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Association between Drug and Vaccine Use and Acute Immune Thrombocytopenia in Childhood

A Case-Control Study in Italy

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Abstract

Background: Immune thrombocytopenic purpura (ITP) is an immune-mediated disease characterized by a decrease in platelet count and, in its more severe forms, by bleeding symptoms. Many drugs have been implicated in the pathogenesis of drug-induced thrombocytopenia in adults; only limited data on drug-related ITP in children have been published.

Objective: Our study was set up to evaluate the consistency of the association between drug and vaccine use and ITP in children.

Study Design: This study is part of an Italian multicentre study on adverse drug reactions in children, coordinated by the Italian National Institute of Health, which was started in November 1999 and is ongoing.

Patients or Other Participants: The study was conducted by enrolling all children aged more than 1 month who were hospitalized through the paediatric emergency department for the following conditions: thrombocytopenia (platelet count $<100\times10^3$/L); acute neurological disorders; non-infectious mucocutaneous diseases and vasculitis; and endoscopically confirmed gastroduodenal lesions and/or clinically defined haematemesis and melaena. Children with chronic pathologies or concomitant diagnoses of cancer or immunodeficiency were not included in our study.

Main Outcome Measure: During hospital admission, a physician interviewed parents using a structured questionnaire. The main aim of the interview was to collect information on drug exposure in a time period of 3 weeks and vaccine exposure in a period of 6 weeks preceding hospitalization. Using a case-control study design, exposure of children with thrombocytopenia (cases) to drugs and vaccines was compared with similar exposure of children

with gastroduodenal lesions and neurological disorders (controls); this allowed us to estimate the odds ratios (ORs) of the occurrence of thrombocytopenia associated with the use of drugs or vaccines.

Results: Up to December 2007, the study population included 387 cases of thrombocytopenia and 1924 controls. Despite the low platelet count, ITP was generally a mild disease, without serious bleeding in the majority of cases and associated with a short length of hospital stay. After adjusting for concurrent use of other drugs, use of the antibacterials was associated with a more than 2-fold increase in the risk of developing ITP (OR 2.4; 95% CI 1.8, 3.1). Mucolytics and NSAIDs were associated with an OR of 1.9; 95% CI 1.2, 2.9 and 1.5; 95% CI 1.0, 2.1 respectively, while paracetamol (acetaminophen) was associated with an OR of 1.5; 95% CI 1.2, 2.0. MMR vaccination was associated with an increased risk of developing ITP (OR 2.4; 95% CI 1.2, 4.7).

Conclusions: The results of this study provide evidence for an association between ITP and exposure to selected antibacterials, NSAIDs, paracetamol, mucolytics and MMR vaccination.

Background

Immune thrombocytopenic purpura (ITP) is an immunomediated disease characterized by a decrease in platelet count and, in its more severe forms, by bleeding symptoms.[1] Although ITP has been known for many years, many unresolved issues regarding its clinical definition, pathogenic mechanism, epidemiology, diagnosis and management still remain.[1]

Some studies have reported an incidence of ITP of five cases/100 000 children per year and a prevalence of 4.6/100 000.[2-4] The aetiology of ITP can be primary (idiopathic) or secondary to different causal agents (drugs, pathologies such as systemic lupus erythematosus, and viral and bacterial infections).[5,6]

Drugs may be involved in the development of thrombocytopenia, either through a direct toxic effect on the bone marrow, resulting in decreased platelet production, or through immune-mediated mechanisms, resulting in increased platelet destruction.[7] Many drugs have been implicated in the pathogenesis of drug-induced thromobocytopenia in adults; those most frequently reported as possible causes are heparin, antibacterials, NSAIDs, cinchona alkaloid derivatives (quinine, quinidine), sulfonamide antibacterials, anticonvulsants, disease-modifying antirheumatic drugs, diuretics and tuberculostatics.[7-12]

On the contrary, limited data on drug-related ITP in children have been published.[13]

In children, ITP has also been described in association with vaccinations; the majority of the cases are attributable to live virus vaccines, mainly the measles, mumps and rubella (MMR) vaccine. The absolute risk of developing ITP after MMR vaccine is estimated to be approximately 1 in 21 000–100 000 inoculations.[14-18] ITP associated with vaccination is generally a mild disease, with few serious bleeding episodes or long-term sequelae, despite the low platelet count found in many of the children.[16,18]

The aim of the study was to estimate, using a case-control design, the consistency of the association between ITP and exposure to drugs and vaccines in childhood.

