

Thrombocytopenic Purpura Following Vaccination in Early Childhood: Experience of a Medical Center in the Past 2 Decades

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Background: The etiology of thrombocytopenia during infancy and early childhood may be different from that of older children, because young children frequently receive vaccines. The following study was performed to understand whether there was a causal relationship between vaccinations and thrombocytopenia.

Methods: We retrospectively studied, through chart review, the relationship between vaccination and thrombocytopenic purpura in 20 children with thrombocytopenia (platelet count $<150 \times 10^3/\text{mm}^3$) under the age of 3 years who were hospitalized between 1989 and 2010. Cases with a history of infectious symptoms/signs between vaccination and the occurrence of thrombocytopenia were excluded. Thrombocytopenia cases not diagnosed as idiopathic thrombocytopenic purpura but as post-vaccination thrombocytopenic purpura should have a similar vaccination-to-thrombocytopenia interval as reported in Western journals, but which should not be more than 9 weeks after vaccination.

Results: Of the 20 cases of thrombocytopenic purpura, 12 followed vaccination and 8 were considered idiopathic. Of the 12 post-vaccination cases, 5 occurred after the second dose of hepatitis B virus vaccine at 1 month of age, 4 occurred after the first dose of diphtheria-tetanus-acellular pertussis-containing vaccine at 2–3 months of age, 2 occurred after the first dose of measles-mumps-rubella vaccine at 16 months of age, and 1 occurred after the first dose of varicella vaccine at 14 months of age. One of these 12 cases, who also had a marked decrease in hemoglobin level without bleeding, was suspected to have Evans syndrome.

Conclusion: Vaccination may be a risk factor for infant thrombocytopenic purpura. [*J Chin Med Assoc* 2010;73(12): 634–637]

Key Words: anemia, thrombocytopenia, vaccination

Introduction

The first thrombocytopenic purpura (TP) case following measles vaccination was reported in 1965,¹ and that following measles-mumps-rubella (MMR) vaccination was reported in 1983.² An active post-marketing surveillance in 1995 found evidence of increased risk of TP 15–35 days following vaccination.³ The first causal association between MMR vaccination and TP was reported in 2001.⁴ More vaccine safety surveillance studies of TP following MMR vaccination

in France, USA and Canada were published in 1996 and 2003.^{5–7}

Most reports of post-vaccination TP are after measles-containing vaccine.⁸ Reports of hematological adverse events following diphtheria-tetanus-pertussis (DTP) vaccination are rare. Only 1 report of 3 cases of acute hemolytic anemia in 1978,⁹ and 1 report of TP in 1993 have been published.¹⁰ Several reports of TP following hepatitis B virus (HBV) vaccination have been published since 1994, when active HBV vaccination was introduced worldwide.^{11–16} One report of



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Evans syndrome following recombinant HBV vaccination was described in an adult in 1992.¹⁶

Here, we report 12 children under the age of 3 years who developed post-vaccination TP during the past 2 decades in our hospital.

Methods

Through chart review, we retrospectively examined 20 TP children under the age of 3 years, who were hospitalized between 1989 and 2010, to search for a relationship between vaccination and TP or the cause of TP. Cases with a history of infectious symptoms/signs between vaccination and the occurrence of thrombocytopenia were excluded. Thrombocytopenia was defined as having a platelet count $< 150 \times 10^3/\text{mm}^3$. Anemia was defined as having a hemoglobin level < 2 standard deviations of the normal level for age. Thrombocytopenia cases not diagnosed as idiopathic TP (ITP) but as post-vaccination TP should have a similar vaccination-to-thrombocytopenia interval as reported in Western journals, but which should not be more than 9 weeks after vaccination.

Results

Twelve of the 20 TP cases were considered to be post-vaccination TP while 8 were not. The mean platelet count of the post-vaccination cases was $8 \times 10^3/\text{mm}^3$ (range, $1-19 \times 10^3/\text{mm}^3$). The mean intervals between

vaccination and TP were: 18 days (range, 6–34 days) following HBV vaccination; 16 days (range, 5–23 days) following acellular DTP (DTaP)-containing vaccination; 1 month following MMR vaccination; and 9 weeks following varicella vaccination.

