V	Severe
2	M	35	None	No	High-grade IVH	MRI: Bilateral PVHI and severe ventriculomegaly (VP shunt)§	Antenatal ICH	5b	13	60¶	CP spastic diplegia GMFCS IV	NA	V, V, V Special needs	
3	M	41	Perinatal asphyxia, SGA	Yes	High-grade parenchymal hemorrhage	MRI: bilateral hemorrhage: multilobular left and temporal lobe right	None	1a	16	49¶	CP spastic tetraplegia GMFCS IV	NA	V, V, V Special needs	
4	M	37	None	No	High-grade IVH	MRI: PVHI and cerebellar hemorrhage**	None	5a	10	70	Complex MND	Clinical	V, V, V Special needs	Mild-to-moderate
5	M	40	SGA	Yes	No	cUS: no abnormalities	Gastro intestinal bleed	5a	10	76	Normal	Clinical	V, V, V Special needs	
6	M	35	None	No	Unknown	Not performed	Petechiae	1a	11	80	Simple MND	Normal	V, V, IV	
7	M	38	Low maternal education level	Yes	No	cUS: no abnormalities	Hematoma, petechiae	1a	16	81	NA	Normal	IV, IV, V	
8	M	39	SGA	Yes	No	cUS: no abnormalities	Petechiae	1a	8	84	Normal	Borderlin e	III, II, II	
9	M	41	None	Yes	No	cUS: echogenicity grade I	Petechiae	1a	14	84	Normal	Normal	V, V, IV	
10	M	38	None	Yes	Unknown	cUS: not performed	Petechiae	1a	9	89	Complex MND	Clinical	IV, I, II	
11	M	40	SGA	Yes	No	cUS: no abnormalities	Petechiae	1a	14	118	Complex MND	Normal	II, I, I	
12	M	41	None	Yes	No	cUS: no abnormalities	Petechiae	1a	13	129	Complex MND	Normal	I, I, I	
13	M	37	SGA	Yes	No	cUS: no abnormalities	Hematoma, petechiae	1a	10	95	Simple MND	Clinical	V, V, II	
14	M	39	None	Yes	No	cUS: no abnormalities	Hematoma, lung bleed	1a	6	95	Simple MND	Normal	IV, IV, I	

GA, gestational age; *wks*, weeks; *PC*, platelet count; *L*, liter; *ICH*, intracranial hemorrhage; *HPA*, human platelet antigen; *IQ*, intelligence quotient; *NDI*, neurodevelopmental impairment; *F*, female; *M*, male; *SGA*, small for gestational age, *MRI*, magnetic resonance imaging; *MND*, minor neurological dysfunction; *ADHD*, attention deficit hyperactivity disorder, *PVHI*, periventricular hemorrhagic infarction; *VP*, ventriculoperitoneal; *CP*, cerebral palsy; *GMFCS*, Gross Motor Function Classification System; *NA*, not assessed; *cUS*, cranial ultrasound.

*Risk factors for NDI were defined as either one of the following: perinatal asphyxia, neonatal sepsis, SGA, prematurity <32 weeks gestational age, and/or low maternal educational level.

†In 14% (2/14 with NDI) of children, neuroimaging was not performed; in 57% (8/14), cerebral ultrasound was performed; and in 29% (4/14), both cerebral ultrasound and MRI were performed.

‡The scoring of the school results is according to the Dutch National Pupil Monitoring System (CITO).[28] The scores range from I to V, in which grade I represents the 20% best scoring children and grade V, the 20% lowest scoring children.

§ICH was detected during the pregnancy at ultrasound, after which IVIg treatment was initiated at 23 weeks of gestational age.

¶IQ was assessed using the Snijders-Oomen nonverbal intelligence test because of problems in language and speech development and communication.

**ICH was detected during the pregnancy at ultrasound, after which IVIg treatment was initiated at 30 weeks of gestational age.