Patients and Methods

This study is part of an Italian multicentre study on adverse drug reactions in children, started in November 1999 and still ongoing, coordinated by the Italian National Institute of Health and involving four paediatric hospitals – Department

of Paediatrics, University of Padua; Giannina Gaslini Paediatric Hospital, Genova; Bambino Gesù Hospital, Rome; and the Santobono-Pausilipon Paediatric Hospital, Naples. The study was set up with the aim of investigating the association between drugs and vaccines and the occurrence of selected medical conditions, using case-control methodology.

All children hospitalized through the paediatric emergency department for the following conditions were included in the study: thrombocytopenia (platelet count $<100\times10^3$/L); acute neurological disorders (convulsions were included only when not associated with fever); non-infectious mucocutaneous diseases and vasculitis; and endoscopically confirmed gastroduodenal lesions (and/or clinically defined haematemesis and melaena). Exclusion criteria were age <1 month and >18 years, and the presence of the following concomitant pathologies: cancer, immunodeficiency, and chronic renal and hepatic failure. Furthermore, children presenting with acute events related to a reactivation of an underlying chronic disease or a congenital anomaly were not included.

During hospital admission, a physician interviewed the parents using a structured questionnaire. The main aim of the interview was to collect information on drug exposure in a time period of 3 weeks (6 weeks for vaccines) preceding hospitalization. We investigated the exposure to all drugs, including herbal remedies and homeopathic products. Data on drug use, such as indication, dose, duration of treatment, prescriber (physician- or self-medication) and other individual data (age, sex, weight, height, chronic diseases and parents' education) were also collected. Parents were asked for febrile infections that occurred in the 3 weeks before hospital admission. The information on the reason for admission came from the paediatric emergency department records, whereas the final diagnosis was retrieved from the clinical records after discharge. Informed consent for utilization of data for research purposes was obtained.

Using a case-control study design, drug or vaccine exposure of children with one of the selected conditions (cases) was compared with that of children with the remaining conditions (controls); this allowed us to estimate the odds ratio (OR) of the occurrence of each condition and the use of drugs or vaccines.

In this study, we present only the results related to ITP and its association with exposure to drugs and vaccines from the beginning of the study in November 1999 to December 2007.

In order to calculate the OR, drug or vaccine exposure of children with thrombocytopenia (cases) was compared with that of children with gastrointestinal lesions and neurological disorders (controls). Children with mucocutaneous diseases were excluded from the control group because the drugs more frequently used by this group of children (i.e. antibacterials and NSAIDs) are also used by children presenting with ITP, thus their inclusion could result in an underestimation of the risks. Multiple logistic regression was used to adjust for potential confounding factors. SPSS (version 15.0, Chicago, IL, USA) was used for data analysis.

Results

During the study period, 4042 children satisfied the inclusion criteria. They included 387 patients with ITP and 3655 patients with other conditions (1573 with neurological disorders, 351 with gastrointestinal lesions and 1731 with mucocutaneous diseases). Children with mucocutaneous diseases were subsequently excluded from the control group for the reasons described in the methods section (figure 1).

The main characteristics of cases and controls are reported in table I.

The mean age at diagnosis of patients with ITP was 4.9 years and there was an equal distribution between sexes. Most cases had very low platelet count (mean platelet count was 10×10^3/L). The onset of ITP in our study population was characterized in 79.3% of cases by bruising and petechiae. Less frequently, patients presented with epistaxis, with or without bruising (7.2%). In 10.3% of cases, the finding of a low platelet count was occasional, without clinical signs or symptoms, emerging during laboratory examinations prescribed by their family paediatrician or performed