Six of the 12 post-vaccination cases had received combined-component vaccines, including 4 cases following DTaP-containing vaccine that occurred before 3.5 months of age, and 2 cases after MMR vaccine at 16 months of age. The other 6 cases received single-component vaccines, including 5 cases after HBV vaccine at 1 month of age, and 1 case after varicella vaccine at 14 months of age.

Among these 12 cases, 1 also had a marked decrease in hemoglobin, but without bleeding. The hemoglobin dropped from 10 g/dL to 8 g/dL in 1 day, with normal stool routine, increased reticulocyte count to 3%, decreased haptoglobin to 36.4 mg/dL, and hemolytic pattern peripheral blood smear. This patient was suspected to have Evans syndrome, and TP occurred after the second dose of HBV vaccination at 1 month and 19 days of age. Four cases had their hemoglobin drop to a mean of 7 g/dL (range, 5.8–8.0 g/dL); they had stool occult blood without gross tarry stool, bloody stool, or gastrointestinal symptoms.

Eleven of the post-vaccination TP cases were treated with intravenous immunoglobulin (IVIG) 2 g/kg over a period of 2–4 days; the remaining case was treated with steroid. All 12 cases recovered within 4 days (range, 1–6 days) without recurrence, even after receiving the same vaccination later on. All of the information above is summarized in Table 1.

Table 1. Patient characteristics, biological data, treatment and outcome

Case	Age	Vaccination date	Vaccine type	TP onset date	Platelet count ($\times 10^3/\text{mm}^3$)	Hb (g/dL)	TP duration	Treatment	Recurrence
1	1 mo 18 d	Aug 31, 1989	2 nd HBV	Sep 16, 1989	3	7.4	4 d	IVIG	No
2	2 mo 6 d	Jun 6, 1990	2 nd HBV	Jun 25, 1990	10	5.8	6 d	IVIG	No
3	2 mo 7 d	Jun 13, 1995	2 nd HBV	Jul 17, 1995	1	7.0	1 d	Steroid	No
4	1 mo 26 d	May 27, 1996	2 nd HBV	Jun 12, 1996	8	10.0	6 d	IVIG	No
5	1 mo 19 d	Mar 25, 2006	2 nd HBV	Mar 31, 2006	3	8.0	5 d	IVIG	No
6	2 mo 26 d	May 8, 2001	2 nd HBV	Aug 4, 2001	8	9.0	1.5 d	IVIG	No
			1 st 3-in-1						
7	3 mo	Apr 9, 2005	1 st 5-in-1	May 2, 2005	5	8.9	5 d	IVIG	No
8	2 mo 9 d	Jun 17, 2006	1 st 5-in-1	Jun 23, 2006	5	8.9	3 d	IVIG	No
9	3 mo 2 d	Dec 10, 2007	2 nd 6-in-1	Dec 15, 2007	2	8.0	6 d	IVIG	No
10	1 yr 4 mo	Oct 20, 1997	1 st MMR	Nov 20, 1997	18	12.7	2 d	IVIG	No
11	1 yr 4 mo	Aug 6, 2002	1 st MMR	Sep 6, 2002	19	10.5	2 d	IVIG	No
12	1 yr 2.5 mo	Feb 11, 2006	1 st varicella	Apr 15, 2006	18	11.8	6 d	IVIG	No

TP = thrombocytopenic purpura; Hb = hemoglobin; HBV = hepatitis B virus vaccination; IVIG = intravenous immunoglobulin; 3-in-1 = diphtheria-tetanus-acellular pertussis-containing vaccine; 5-in-1 = 3-in-1 + Haemophilus influenzae type b + inactive polio virus; 6-in-1 = 5-in-1 + HBV; MMR = measles-mumps-rubella vaccination.

Of the 8 ITP cases, all had a history of recovery from recent virus infection such as upper respiratory tract infection.

Discussion

In Taiwan, the current vaccination policy is: 3 doses of HBV vaccine, which are given in the first 5 days after birth, then at 1 month and finally at 6 months; 4 doses of DTaP-containing vaccine, which are given at 2, 4, 6 and 18 months; varicella vaccine, which is given at 1 year; and MMR vaccine, which is given at 15 months. Whole-cell DTP vaccine (trivalent) has been imported since 1954, DTaP (trivalent) since 1998, DTaP-*Haemophilus influenzae* type b (Hib)-inactivated polio virus (pentavalent) since 2002, and pentavalent-HBV (hexavalent) since 2005.