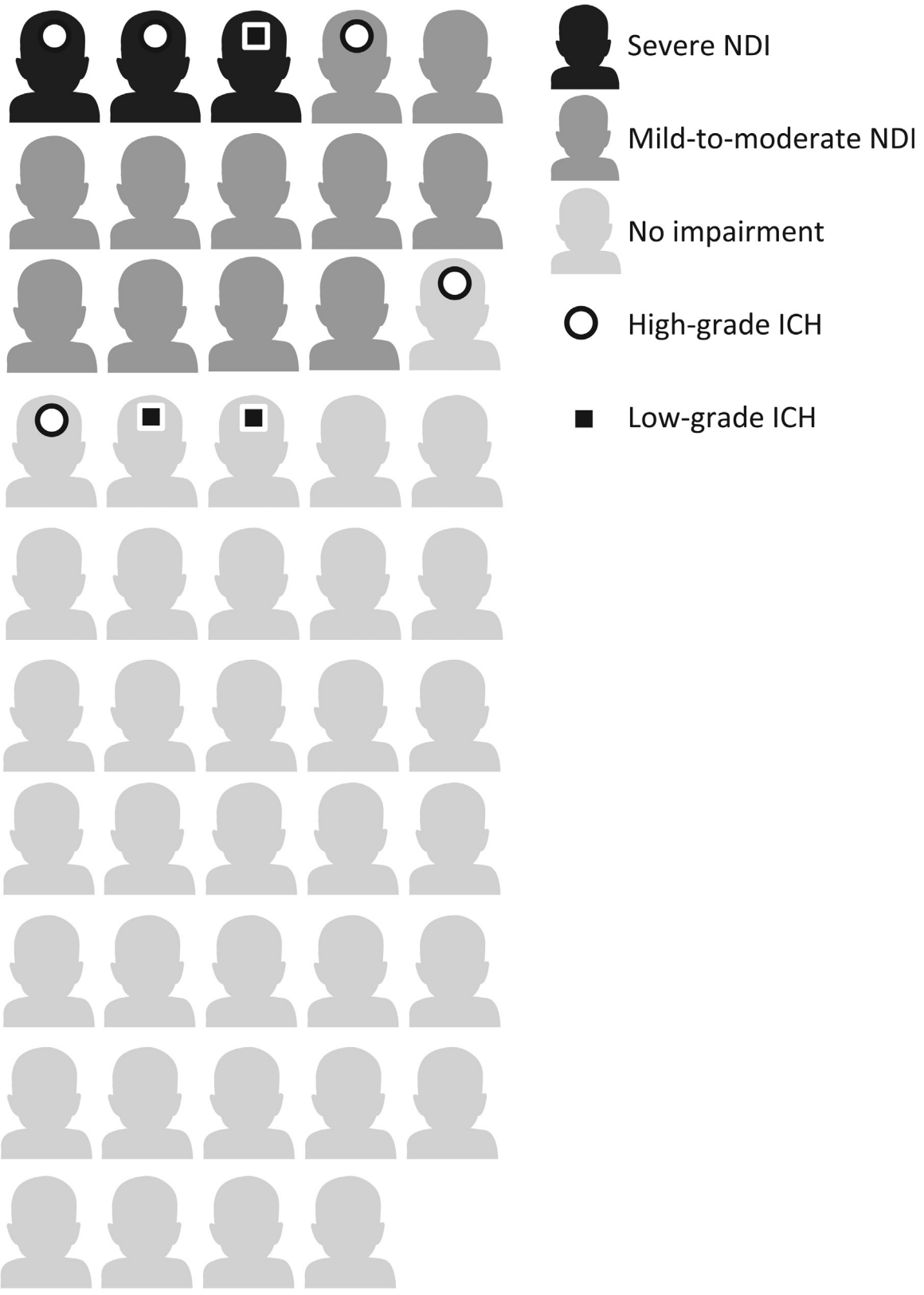

Figure 2. Neurodevelopmental outcome of 44 FNAIT cases. *FNAIT*, fetal and neonatal alloimmune thrombocytopenia; *NDI*, neurodevelopmental impairment; *ICH*, intracranial hemorrhage.

Table V. Clinical characteristics of the children with and without NDI

Variables	Children with NDI n = 14	Children without NDI n = 30
HPA specificity, *n* (%)		
HPA-1a	10 (71)	25 (84)
HPA-5a	2 (14)	0
HPA-5b	2 (14)	3 (10)
HPA-1a + HPA-3a	0	1 (3)
HPA-1a + HPA-5b	0	1 (3)
First pregnancy, *n* (%)	7 (50)	16 (53)
Gestational age at delivery, weeks$^{+\ days}$, median (IQR)	39^{+5} (37^{+5} – 40^{+6})	38^{+3} (36^{+3} – 40^{+3})
Prematurity (<37 weeks gestational age), *n* (%)	2 (14)	5 (17)
Female sex, *n* (%)	1 (7)	8 (27)
Apgar score 1 minute after birth, median IQR	9 (8 – 9)	9 (8 – 9)
Apgar score 5 minutes after birth, median (IQR)	10 (9 – 10)	9 (9 – 10)
Perinatal asphyxia, *n* (%)	1 (7)	2 (7)
SGA (birth weight <10th percentile), *n* (%)	6 (43)	3 (10)
Neonatal sepsis, *n* (%)	1 (3)	0
Perinatal asphyxia, *n* (%)	2 (14)	1 (3)
ICH, *n*/N (%)		
Low-grade ICH	1 (7)	2 (7)
High-grade ICH	3 (21)	2 (7)
Platelet count < 25 × 10^9/L, *n* (%)	10 (71)	21 (70)
Low maternal education level, *n* (%)	2 (17)	2 (7)

HPA, human platelet antigen; *SGA*, small for gestational age; *ICH*, intracranial hemorrhage; *L*, liter.