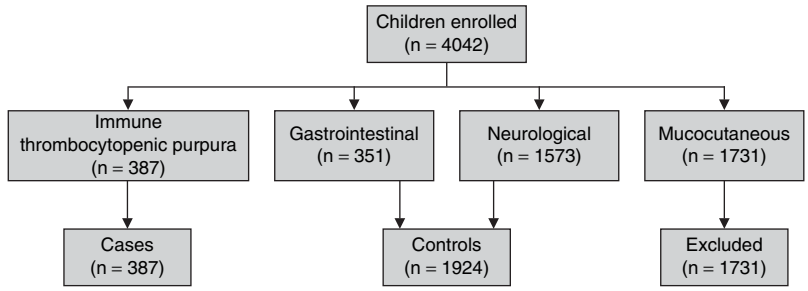

Fig. 1. Selection of cases and controls.

in the paediatric emergency department for other indications different from ITP. None of the children with bleeding were haemodynamically unstable, no child with ITP developed intracranial haemorrhage and no child died (table II).

Fifty-nine percent of ITP patients were exposed to drugs during a period of 3 weeks before hospital admission. The most frequent indications for the use of drugs were upper respiratory tract infections, fever, otitis and pain/headache. In total, 181 children (46.8%) with ITP had an infection in the 3 weeks preceding the hospitalization. The main diagnoses were upper respiratory tract infections (35%), fever (27%), flu (11%), gastroenteritis (6%) and otitis (3%). Fifty-five percent of control patients were exposed to drugs for the same indications as the cases.

In the case-control analysis, we focussed on the classes of drugs with at least ten exposed cases (table III). The use of antibacterials, paracetamol (acetaminophen), mucolytics and anti-inflammatory drugs was associated with an increased risk of thrombocytopenia, while corticosteroids were not. After adjusting for potential confounding factors due to concurrent use of other drugs, the use of antibacterials was associated with a more than 2-fold increase (OR 2.4; 95% CI 1.8, 3.1). In particular, penicillin use had an OR of 1.9; 95% CI 1.3, 2.7, cephalosporin, 2.3; 95% CI 1.6, 3.4 and macrolides, 2.6; 95% CI 1.6, 4.2. Mucolytic use was associated with an almost 2-fold increase in risk (OR 1.9; 95% CI 1.2, 2.9). An increased risk of thrombocytopenia was associated with NSAID (OR 1.5; 95% CI 1.0, 2.1) and paracetamol (OR of 1.5; 95% CI 1.2, 2.0) use, but not with corticosteroid use (OR 0.8; 95% CI 0.5, 1.3) (table III).

Table IV reports the specific drugs more frequently used in our population, with at least ten users among ITP patients.

Eleven percent of cases and 10% of controls were vaccinated in the 6 weeks preceding hospital admission. The OR estimated for ITP within 6 weeks after vaccination was 0.9; 95% CI 0.6, 1.3 for all vaccines, and 2.4; 95% CI 1.2, 4.7 for the MMR vaccination (table V).

Discussion

All epidemiological studies performed on thrombocytopenia in childhood differ from each other largely in methodology used, inclusion and exclusion criteria, and duration. In our study, the mean age at presentation of ITP was 4.9 years. Studies by Kuhne et al.[19] and Watts[20] reported that the mean age of acute ITP was 5.1 and 5.2 years, respectively.

We observed that both sexes were equally affected. This finding was, in part, confirmed by Kuhne and colleagues[21] who described an equal

Table I. Characteristics of the study population

Characteristic	Cases	Controls
Number	387	1924
Mean age [y (SD)]	4.9 (3.5)	5.7 (4.9)
Females (%)	46.2	45.7
Mean length of hospital stay (days)	5.5	3.6
Children exposed to drugs (%)	58.9	55.2
Children exposed to vaccines (%)	11.1	10.4

Table II. Most common signs and symptoms at presentation[a]

Clinical signs and symptoms at presentation	No. (%)
Bruising, purpura or petechiae	307 (79.3)
Epistaxis (with or without bruising)	28 (7.2)
Occasional finding without signs or symptoms	40 (10.3)
Other	12 (3.2)

a Mean platelet count (25th–75th percentile) was 10×10^3/L ($5–21\times10^3$/L).

