A PROSPECTIVE COMPARATIVE STUDY OF 2540 INFANTS AND CHILDREN WITH NEWLY DIAGNOSED IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) FROM THE INTERCONTINENTAL CHILDHOOD ITP STUDY GROUP

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Objective To analyze prospectively the impact of age at diagnosis in childhood idiopathic thrombocytopenic purpura (ITP).

Study design International registry from June 1997 to May 2001, with analysis of data from baseline and 6-month-follow-up questionnaires.

Results Data from 2540 patients were analyzed, including 203 infants (7.6%), 1860 children ≥1 to <10 years of age (69.1%), and 477 children and adolescents between ≥10 and <16 years of age (17.7%). The mean platelet count at diagnosis was similar in all three groups, as was the percentage of patients with initial platelet count $<20 \times 10^9$/L. The male/female ratio was highest in infants and decreased with age ($P = .009$). Immunoglobulin therapy was used more often in infants and corticosteroids in patients ≥10 years of age. Follow-up information at 6 months was available for 1742 children (68.6%). Chronic ITP was seen less frequently in infants (23.1%) than in children >10 years of age (47.3%, $P < .0001$). Intracranial hemorrhage occurred in 3 of 1742 children during the first 6 months after the diagnosis of ITP.

Conclusions Pediatric patients with ITP from infancy to adolescence exhibit heterogeneity in clinical, demographic, and treatment factors. *(J Pediatr 2003;143:605-8)*

Idiopathic or immune thrombocytopenic purpura (ITP) is a bleeding disorder of infants, children, and adults. Antibody-coated platelets are removed from the circulation by the monocytic phagocytic system, resulting in a shortened platelet survival. The majority of affected children have the acute form of ITP, defined by a duration of thrombocytopenia ($<150 \times 10^9$/L) of <6 months. Approximately 20% of children and the majority of adults have chronic ITP, which lasts 6 months or longer.

Most published studies of ITP in children have included patients of all ages as a single group. A retrospective review by Lowe and Buchanan[1] demonstrated that adolescent patients are at greater risk of having chronic ITP than younger children. Since children of different ages may have differing clinical courses, better delineation of the natural history of ITP in each age group is needed. In particular, information about ITP during the first year of life is limited. To achieve this goal, prospective data obtained from the Intercontinental Childhood ITP Study Group (ICIS) were analyzed to determine the clinical characteristics, complications, and management decisions for three specific groups of children with ITP: infants, children 1 to 10 years of age, and children and adolescents 10 to 16 years of age.

METHODS

Registry

The ICIS Registry was initiated in 1997 to obtain prospective data on the natural history of ITP in children.[2] Informed consent was obtained as required by local institutional review boards.

ICH	Intracranial hemorrhage	ITP	Idiopathic thrombocytopenic purpura
ICIS	Intercontinental Childhood ITP Study Group	IVIG	Intravenous immunoglobulin

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*All participating investigators and institutions are acknowledged at www.unibas.ch/itpbasel.

Supported in part through an unrestricted grant from Novartis Pharma AG.

Submitted for publication Feb 20, 2003; revision received June 13, 2003; accepted Aug 22, 2003.

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0022-3476/2003/$30.00 + 0

10.1067/S0022-3476(03)00535-3

Questionnaires

The baseline questionnaire included demographic information, date of diagnosis, platelet count at diagnosis, presence of a prior infectious illness, whether a bone marrow aspirate was performed, whether the patient was admitted to the hospital, and prescribed treatment (intravenous immunoglobulin [IVIG] or corticosteroids). After 6 months, a follow-up questionnaire was requested to distinguish acute and chronic ITP. In addition, the second questionnaire established whether the patient had bleeding episodes during the 6-month-period, whether intracranial hemorrhage (ICH) occurred, and whether the patient received any platelet-enhancing treatment during the evaluation period.

Diagnosis

The diagnosis of ITP was determined by the local physician on the basis of history and physical examination; a complete blood count revealing isolated thrombocytopenia (platelet count $<150 \times 10^9$/L), normal hemoglobin concentration, white blood cell count, and peripheral blood smear; and absence of underlying conditions such as HIV, systemic lupus erythematosus, or malignancy. A bone marrow aspirate, serological studies for infectious and rheumatic diseases, and coagulation studies were performed as clinically indicated. Treatment decisions were left to each physician participating in the Registry.