Table VI. Behavioral functioning and school performance results

Category	Variables	*n* = 44
Behavioral functioning*	Clinical behavior problems, *n*/N (%)	
	Total	5/41 (12)
	Internalizing	6/41 (15)
	Externalizing	0
School performance results †	Reading comprehension score, *n*/N (%)	
	I	10/43 (23)
	II	9/43 (21)
	III	5/43 (12)
	IV	9/43 (21)
	V	10/43 (23)
	Spelling score, *n*/N (%)	
	I	16/43 (37)
	II	8/43 (19)
	III	7/43 (16)
	IV	4/43 (9)
	V	8/43 (19)
	Arithmetic/mathematics score, *n*/N (%)	
	I	14/43 (33)
	II	8/43 (19)
	III	2/43 (5)
	IV	6/43 (14)
	V	13/43 (30)

*Behavior questionnaire was not applicable in 2/44 (5%) children due to severe developmental problems and missing in one (2%) child.
†School performance results were not available for 1/44 (2%). Four children (4/44, 9%) attended special needs education.

The proportion of children diagnosed with CP in our study was higher than in the general population, 5% vs 0.2%[27] Both children with CP had an antenatally acquired ICH. In total, 9% of the children were in special needs education, which is more than the regular population.[28]

This study shows that children with FNAIT without ICH may be at risk of mild-to-moderate long-term impairment, and the risk of mortality and severe impairment is especially high for children with ICH. These findings stress the importance of preventing severe bleeding in FNAIT and therefore the development of assays that can identify pregnancies at risk for bleeding within HPA-alloimmunized pregnant women. By identification of these pregnancies, antenatal treatment could prevent the occurrence of ICH and cerebral injury and thereby the associated adverse outcome.

The knowledge provided by this study will be of help for obstetricians and neonatologists counseling parents of a child affected by FNAIT. FNAIT survivors are at risk of neurodevelopmental problems, in particular children affected by ICH. To improve the neurodevelopment of children affected by FNAIT that were not antenatally treated with IVIg, adequate follow-up care should be provided. Additionally, the results of our study underline the importance of performing neuroimaging in children newly diagnosed with FNAIT.

A limitation of this study is the absence of a control group. Yet, by using standardized tests based on a normative sample, it is possible to compare the results to the population norms. Another limitation is that not all eligible children were included in the study, since 21% of the eligible children did not undergo neurodevelopmental assessment. However, when comparing the included children to those who did not undergo neurodevelopmental assessment, the clinical characteristics were similar. Although most parents or caregivers did not specify the reason for not wanting to participate, some indicated that it had to do with being confronted with the disease again or participation requiring too much effort. One further constraint of our study was that it was a single-center study including only children referred to the LUMC. Between 2002 and 2014, 195 children were diagnosed with FNAIT at our national reference laboratory (Sanquin) of which 67 (34%) were referred to the clinical expertise center (LUMC). A strength of the current study is that it is the first to assess the long-term neurodevelopmental outcome of children newly diagnosed with FNAIT using standardized psychometric tests and neurological tests and incorporating school performance results. In addition, our study included children at an older age than in previous studies, thereby providing a more reliable and accurate view of the long-term development of these children.

In conclusion, children newly diagnosed with FNAIT who survived the neonatal period are at high increased risk of long-term neurodevelopmental problems and therefore should have postnatal neuroimaging and be monitored adequately in a standardized follow-up program. Severe NDI

and mortality are predominantly observed among children with ICH. In addition, a quarter of the children in this cohort suffer from mild-to-moderate impairment, suggesting that the risk of NDI is high also in children without ICH. ■

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CRediT Authorship Contribution Statement

Thijs W. de Vos: Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Maud van Zagten:** Investigation, Writing – original draft. **Masja de Haas:** Conceptualization, Funding acquisition, Writing – review & editing. **Dick Oepkes:** Conceptualization, Writing – review & editing. **Ratna N.G.B. Tan:** Investigation, Writing – review & editing. **C. Ellen van der Schoot:** Conceptualization, Writing – review & editing. **Sylke J. Steggerda:** Investigation, Writing – review & editing. **Linda S. de Vries:** Investigation, Writing – review & editing. **Enrico Lopriore:** Conceptualization, Methodology, Writing – review & editing. **Jeanine M.M. van Klink:** Conceptualization, Supervision, Writing – review & editing.

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