ORIGINAL ARTICLE

A Study on The Incidence and Maternal/Neonatal Characteristics for Fetal and Neonatal Alloimmune Thrombocytopenia at Malaysia National Blood Centre

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ABSTRACT

Introduction: Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is an uncommon condition due to maternal alloimmunization of fetal platelet leading to thrombocytopenia in fetal and neonate. Our study determine the incidence, common platelet alloantibodies and the associated maternal and neonatal factors of FNAIT in Malaysia. **Methods:** Matched case control study of FNAIT and control (39 FNAIT cases and 39 randomly selected controls) through retrospective record review from the year 2011 to 2019 was performed at National Blood Centre, Malaysia. Data were analysed using Statistical Package for Social Sciences (SPSS) version 26.0. Differences between cases and controls were evaluated using chi-square test for categorical variables and t-test or Mann-Whitney test for normally and non-normally distributed variables. **Results:** The incidence of FNAIT in Malaysia was 0.85 per 100 000 live births. Common anti-Human Platelet Antigen (-HPA) identified in this study were Anti-HPA-5b, Anti-HPA-3a and Anti-HPA-5a. Fifty-eight (58%) (p=0.012) of mothers in the study were younger than 35 years old, of Malay ethnicity and multiparous. Malay mothers were five times more likely to develop FNAIT as compared to non-Malay. For neonates, the most significant factor associated with FNAIT was the neonatal presentation. Symptomatic neonates were more likely to develop FNAIT. Whereas, the neonates onset of presentation, platelet count and blood group were not significantly different than in control group. **Conclusion:** Incidence of FNAIT among Malaysians was lower than reported in the literature. Malay mothers and neonates presenting with symptoms are more likely to have FNAIT.

Keywords: Fetal and neonatal alloimmune thrombocytopenia (FNAIT), Incidence, Human platelet antigen

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INTRODUCTION

Platelet is a unique blood component. It is minute in size and originates from fragments of megakaryocytes. Primary role of platelet is to secure haemostasis when there is damage in the blood vessel wall. Bleeding risk increases when there is impaired platelet function or thrombocytopenia (1). Platelet has no nucleus and possesses various organelles and secretory granules. Numerous glycoproteins (GPs), human blood group antigens and human leukocyte antigen (HLAs) are found on its surface. Platelet-specific antigens found on glycoproteins complexes (GPIIb, GPIIIa, GPIba, GPIbb, GPIa and CD109) are designated as Human Platelet Antigen (HPAs). There are about 35 HPAs identified so far (2). Twelve antigens which are HPA-1a/b, HPA-2a/b, HPA-3a/b, HPA-4a/b, HPA-5a/b and HPA-15a/b are classified as biallelic system with 'a' denoting a higher frequency antigen and 'b' denoting lower frequency antigen (3). HPA allele frequency and distribution vary according to ethnicity and countries (4).

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) is a rare platelet disorder affecting fetus and neonate due to feto-maternal platelet incompatibility leading to bleeding manifestation in some. Fetus in second trimester onwards and neonates have platelet counts above 150 x 109/L. Thrombocytopenia is encountered in about 25% of cases in the neonatal intensive care unit (NICU) (5). FNAIT is suspected when there is isolated thrombocytopenia without any precipitating factors

such as infections (6). FNAIT is somewhat analogous to haemolytic disease of the fetal and newborn which is due to red cell incompatibility. In FNAIT, the unrecognized platelet antigen found on fetus (which is paternally inherited) would trigger sensitization in the mother. The mother then produces antibody to bind this foreign antigen leading to platelet destruction and thrombocytopenia in the fetus and neonates (7). FNAIT is found in 1 of 800 to 2000 pregnancies (8). Frequently, anti-HPA-1a is implicated in FNAIT among Caucasian (9). FNAIT due to HPA-1a antibodies among East Asian are extremely rare and was due to low prevalence of HPA-1b homozygosity. The HPA-4b is more common in East Asian population and this antibody accounts for 72% of FNAIT in Japan (10).

FNAIT may occur as early as second trimester and resolve spontaneously within 1 to 3 weeks after delivery (11). Neonates born with FNAIT could be asymptomatic, have purpura or hematoma or other bleeding manifestations. Intracranial haemorrhage which is the most feared presentation occurs in about 10-30% of severe thrombocytopenia in FNAIT. This condition may lead death and long term neurological sequelae (11). Intracranial haemorrhage may recur in subsequent pregnancies (12) and therefore it is important to identify FNAIT so that mothers at risk could be managed appropriately. Due to this, predicting factors in mother and neonates associated with FNAIT had always been and is still a subject of interest for decades.

