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Idiopathic Thrombocytopenic Purpura Is More Severe in Children with a Recent History of Vaccination

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ABSTRACT

Background: Idiopathic thrombotic thrombocytopenia (ITP) the most common cause of acute onset thrombocytopenia in children, can be classified as primary (idiopathic) or secondary to different causal agents (drugs, vaccination, infections).
Objectives: This study is aimed to observe the severity of ITP based on the probable cause of the disease, specifically vaccination.
Patients and Methods: This retrospective observational study surveyed the records of all patients, aged 1 to6 months, who were admitted with the diagnosis of ITP at Mofid Children's hospital in a 5 year period (2005-2010). Based on history of recent vaccination (< 6 weeks), patients were divided into two groups. The severity of ITP, described by the platelet count, was then compared between the recently vaccinated and not recently vaccinated groups. Severe ITP was defined as platelet count below 20,000/mm^3. All ITP patients with concomitant diseases, diagnoses other than ITP, or simultaneous history of vaccination and probable virus infection were excluded.
Results: 51 patients were enrolled in this study (mean age = 3.86 ± 1.53 months; males = 32 [62.7%]). In 33 (64.7%) patients the platelets level was below 20000 /mm^3. Thrombocytopenia following vaccination was observed in 25 (49%) patients. The number of patients with platelet count below 20000 /mm^3 was significantly higher in the recently-vaccinated group (P value = 0.006). ITP was more frequent in the recently vaccinated children under 3 months of age (P Value = 0.03).
Conclusions: In this study, a higher rate of more severe ITP in recently vaccinated young children was observed in comparison with other probable etiologies. Further investigations are needed to explain this finding.

Keywords: Purpura, Thrombocytopenic, Idiopathic; Vaccination; Child

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Implication for health policy/practice/research/medical education:
Findings of this study could help to make policies to prevent ITP following Vaccination.

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1. Background

The most common cause of acute onset thrombocytopenia in an otherwise healthy child is idiopathic thrombocytopenic purpura (ITP) (1). Visible symptoms of ITP include the spontaneous formation of petechiae and purpura, especially on the extremities, bleeding from the nostrils or at the gums and menorrhagia. Which between them, the latter occurs if the platelet count is below 20,000 per mm^3 (2, 3). ITP can be classified as primary (idiopathic), or secondary to different causal agents (drugs, vaccination, infections) (4, 5). The primary treatment goal is more to prevent severe bleeding rather than achieving normal platelet counts. The incidence of ITP is estimated at 50–100 new cases per million per year (6, 7). ITP in children is usually self-limiting, with a typically acute onset and frequently occurring a few days or weeks after viral infection or vaccination (8-12). At least 70 percent of childhood cases will end up in remission within six months, even without treatment (7, 13-16).

Thrombocytopenia resolving before 6 months is called acute and is mostly observed in children. The male to female ratio in childhood cases are roughly equal for both genders (16, 17).

The clinical picture of post-vaccination ITP is believed to be similar to that of childhood ITP (18). Acute ITP was considered to be associated with the use of a vaccine in case there was no recognized etiology and the interval between vaccination and onset of acute ITP symptoms was within 5 weeks (19). However, none of the routine childhood vaccines given in the first year of life was known to be significantly associated with an increased risk of ITP (20). Studies reporting a link between MMR vaccination and ITP have been criticized because concomitant viral infections have not usually been excluded. ITP appears to arise following the measles, mumps, and rubella vaccine, although the incidence is very rare (18, 21, 22).

2. Objectives

This study goal was to observe the severity of clinical manifestations of ITP among 1-6 month old children admitted to Mofid Children's hospital within a 5 year period, based on probable etiologies of the disease.

3. Patients and Methods

This retrospective observational study surveyed the records of all patients, aged from 1 month to 6 months, who were admitted with the diagnosis of ITP at Mofid Children's hospital in a 5 year period from March 2005 untillMarch 2010. Exclusion criteria included concomitant infectious disease, renal impairment, hepatic disease, blood dyscrasia, or diagnoses other than ITP. Also those who had a recent history of vaccination and suspicious viral infection simultaneously were excluded.

Severe ITP was defined as platelet count below 20,000/mm^3. Studied variables included: demographic characteristics, platelets counts at the time of admission, one month after the diagnosis and 6 months after the treatment and result of the bone marrow aspiration (BMA).

Based on the presence of a history of recent vaccination in less than 6 weeks before the diagnosis of ITP or more than 6 weeks, patients were divided in to two groups and the severity of ITP based on platelet count was then compared between the recently vaccinated and not recently vaccinated groups.

Collected data were analyzed using SPSS software (version 15.0, Chicago, IL, USA). The data for continuous variables were reported as means ± standard deviation. For intergroup comparisons, the Chi-square test was used. The Mann-Whitney U-test and Student T-test were subsequently used for comparing group means. A P-value below 0.05 was considered significant.

4. Results

A total of 51 patients were eligible to enter this observational study (Mean age = 3.86 ± 1.53 months; males = 32 [62.7%]). Median age of the children was 3 months and infants between 1 to3 months were the largest age group. In 33 patients (64.7%) platelet level was under 20,000/mm^3. General characteristics of the patients are summarized in *Table 1*. No death or intracranial bleeding was reported in the study population.