distribution between sexes in children older than 1 year of age, whereas in small children they observed a predominance of boys. Other authors described a predominance of boys among children under 10 years of age.[22-24]

In our population, the onset of ITP was generally acute – patients presented with bruising and petechiae in 79% of cases and, less frequently, epistaxis (7%). Only 10% of cases presented with a low platelet count without clinical signs or symptoms. For different authors, in most cases physical examination at presentation was remarkable for the cutaneous manifestations of severe thrombocytopenia (bruising and petechial rash). Mucosal bleeding occurred less frequently.[4,20,23,25] In children with acute ITP, the key laboratory finding was an isolated and often severe thrombocytopenia. In our patients, the mean platelet count was 10×10^3/L. Other studies reported that in more than 50% of cases, platelet count at presentation was $<20\times10^3$/L.[4,19,20,24-26]

According to the literature,[2-4] despite the low platelet count, ITP was generally a mild disease in the majority of cases, without serious bleeding and with a short-lasting course (the mean length of hospital stay was about 5 days).

The purpose of this study was to evaluate the consistency of the association between drug and vaccine use and ITP requiring hospitalization in children. In order to provide risk estimates, data were analysed according to a case-control study design.

Drug or vaccine exposure of children with one of the selected conditions was compared with that of children with the remaining conditions. This design was used to ensure that case and control patients, all of whom were hospitalized, were as comparable as possible with regard to their drug exposure ascertainment. In fact, one of the limits of case-control studies is the so-called recall bias, a difference in the accuracy of recall between cases and controls with regard to their drug exposure history. For this reason, it was decided not to select controls from the general population. We are confident that children included in the control population provided a valid estimate of the source population of our cases. This is because they represented children with acute conditions, admitted through the same Paediatric Emergency Departments, whose histories were taken in a similar way. Considering how the information on previous drug use was gathered, the possibility of a differential recall bias is very low. As this study was conducted in the Paediatric Emergency Department, it was not possible to investigate the pathogenetic role of drugs in ITP development.

Table III. Drug class exposure (with at least ten users in immune thrombocytopenic purpura [ITP] patients) and estimated odds ratio for ITP

Drug	Cases (n = 387)	Controls (n = 1924)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Antibacterials	107	286	1.5 (2.0, 2.7)	2.4 (1.8, 3.1)
penicillin	43	120	1.3 (1.9, 2.9)	1.9 (1.3, 2.7)
cephalosporin	43	98	1.6 (2.4, 3.6)	2.3 (1.6, 3.4)
macrolides	27	53	1.7 (2.9, 4.9)	2.6 (1.6, 4.2)
Mucolytics	30	80	1.3 (2.2, 3.5)	1.9 (1.2, 2.9)
NSAIDs	50	174	1.1 (1.5, 2.2)	1.5 (1.0, 2.1)
Paracetamol (acetaminophen)	86	296	1.6 (1.2, 2.2)	1.5 (1.2, 2.0)
Corticosteroids	28	157	0.6 (0.96, 1.5)	0.8 (0.5, 1.3)

a OR adjusted for the concomitant use of other drugs.

OR = odds ratio.

Table IV. Drugs frequently used in our population (with at least ten users in immune thrombocytopenic purpura patients)

Drug	Cases (%) [n = 387]	Controls (%) [n = 1924]
Paracetamol (acetaminophen)	86 (22.2)	296 (15.4)
Amoxycillin and clavulanic acid	29 (6.9)	80 (4.2)
Clarithromycin	18 (4.3)	32 (1.7)
Niflumic acid	17 (4.1)	30 (1.6)
Cefaclor	14 (3.3)	35 (1.9)
Amoxycillin	14 (3.3)	37 (2.0)
Betamethasone	11 (2.6)	89 (4.7)
Beclometasone	11 (2.6)	80 (4.2)
Cefixime	11 (2.6)	23 (1.2)
Ibuprofen	11 (2.6)	34 (1.8)
Ambroxol	11 (2.6)	33 (1.8)

We found that the use of antibacterials, mucolytics and NSAIDs during the 3 weeks before hospital admission for ITP was associated with an increased risk of thrombocytopenia. After adjusting for concurrent use of other drugs, the use of antibacterials such as penicillin, cephalosporin and macrolides, was associated with an almost 2-fold increase with small differences among these classes.