Many previous literatures on FNAIT have been focusing on Caucasion population. Different population may have different incidence and platelet alloantibodies that contribute to FNAIT. Hence, the aim of our study is to determine the incidence and the platelet alloantibodies identified in our population. Besides that, another purpose of our study is to identify the maternal and neonatal characteristics of FNAIT in Malaysian population.

MATERIALS AND METHODS

Ethical consideration

This study was approved by Universiti Sains Malaysia (USM) Human Research Ethics Committee (Approval number: USM/JEPeM/18110724) and Medical Research Ethics Committee, Ministry of Health (Approval number :NMRR-18-3817-44392).

Study design, sample size calculation and sampling method

Matched case control study of FNAIT cases and control through retrospective record review was performed at National Blood Centre, Malaysia. Data were collected retrospectively from the year 2011 to 2019.

Sample size formula used for this matched case-control study was calculated according to previous study (14). In this study, alpha was set as 0.05, power as 80%, odds ratio as 8, correlation coefficient as 0.2 and prevalence of 5%. The final sample for each group was 39. Therefore, a total of 78 cases and controls were recruited in this study.

All 39 positive cases of FNAIT and 39 randomly-selected control cases during study period who fullfill the inclusion and exclusion criteria were recruited.

Inclusion criteria

- Neonates and infants with thrombocytopenia referred to National Blood Centre Kuala Lumpur (NBC) for confirmatory testing of clinically suspected FNAIT between 2011 and 2019.
- For cases, all confirmed FNAIT due to anti-HPA alloantibodies were included.
- Controls were those with no detectable platelet alloantibodies, which were randomly selected systematically using Microsoft Excel 2016.
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Exclusion criteria

- Cases with detectable platelet alloantibodies other than anti-HPA antibodies such as anti-HLA class I, anti-GPIIb/IIIa, -Ia/IIa, -Ib/IX, -CD 109.
- Controls with missing data

Cases and controls test request forms were traced manually. Information on number of annual test request, blood group and type of platelet antibodies were traced manually from the request form and Blood Bank Information System version 2 (BBIS v2).

Data analysis

Descriptive statistics were estimated for cases and controls, separately. Differences between cases and controls were evaluated using chi-square test for categorical variables and t-test or Mann-Whitney test for normally and non-normally distributed variables, respectively. Statistical significance was defined as $p<0.05$. Crude odd ratios and 95% confidence intervals were estimated from conditional logistic regression. Multivariable logistic regression was performed by including all the variables that showed a p-value of less than 0.25 in the above mentioned descriptive analysis. Variables with highest beta coefficient as well as being significant will be considered as the most influential variable in this study. Data were analysed using Statistical Package for Social Sciences (SPSS) version 26.0 for window software (SPSS, Chicago Illinois, USA).

RESULTS

The incidence rate of FNAIT was between 0.19 and 2.3 per 100,000 live births from 2011 to 2019 as shown in Table I. The overall incidence rate was 0.85 per 100,000 populations during the study period.

There were total of 39 cases of FNAIT and the type of

Table I: Incidence rate of FNAIT from 2011 to 2019 at the National Blood Centre

Year	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
Test number	35	50	43	53	61	62	66	82	60	512
FNAIT cases	12	3	8	1	1	1	7	4	2	39
Live births*	511594	526012	503914	528612	521136	508203	508685	501945	487957	4598058
Incidence Rate~	2.3	0.57	1.59	0.19	0.19	0.2	1.38	0.8	0.41	0.85

*Source from Department of Statistics Malaysia
~Incidence rate measured as per 100,000 live births

platelet antibodies are as shown in Table II. In average, there were 4.3 FNAIT cases detected yearly between 2011 and 2019. Year 2011 had the most number of FNAIT cases (12 cases). Fig.1 is a histogram tabulation of types of antibodies detected. The commonest HPA platelet antibody detected in NBC is Anti- HPA-5b (13 cases) accounting for one third of FNAIT. Anti-HPA-3a, Anti-HPA-5a and Anti-HPA-15a were the next most common antibodies detected in FNAIT with five cases each. Two cases had combination of Anti-HPA-2a with Anti HPA-5b and the other one was Anti-HPA-2b with Anti-HPA-15b. There was only one case of FNAIT implicated due to Anti-HPA-1a.