In this study, the first dose of trivalent or pentavalent vaccine before 3 months of age resulted in TP, while the second, third and fourth doses at 4, 6 and 18 months did not. In addition, the second dose of hexavalent vaccine at 3 months resulted in TP. Therefore, rather than considering whether it is the first or second dose of a vaccine, we suspect that infants older than 4 months of age will not have TP after receiving DTaP-containing vaccination. Because TP following Hib vaccine or inactivated polio vaccine has not been reported, but TP has been reported after DTaP vaccine, we suspect that the DTaP component in pentavalent vaccine will lead to TP.¹⁰

The interval between vaccination and TP in this study is the same as that reported by others, especially the longer interval between measles-containing vaccine and TP. But the interval between varicella vaccine and TP was 9 weeks in our study, although it was only 6 weeks in other reports.^{7,8,17-20} This difference needs large-scale case study in Taiwan to verify whether our case was of ITP or post-varicella vaccine TP.

Two of the ITP cases had received MMR or measles vaccine 1.5 months previously and had had upper respiratory tract infection 10 days before TP. Western investigators have reported that TP occurs within 1 month following measles-containing vaccination. As for our 2 cases, 1.5 months is a rather long interval to correlate with vaccination, so we assumed that they were not of post-vaccination TP.

Three TP cases following DTaP-containing vaccination were with pentavalent or hexavalent vaccines between mid-2005 and the end of 2007; the other case was after DTaP vaccination in 2001. There was no case between 2001 and 2005. Four TP cases following HBV vaccination occurred between 1989 and

1996, and 1 case occurred in 2006. There were no cases between 1996 and 2006. So, in this study, there were clustered occurrences over specific years for DTaP-containing or HBV vaccines. These findings need further large-scale country-wide review to clarify their significance. Two cases of TP before 1992 occurred following plasma-derived HBV vaccination in this study. But no other TP case following plasma-derived HBV vaccination has previously been reported.¹⁴ No TP following Japanese B encephalitis vaccination, oral polio vaccination, or rotavirus vaccination was found in our study. TP following influenza or pneumococcus vaccination has been reported by other investigators, but did not occur in this study.^{7,21}

The most frequent cause of post-vaccination TP in this study was HBV vaccination, followed by DTaP, and then MMR. However, in Western reports, MMR vaccination was the most frequent cause, followed by DTP and then HBV.⁷

There is discussion on whether or not such severe thrombocytopenia after vaccination is immune-mediated.²² Although childhood ITP has an 85% recovery rate, it will sometimes relapse months or years later. All of our post-vaccination TP cases recovered and did not experience recurrence even after the same vaccination months later. Post-vaccination TP has the same clinical picture and treatment options as ITP. The first-line treatment option for ITP is usually steroids. However, all except 1 of our post-vaccination TP cases were treated with IVIG to avoid any steroid-related complication in infants. The usual timing of further vaccination after previous IVIG treatment is 6 months later. But our pediatricians sometimes administer further vaccinations earlier than that, resulting in reduced antibody production. So, from this study, our treatment suggestion for post-vaccination TP is short-term steroids, on the basis of there being no recurrence and benign course in our cases, to avoid further vaccination delay.

Through several types of laboratory tests, including red blood cell morphology of peripheral blood smear, reticulocyte count and haptoglobin, we suspected that the patient who had anemia had immune hemolytic anemia. We did not perform further detailed laboratory examinations to prove this because it is not practical to draw more blood from such a small baby, and it is not easy to prove autoimmune hemolytic anemia without detailed tests.^{9,23} So, this case was only suspected to be Evans syndrome following HBV vaccination, and different from Western reports following DTP vaccination in adults. It is possible that the impracticality of drawing a sufficient amount of blood for unequivocal diagnosis is the reason for why there

is no report of Evans syndrome following vaccination in infants and children.¹⁶

Because of the limited case number in our study, a country-wide large-scale retrospective review of the issues examined in this report, and prospective studies to compare the pros and cons of treatment with steroids or IVIG, should be conducted.

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