Classification

Patients were arbitrarily classified according to age at diagnosis of ITP. Infants younger than 3 months were excluded from the study to avoid inclusion of patients with thrombocytopenia secondary to maternal alloantibodies or autoantibodies. Group 1 consisted of infants >3 months of age but <12 months. Children ≥12 months of age and <10 years were assigned to group 2, and children and adolescents ≥10 years of age but <16 years of age defined group 3.

Statistics

The data were grouped according to age (groups 1 through 3). The Mann-Whitney test was used to detect differences between group 1 and either group 2 or group 3. In addition, all comparisons were done with the *t* test, based on the logarithms of the measured values. The conclusions were similar with both methods; only *P* values from nonparametric methods were reported. With data divided into classes according to two variables (as age groups versus initial treatment), the data splits in classes with dimensions 2×2 to 3×4. First, the classic χ^2 test according to Pearson was performed; in addition, all tables were analyzed with the Fisher exact test. This was done for the (2×2) as well as for $(r \times s)$ tables (r, s ≥2). In some situations with a large number of cases and classes, the program STATA (Release 7.0, STATA Corp, College Station, Tex) had not been able to calculate the *P* value; therefore, StatXact (CYTEL Software Corp, Cambridge, Mass) was used with the Monte Carlo option. The *P* values given are those of the exact test; both methods lead to the same decisions. In some special situations (male/female ratio), the trend according to age was tested by means of logit regression. A value of $P < .05$ was considered statistically significant.

RESULTS

A total of 220 physicians from 39 countries and 147 institutions enrolled patients in the ICIS Registry. The number of enrolled patients varied: >50 patients by 12, 21 to 50 patients by 24, 11 to 20 patients by 29, 6 to 10 patients by 33, and <5 patients by 122 physicians. The patients presented in this analysis include the 2031 patients described earlier,[2] with additional subjects added in the year before study closure in May 2001.

Patient Demographics and Clinical Characteristics of ITP

From June 1997 to May 2001, 2690 children with newly diagnosed ITP were enrolled in the Registry (Table). Data from 150 registered children were excluded from this analysis because of age <3 months (81 children) or >16 years (69 children). Of 2540 eligible patients, 203 (7.6%) were infants (group 1), 1860 (69.1%) were children 1 to 10 years of age (group 2), and 477 (17.7%) patients were 10 to 16 years of age (group 3).

The male/female ratio was highest in infants, with a decreasing trend toward older age ($P = .009$). The mean initial platelet count (± SD) of infants at presentation was $14.6 \pm 16.5 \times 10^9$/L, which was similar in the two other groups ($P = .53$). The percentage of patients with an initial platelet count of $<20 \times 10^9$/L in the three groups was also similar (76.7%, 78.5%, and 75.2%, respectively). Initial platelet counts did not differ by sex.

An infection was present before the diagnosis of ITP in 56% (1404/2507) of patients, the majority within 21 days before the diagnosis of ITP. An infection before diagnosis of ITP was most common in children 1 to 10 years of age (60.2%) and occurred less frequently in infants and in children 10 to 16 years of age (52.0% and 41.2%, respectively).

Treatment: Platelet-Enhancing Therapy and Observation

Initial therapy is shown in Figure 1, and initial platelet counts of patients receiving drug treatment are illustrated in Figure 2. The percentage of children admitted to the hospital decreased with increasing age ($P < .05$).

Acute and Chronic ITP

A 6-month follow-up platelet count was obtained at a mean of 169.5 ± 83.5 days from diagnosis in 1742 of 2540 patients (68.6%), including 134 of 203 (66.0%) in group 1, 1297 of 1860 (70.0%) in group 2, and 311 of 477 (65.2%) in group 3. Chronic ITP occurred significantly less frequently in infants than in older children ($P < .0001$): group 1, 23.1%; group 2, 28.1%; and group 3, 47.3%. The number of children