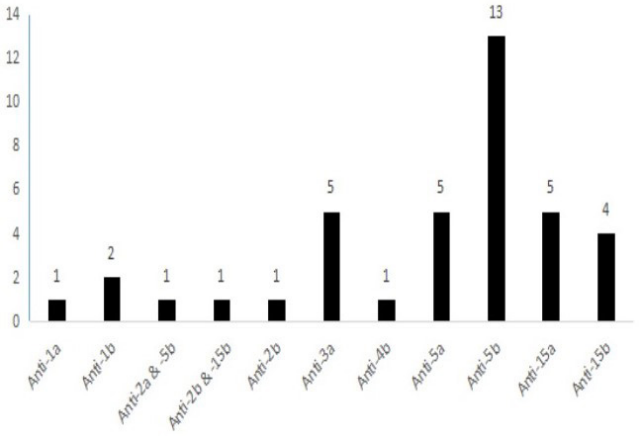

Figure 1: Number of FNAIT cases according to types of platelet antibodies detected from the year 2011-2019 at the National Blood Centre

Table III represents maternal and neonatal characteristics between cases and controls. The mean maternal age in this study was 30.6 years old in FNAIT cases and 30.4 years old in control. Majority of mothers in both cases and controls were younger than 35 years old. There is no significant (p=0.125) association between maternal age and FNAIT in this study. Distribution of ethnicity was rather close with 58% were Malays and 42% were non-Malays in FNAIT cases. Whereas in control group, the majority (84%) of the cases were Malays. Malay mothers were four times more likely to develop FNAIT as compared to non-Malay mothers and this was statistically significant (p=0.012). Approximately 20% of mothers were primigravida in cases and controls. Maternal parity did not show any significant difference

Table II: Types of HPA platelet antibodies detected among FNAIT cases from year 2011 to 2019 at the National Blood Centre

HPA Platelet Antibody	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total (%)
Anti-1a	1	0	0	0	0	0	0	0	0	1 (2.6)
Anti-1b	0	0	1	0	0	0	0	1	0	2 (5.1)
Anti-2a & Anti-5b	1	0	0	0	0	0	0	0	0	1 (2.6)
Anti-2b & Anti-15b	1	0	0	0	0	0	0	0	0	1 (2.6)
Anti-2b	0	0	0	0	1	0	0	0	0	1 (2.6)
Anti-3a	0	1	1	0	0	1	1	0	1	5 (12.8)
Anti-4b	0	0	0	0	0	0	1	0	0	1 (2.6)
Anti-5a	3	1	1	0	0	0	0	0	0	5 (12.8)
Anti-5b	3	0	2	1	0	0	5	2	0	13 (33.3)
Anti-15a	1	1	2	0	0	0	0	0	1	5 (12.8)
Anti-15b	2	0	1	0	0	0	0	1	0	4 (10.2)
Total	12	3	8	1	1	1	7	4	2	39 (100)

Table III: Maternal and neonatal characteristics of FNAIT cases and matched controls and their associated crude odd ratios

Characteristics	Cases n (%)	Controls n (%)	Crude OR	95% CI	*p*-value
1. MATERNAL FACTORS					
Age (n=74)					
Age (years)^	30.6(6.8)	30.4(4.7)			0.021
≥35 years old	9 (26)	4 (10)	1		
<35 years old	26(74)	35 (90)	3.01	0.84,10.92	0.125
Ethnicity (n=77)					
Non-Malay	16(42)	6(16)	1		
Malay	22(58)	33(84)	4.00	1.36,11.81*	0.012
Parity (n=59)					
Multigravida	17(77)	29(78)	1		
Primigravida	5(23)	8(22)	0.94	0.26,3.33	<0.999
Blood group (n=73)					
Non-O	20(59)	21(54)	1		
O	14(41)	18(46)	1.22	0.48,3.10	0.814
2. NEONATAL FACTORS					
Onset (n=73)					
Median onset (days)~	6 (1-16)	7 (3-20)			0.848
>3 days	23(68)	27(69)	1		
≤3 days	11(32)	12(31)	0.93	0.2.50	<0.999
Presentation (n=63)					
Symptomatic	20(59)	11(28)	1		
Asymptomatic	14(41)	28(72)	0.46	0.04,0.86*	0.010
Platelet count (n=72)					
Mean platelet^	31 (25)	41 (32)			0.219
>50	7(20)	13(35)	1		
≤50	28(80)	24(65)	0.46	0.16,1.34	0.192
Blood group (n=73)					
Non-O	25(74)	21(54)	1		
O	9(27)	18(46)	2.38	0.89,6.40	0.095

^Mean (SD); SD, Standard deviation; independent t-test was used to compare means
~Median (IQR); IQR, Interquartile range; Mann-Whitney test was used to compare medians
* Significant

in occurrence of FNAIT between cases and controls. Similarly, there was no significant difference between maternal blood groups in FNAIT cases and control groups.