Table 1. General Characteristics of the Study Population

Characteristic[a]	Total Population (n=51)
Age, d[b]	41.5 (1-180)
Male Gender, No.(%)	32 (62.7)
Baseline platelet count, /mm^3	15150.50 (1000-32000)
Platelet count after 1 month, /mm^3	183700.00 (26000.00-460000.00)
Platelet count after 6 months, /mm^3	221360.00 (39000.00-594000.00)
Platelet count less than 20000/mm^3	33 (64.7)
Rise of platelet count after 1 month, No.(%)	7 (13.7)
Rise ofmegacaryocytes, No.(%)	48 (94.1)

[a] Data are shown as frequency (percentage) or median (min, max).
[b] Age by days

History of recent vaccination was detected in 25 (49%) patients and there was no history of vaccination within the past 6 weeks in 26 (51%) patients. There was a significant difference between the recently vaccinated and not recently vaccinated group regarding platelet count (P = 0.006) (*Table 2*). Also, more patients had platelet counts less than 20,000/mm^3 in the recently-vaccinated ITP

group (P = 0.08). Platelet count after one month was significantly lower in the recently vaccinated group (P = 0.03), although there was no meaningful difference in platelet counts after 6 months.

Table 2. Comparing the Study Characteristics Between the Two Study Groups

Characteristic[a]	Recently-Vaccinated (n=25)	Not-recently Vaccinated (n=26)	P-value
Age, d	40.3 (1-180)	41.4 (1-180)	0.24
Male Gender, No. (%)	14 (56.0)	18 (69.0)	0.33
Baseline platelet count, /mm^3	14000 (1000-23500)	18000 (8000-32000)	0.006
Platelet count after 1 month, /mm^3	17500 (26000-460000)	190000 (29000-410000)	0.03
Platelet count after 6 month, /mm^3	220000 (39000-520000)	235000 (45000-594000)	0.16
Platelet counts less than 20000, No. (%)	19 (76.0)	14 (53.8)	0.08
Rise of platelet after 1 month, No. (%)	4 (16.0)	3 (11.5)	0.47
Rise ofmegacaryocytes,No. (%)	24 (96.0)	24 (92.6)	0.87

[a] Data are shown as frequency (percentage) or median (min- max).

Only one patient in the recently vaccinated group had serious bleeding and received blood transfusion. Bone marrow aspiration showed an increase in the number of megacaryocytes in 48 (94.1%) patients without any significant difference between the two groups.

Treatment options in the study population included corticosteroids in (46.3%) patients, intravenous immunoglobulin (IVIG) in (74.3%) patients and anti-D immunoglobulin in (6.6%) patients. No drug complication was reported in the study population. Response to treatment as described by platelet count at the end of the first month was not different between the groups. In other words, the rise of platelet count after one month was not significantly different between the recently vaccinated and not recently vaccinated group (P = 0.47).

Moreover, rise of megacaryocytes was not statistically different between the two groups (P = 0.87).

Those who had hemorrhagic symptoms were treated with Cyclosporine (86.1%), IVIG (13.9%), Danazol (13.9%), Anti-D (11.1%), Interferon A (5.6%), Vincristin (2.8%), Azatioprin (2.8%) and Anti CD20 antibody (2.8%). In case of inappropriate response to initial treatment, patients received combination therapy. Type of prescribed medications did not have any significant influence on the time to remission or platelet level after one month in both groups.

5. Discussion

This Study aimed to observe the relation between the etiology and clinical characteristics of primary ITP in infants aged between 1 to 6 months, by reviewing the records of surviving patients at Mofid Children's hospital within a 5 year period. It was observed that vaccine-related ITP results in more severe clinical manifestations in compared to other ITP etiologies.

In Iran, 11 children are vaccinated with OPV, HBV vaccine and BCG at birth. They receive OPV and DPT at 2, 4 and 6 months of age and HBV vaccine again at 2 and 6 months of age. Although we did not find an increased risk of ITP for any of the commonly given childhood vaccines, there was a significant relationship between a recent history of vaccination and severity of the acute disease in comparison with other probable etiologies. MMR has been proposed as the culprit in young children with an incidence of 1 to 3 children every 100,000 vaccine doses (5, 12, 23-25); however, MMR is injected at 12 and 18 months of age and this vaccine cannot be considered as the cause of ITP in the current study population. Development of ITP following other vaccines, particularly DPT, is restricted to few cases and the data is insufficient to assume a causal relationship (12, 26, 27). Several epidemiologic studies have been performed about ITP in children (20), however, they have not explored the severity of the disease based on the probable etiology (5).

Age and gender are the two most important factors in all studies about ITP in children (28). Although a female predominance is reported in previous studies (29), there was not a significant difference in our study population regarding gender. ITP is self-limiting and not life-threatening in most cases (4). Although complications of ITP in children are rare, they can be dangerous (30). In our study, no serious complication was observed. This may be due to early diagnosis and admission in the hospital.

In cases with platelet count < 10000/mm^3, steroids may be prescribed without any proven benefit (30). IVIG is suggested as the drug of choice by the American Society of Hematology, although it has no benefit over corticosteroids (31). There are no data showing that the treatment affects either short or long term clinical outcome of ITP (30, 32). In our study, there was no significant difference between the prescribed medications regarding time to remission and rise of platelet counts after one month.

Few cases have been reported to demonstrate a drop in the platelet count following the vaccine repeat (33, 34). However, there are more reports showing no evidence of recurring of

post vaccination ITP after repeating the vaccination (35, 36).

In this study, we considered duration of 6 weeks from the vaccination to the onset of the ITP syndromes. On the other hand, the vaccination intervals based on the national Vaccination Program is 2 months. Therefore, the cases that developed ITP in the last 2 weeks of the vaccination interval were considered as not recently vaccinated.

Conclusion:In this study, a higher rate of more severe ITP in recently vaccinated young children was observed, in comparison with other probable etiologies. In order to reach a more accurate result, studying the same topic on children older than 1.5 years is recommended.

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Authors' Contribution

None declared.

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