Literature reports refer to several drug classes implicated in the pathogenesis of drug-induced thrombocytopenia in adults.[7-12] Most of these are not frequently used in the paediatric population. NSAIDs and antibacterials are used in both adults and children, even if different drug classes have a different prevalence of use in these populations. For example, cotrimoxazole, which is frequently prescribed in adults, is now not commonly used in children and for this reason we could not provide an estimation of its risk. Apart from these considerations, the role of such drugs in the development of ITP remains unclear.

In our population, about half of the cases were preceded by an infectious illness, especially upper respiratory tract infections. In a minority of cases, children affected by ITP had specific viral illnesses (chickenpox, mumps, rubella, infectious mononucleosis, etc.) in the previous 3 weeks. This finding of infectious illness preceding the diagnosis of ITP is within the range of other European studies.[22]

The drugs we found associated with ITP development are widely used to treat infections in children. It has to be considered that the indication for use (viral infections, upper respiratory tract infections, etc.) may represent an alternative explanation to the occurrence of ITP. Nevertheless, when drugs or drug categories have the same indications for use, confounding by indication should not influence the comparison of the different risk estimates.

An association between MMR vaccination and ITP has been widely described in the literature. In our study, the OR of developing ITP during the 6 weeks following MMR vaccination was 2.4; 95% CI 1.2, 4.7. Other studies evaluating the risk of developing ITP after MMR vaccine[16,17] have found a relative risk of 6.3; 95% CI 1.3, 30.1 and a relative incidence of 3.27; 95% CI 1.49, 7.16, respectively.

We did not estimate the incidence of developing ITP after MMR; in other studies, it resulted in approximately 1 in 21 000–40 000 inoculations, with two of three cases being attributable to the vaccine.[14-17] This is considerably less than the risk of developing ITP after natural measles (which is common), rubella (estimated to be about 1 in 3000 cases) or mumps (which is rare).[17]

Concerning follow-up, this study did not evaluate sequelae or recurrence of ITP after subsequent vaccinations or after the administration of the second dose of MMR. In the literature, recurrence is a rare event.[17,26] Furthermore, some studies provide clear evidence that children with a history of ITP prior to the first dose of MMR vaccination are not at an increased risk for a vaccine-associated episode and that

Table V. Vaccination exposure and estimated odds ratio for immune thrombocytopenic purpura after vaccinations

Vaccine	Cases (n = 387)	Controls (n = 1924)	Adjusted OR[a] (95% CI)
All vaccines	43	197	0.9 (0.6, 1.3)
Measles, mumps and rubella	14	27	2.4 (1.2, 4.7)
Other vaccines	29	170	0.7 (0.5, 1.1)

a OR adjusted for age and use of drugs.

OR = odds ratio.

vaccine-associated cases tend to be milder than others.[14-17]

Conclusions

This is the first study that aims at estimating the risk of developing ITP following exposure to common drugs or vaccines in the paediatric population using a case-control design. Other strengths of the study are its size and multicentre nature, with the opportunity to study a large population of children affected by a rare disease.

The results of this study provide evidence for an increased risk of developing ITP following exposure to antibacterials, NSAIDs, paracetamol and mucolytics, underlining the importance of a careful evaluation of risks and benefits for a more rational use of drugs in children. In interpreting these findings, we have to consider that the presence of infectious illness in half of our patients could represent a source of bias and that we have not investigated the pathogenetic role of drugs in ITP development. It is important in developing a more rational use of drugs in children, to further evaluate carefully the risks and benefits of their use.

We also confirmed an increased association between MMR vaccination and ITP, as described in the literature. As the risk of ITP after vaccination is smaller than the one after natural infections with these viruses, it is clear that the benefits of vaccination programmes greatly exceed the significance of this possible adverse effect. Although thrombocytopenia is initially severe, the subsequent course is generally benign and short-lasting.

Further studies are required to increase knowledge on this topic; whereas several studies have been performed in the adult population, in children they are still lacking.

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