The median onset of presentation in neonates was 6 days in cases and 7 days in controls. About two third of neonates in FNAIT cases and controls had presented after 3 days with thrombocytopenia. There is no difference between onset of presentation between cases and controls (p= 1.000). Neonates with FNAIT were more likely to show symptoms (59%) than controls (28%) and this was significant (p= 0.010). Mean platelet count in FNAIT cases was $31x10^9$/L and controls was $41x10^9$/L (p=0.219). There were 28 (80%) FNAIT cases and 24 (65%) control cases with platelet count of less than $50x10^9$/L, nonetheless the difference was not significant (p= 0.192). Neonates with non-O blood group were 74% in FNAIT cases and 54% in controls. Blood group did not appear to be significant between cases and controls (p= 0.095).

Maternal variables (age of less than 35 years old and Malay ethnicity) as well as neonatal variables (symptomatic presentation, platelet count less than 50 $x10^9$/L) that showed p-values of less than 0.25 in Table III were entered in a multivariate logistic regression simultaneously for identifying the most influencing variables associated with FNAIT (Table IV and Table V).

Table IV: Maternal factors that were associated with FNAIT

Factors	Adjusted OR	p-value	95% CI	
Age (<35 years)	4.3	0.033	1.1	16.6
Ethnic (Malay)	4.8	0.008	1.5	15.2

R square: 0.188

Table V: Neonatal factors that were associated with FNAIT

Factors	Adjusted OR	p-value	95% CI	
Symptomatic presentation	11.8	0.026	1.3	103.0
Neonatal platelet count (<50x10⁹/L)	3.5	0.065	0.9	13.0
Neonatal blood group	0.5	0.242	0.1	1.6

R square: 0.240

Table IV depicts the most significant maternal factors that contributed to FNAIT was age (<35 years) and ethnic group Malay. Younger mothers (<35 years) were four times more likely to have neonates with FNAIT compared to mother whose age were equal and greater than 35 years (p<0.05). Malay ethnic group was associated five times more likely of having FNAIT compared to non-Malay ethnic group (p<0.05).

The most influential neonatal factor contributing to the

FNAIT was neonatal presentation (OR 11.773, p-value 0.026) as represented in Table V. Neonates who were symptomatic were more likely to have FNAIT.

DISCUSSION

Platelet Serology Laboratory at the NBC is the referral center performing platelet antibody testing for Malaysia. To the best of our knowledge, this was the first study to measure incidence of FNAIT in Malaysian population. Total live births in Malaysia is about 500 000 per year. Although the test requests per year is increasing, the number of FNAIT cases detected was rather unpredictable. The highest FNAIT cases was in 2011 with a total of 12 cases. After evaluating the details of the requests, we assume that highest detection of positive FNAIT cases in that year because most of the cases were referred from university-based and tertiary hospitals where likely field experts and senior clinicians are available for consultation. Therefore, requests being made are probably based on only highly suspicious of FNAIT. Test requested in subsequent years were noted to be from across the country including district hospital based on thrombocytopenia alone which were seen in test requests in subsequent years.

Based on our findings, the incidence rate of FNAIT was 0.19 to 2.3 per 100,000 live births with overall incidence rate of 0.85 per 100,000 live births between 2011 and 2019. The incidence of FNAIT reported by previous studies are ranged between 1 in 350 to 1 in 2000 in Caucasian (7) (15) (16) (17) . In Norway, there were 7.5 FNAIT cases detected in unscreened population as compared to 53 cases diagnosed in screened population (18). The incidence of FNAIT in Asian population is not well known (10). The lower incidence reported in our study could be due to underreporting. Previous studies also commonly mentioned underreporting in FNAIT (19, 20). Lack of awareness of this rare condition might be a contributing factor. Mild thrombocytopenia among asymptomatic neonates are also possibly unnoticed as the nature of the disease is self-limiting after several days or weeks. Neonates in our study were suspected of having FNAIT probably after bleeding manifestation or were found to be thrombocytopenic due to other causes such as infections or maternal immune thrombocytopenia.