Table. Patient characteristics, hospitalization, and bone marrow aspiration

	Group 1 (n = 203)	Group 2 (n = 1860)	Group 3 (n = 477)
Mean age (y ± SD)	0.58 ± 0.22	4.5 ± 2.46	12.62 ± 1.71
Male/female subjects	128:74	992:853	245:229
Male/female ratio	1.73	1.16	1.07
(95% CI)	(1.29–2.33)	(1.06–1.28)	(0.89–1.68)
Mean platelet count ($\times 10^9$/L)	14.6 ± 16.5	15.0 ± 18.3	18.4 ± 24.7
Admitted patients (%)	155 (77.1)	1321 (72.1)	323 (69.5)
Patients with bone marrow aspiration (%)	100 (50.5)	891 (49.2)	233 (50.6)

with chronic ITP and a platelet count of $<20 \times 10^9$/L at 6 months was 7 of 134 children (5.2%) in group 1, 69 of 1297 children (5.3%) in group 2, and 29 of 311 children (9.3%) in group 3. Mean age and male/female ratio of children with acute and chronic ITP was not statistically different. The mean initial platelet counts of infants with acute and chronic ITP were not statistically different (15.0 and 14.1×10^9/L, respectively). However, in older children (groups 2 and 3), initial platelet counts were significantly higher in those with chronic than in those with acute ITP (18.5 versus 13.3×10^9/L in group 2, $P < .0001$, and 21.7 versus 15.0×10^9/L in group 3, $P = .009$).

Intracranial Hemorrhage

During the observation period of up to 6 months after diagnosis, ICH occurred in 3 of 1742 patients (0.17%) at ages 1.4 (patient 1), 8.5 (patient 2), and 14.9 years (patient 3). All three patients were female, with initial platelet counts of 11, 8, and 16×10^9/L. Patients 1 and 2 had an infection within 14 days before the diagnosis of ITP. At the time of diagnosis of ITP, patient 1 did not receive drug treatment, patient 2 received corticosteroids, and patient 3 received a combination of corticosteroids and IVIG. Follow-up data after 6 months were available for patients 2 and 3 (personal communication). Patient 2 had an ICH 4 months after the diagnosis of ITP and had a favorable outcome without neurologic sequelae (follow-up time, 4.5 years). Patient 3 died shortly after ICH, which occurred within the first week after the diagnosis of ITP.

DISCUSSION

The current understanding of childhood ITP is based primarily on retrospective analyses, including case series and a few prospective studies, limited by short follow-up and with emphasis on the velocity of platelet count increases in response to platelet-enhancing drug therapies. Retrospective analyses have been limited by poor data quality control, biased selection of study population, and incongruity of study objectives and end points. The paucity of data has caused much debate and controversy over the treatment of children with ITP. The seminal publication of George and Davidoff[3] to develop ITP

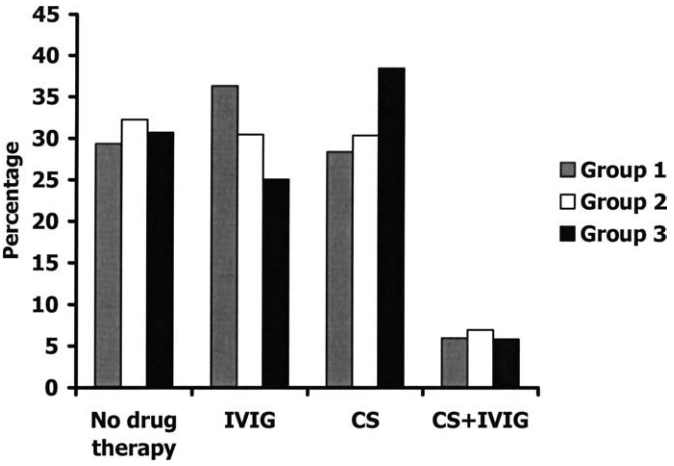

Fig 1. Intravenous immunoglobulin (IVIG) was used most frequently in infants ($P = .009$), whereas corticosteroids (CS) were used most often in adolescents ($P = .01$). Observation without drug treatment was applied similarly in all three age groups.

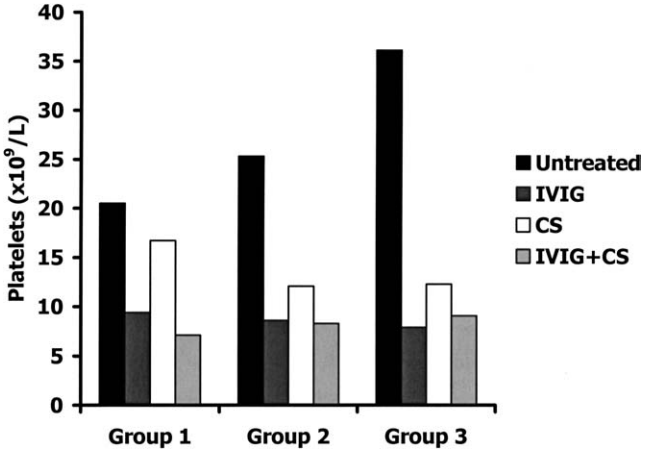

Fig 2. Untreated patients had highest initial platelet counts, with a maximum in adolescents and a minimum in infants. Group 1 versus group 3, $P = .001$; group 1 versus groups 2 and 3, $P = .05$. Lowest initial platelet counts occurred in children treated with intravenous immunoglobulin (IVIG), with similar frequency in all age groups. Patients treated with corticosteroids (CS) had higher initial platelet counts compared with children receiving IVIG or a combination of IVIG and CS. Moreover, group 2 and 3 children treated with CS had lower initial platelet counts than infants, $P < .001$.

treatment guidelines for children and adults described this lack of evidence regarding the management of ITP. Based on a systematic literature review, the authors concluded that rigorous clinical trial data are needed on which to base recommendations for the care of patients with ITP.[4] In response to this controversy, an international group of researchers established ICIS in 1997 for the purpose of developing a network of interested physicians to collect prospective data on childhood ITP and to generate hypotheses in the planning of future clinical research.

In this report from the prospective international ITP registry, data on infants and older children were systematically collected to contribute knowledge to the natural history and

management of ITP for these age groups. Although the registry has resulted in a large data set representing a rich source of information, it has limitations, including a bias caused by the voluntary registration mechanism. It is recognized that children and adults have different rates of acute and chronic ITP. In addition, children with chronic ITP typically have a less severe course and a high potential for spontaneous or therapy-induced remission.[3] There is still much that is unclear about the age-related clinical expression of ITP in children. In a retrospective review, Lowe and Buchanan recently reported the clinical characteristics of ITP in teenagers and found a high rate of chronic diseases (57%), which was quite similar with our finding of a 47.3% incidence in older children and adolescents in group 3.[1]

The natural course of ITP in infants is poorly described in the literature. Several features distinguished infants from older children with ITP: (1) higher male/female ratio in infants, which was recently reported by others,[2,5,6] (2) less frequent occurrence of infection before ITP than in children 1 to 10 years of age, which may be due to less contact with other children, and (3) less frequent occurrence of chronic ITP. The male predominance in infants is not yet explained. Respiratory tract infections occur more frequently in boys than in girls during infancy and childhood,[7] but other unknown predisposing factors probably are present.

Differences in treatment were also observed for the three age groups. Infants were more likely to be admitted to the hospital and treated with IVIG, whereas corticosteroids were used most frequently in older children and adolescents. Although preferred treatments differed for each group, the number of patients who did not receive platelet-enhancing therapy was similar across all ages. This observation raises the possibility that treatment choices reflected practical decisions more than a medical rationale to use specific drugs.

The increased rate of hospitalization and use of IVIG in infants probably reflects the impression that infants may be at higher bleeding risk, resulting in a more aggressive therapeutic approach. A survey of practicing pediatric hematology and oncology specialists demonstrated that an 18-month-old patient is more likely to be treated than an older child.[8] This probably reflects physician and family concerns that the activity of older infants and toddlers cannot be easily controlled and that they are at risk for minor head trauma many times each day. Our preliminary data suggest that ICH in this population is as uncommon as in older children during the first 6 months after the diagnosis of ITP. The hemostatic system in patients with ITP may provide adequate protection from hemorrhagic complications, even when platelet counts are $<20 \times 10^9$/L.[9-11] It has been demonstrated that an increased number of large and reticulated platelets may occur in patients with ITP, promoting adhesion and aggregation more effectively than in thrombocytopenia caused by bone marrow failure.[12,13]

The results of this study emphasize age as a feature of ITP, with further evidence that pediatric patients with ITP do not represent a homogenous patient population and that differences in natural history exist among the three age groups studied. These observations highlight that specific age-dependent differences, such as the higher male/female ratio, the lower rate of chronic ITP in infants, and different treatment aspects found in the three age groups, are of importance in guiding treatment decisions and planning future clinical trials.

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