The commonest platelet antibody detected in our study was anti-HPA-5b, followed by anti-HPA-5a, anti-HPA-3a, anti-HPA-15a and anti-HPA-15b. This finding was supported by previous study between 2008-2013 which concluded common alloimmunization in FNAIT and platelet refractoriness among Malaysian Malays were due to anti-HPA-3a, anti-HPA-5a and anti-HPA-5b. (21). Among Japanese, the commonest HPA antibodies are anti-HPA-5b and anti-HPA-4b (10). Anti- HPA-4b is commonly found among Japanese and Korean but had also been seen among Chinese and Indians (22). HPA antibodies other than anti-HPA-1a do not usually cause life threatening bleeding. Presentation are often asymptomatic or mild bleeding such as petechial rash or purpura, therefore, diagnosis could be missed or delayed. In contrast, anti-HPA-1a is responsible for about 80-85% of FNAIT in Caucasian population (9, 20, 23, 24). Intracranial haemorrhage are seen in 10-26% with anti-HPA-1a rather than other anti-HPAs (20). There was only one FNAIT case due to anti-HPA-1a in our study. In a large Japanese study of almost 30 000 screened samples, there was not even one FNAIT case due to anti-HPA-1a detected (10). These findings support that the anti-HPA-1a is less commonly seen in Asian population. FNAIT due to Anti-HPA-4b is more common among Japanese and seen only in one case in our study. Thus, it is important to note that anti-HPA-4b is not common among Malaysian where Malays predominate the population. These findings highlight the importance of obtaining patient's demographic information when FNAIT is suspected as interracial marriage is common occurrence among our population.

Another interesting antigen known as CD-36 (also known as anti-Naka) is present on platelets and monocytes. CD-36 deficiency is present among Asian mainly Chinese and Japanese population but rarely seen among Caucasians (25). CD-36 deficiency among Malaysian blood donors revealed prevalence of 2.5% in our population (26). Development of antibody against CD-36 in the CD-36 deficient individuals had been implicated in immune thrombocytopenia such as platelet refractoriness and FNAIT (25). Investigation of anti-CD-36 may be warranted in ruling out FNAIT in our population in future.

Most of mothers in the study were younger than 35 years old and had shown higher chance of developing FNAIT, although the finding is not significant. Most of the mothers implicated with FNAIT in previous studies were also from younger than 35 years old (27). Maternal ethnicity is an important associated parameter for FNAIT in our study. Malays comprise more than two thirds of Malaysian population. Non-Malays consist of Chinese, Indians and other minorities. From our analysis, Malay mothers are almost five times more likely to develop FNAIT as compared to non-Malays. Simple rational to this may be due to the larger number of requests from Malay patients however more complex studies such as HPA genotyping or genetic based analysis may be warranted to further investigate this finding. It is well known that HLA-DRB3*01:01 allele is associated with alloimmunization of anti-HPA-1a and severe FNAIT. Recent study also extensively studied on the zygosity status of the HLA-DRB3*01:01 allele in predicting severe FNAIT (28). It would be interesting to study such association with common anti-HPA antibodies found in our population since this information is lacking. Investigation such as measurement of the implicated antibody level may also be useful. Antibody level measurement were found to correlate with severity

FNAIT as found in other studies (29).

Obstetric history is important as alloimmunization may occur due to fetomaternal haemorrhage during delivery or miscarriage (20). There were more multigravida mothers as compared to primigravida, which could be could be due to heightened immune response in subsequent pregnancies (23). In contrast, Kamphuis reported decreased antibody levels in pregnancy among multiparous women whereas levels were raised in the first sensitization in primigravida (30). It is therefore, important to take note that FNAIT may occur even in the first pregnancy unlikely red cell alloimmunization seen in ABO or Rhesus incompatibility.

Maternal factor such as parity was not significant in the development of FNAIT as compared to controls in our study. Blood group A was found to be associated with severe FNAIT as compared to blood group O (31). However, our study did not find significant difference in blood group between FNAIT and controls. Larger number of cases is needed to compare the difference between blood groups.

The most important neonatal parameter is the presentation of FNAIT. From our analysis, asymptomatic presentation is less likely to develop FNAIT. Bleeding manifestation seen in our FNAIT cases were rather mild such as petechial rash, purpura and hematoma. Two neonates had intracranial haemorrhages due to anti-HPA-5b. There was no intrauterine death due to FNAIT in our study. Since neonates with symptoms are more likely to FNAIT in our population, parents should be educated to look for these symptoms and seek professional advice early. FNAIT tend to be less severe in our population, nevertheless, diagnosis should not be missed as it is.

CONCLUSION

Based on our study, FNAIT remains as a rare condition even in our population. The low incidence of FNAIT could be due to underreporting. Malay mothers and symptomatic neonates with thrombocytopenia are more likely to have FNAIT . Although the sample size was small, the findings from our study may help to highlight the incidence and create awareness regarding FNAIT in our population. For future study, a larger sample size is required and the findings may provide more relevant information for clinicians in predicting this condition in the future .

ACKNOWLEDGEMENTS

Special appreciation to all staff at National Blood Centre, mainly the Platelet Serology Lab for their cooperation and support for this study.

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