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Pediatric Immune Thrombocytopenic Purpura (ITP): a 12 year Retrospective Study at a Single Center.

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Pediatric Immune Thrombocytopenic Purpura (ITP): a 12 year Retrospective Study at a Single Center.

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ABSTRACT

**Pediatric Immune Thrombocytopenic Purpura (ITP):
a 12 year Retrospective Study at a Single Center**

By Carolyn M. Bennett

ITP is a common acquired bleeding disorder of childhood that usually resolves spontaneously and has a low risk of serious bleeding. About 20-30% of children have chronic ITP which lasts beyond 6 months. Chronic ITP is a more serious disease due to the higher bleeding risk and need for ongoing therapy. Few studies have analyzed outcomes in large numbers of children with chronic ITP. No risk factors have been defined which predict chronic disease, bleeding risk, response to therapy or other outcomes. The objective of this study is to review the characteristics of a large cohort of pediatric patients with ITP at a single center.

Four hundred and ninety-eight patients with ITP were evaluated. The incidence of serious bleeding was low (7.8%). There were no intracranial hemorrhages or ITP-related deaths. Most patients (85.5%) received initial therapy with an overall response rate of 80.3%. The most common therapies were corticosteroids (35.3%), IVIG (25.1%) and anti-D (22.7%). Only 14.5% had no reported therapy. Fifty one patients underwent splenectomy (10.2%) with 84% response.

Chronic ITP was observed in 176 patients (35.3%). Acute ITP patients had lower platelet counts (mean 12.8 vs. 18.2 x 10^9/L) and were younger (5.8 vs. 9.6 years) than chronic ITP patients. Platelet count over 10 X 10^9/L and age over 10 years at presentation were associated with chronic disease. While the risk of bleeding in patients with chronic ITP was low, it was higher than that of acute ITP. Gender and response to therapy were not risk factors for chronic ITP.

Twenty four patients (4.8%) had Evans syndrome; chronic ITP with autoimmune hemolytic anemia. There were no significant differences between Evans syndrome and chronic ITP patients. Evans syndrome patients were no more likely to bleed or be refractory to therapy.

In general, children with chronic ITP have good outcomes. The risk of serious bleeding and death is low. Therefore, treatment should be individualized and focused on bleeding symptoms and prevention of treatment toxicity. Severe and refractory disease remains a challenging clinical problem. Studies are needed to define the biology of ITP and guide in the development of new targeted therapy.

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INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an acquired bleeding disorder that is caused by antibody mediated destruction of normal platelets by the immune system resulting in thrombocytopenia and bleeding. There are two forms of ITP, acute and chronic. Acute ITP occurs almost exclusively in children who typically present suddenly with severe thrombocytopenia and evidence of mucocutaneous bleeding. Serious bleeding is uncommon and the thrombocytopenia usually resolves spontaneously with or without therapy in weeks to months. Chronic ITP is more common in adults and is defined by immune thrombocytopenia that persists beyond 6 months. The majority of adults have chronic ITP, while only 20-30% of children develop chronic thrombocytopenia lasting beyond 6 months.

Despite a great deal of research regarding ITP, the cause remains unclear. Immune mediated destruction of platelets is a major part of the pathophysiology, but the underlying mechanisms which trigger autoantibody production are poorly defined. At diagnosis, there are no known risk factors which predict the development of chronic disease in children. No variables are instructive in predicting response to therapy or bleeding risk. Identifying factors which are associated with chronic disease, response to therapy or bleeding risk would be invaluable in the treatment of this disease and would help guide the development of new therapies.

This study was designed to evaluate a large group of pediatric patients with ITP to determine the natural history of the disease, specifically with respect to clinical course, treatment modalities, complications and outcomes and to identify risk factors associated with chronic disease.

BACKGROUND

ITP is one of the most common acquired bleeding disorders of childhood with an incidence of about 4 per 100,000 children per year in the United States. ITP is an immune-mediated disorder that is defined clinically by low platelets in the absence of other associated causes of thrombocytopenia (1). Anti-platelet antibodies are produced which cause platelet destruction by macrophages in the spleen. The causes of antibody production have not been clearly defined.

Children with ITP typically present with sudden onset of mucocutaneous bleeding and severe thrombocytopenia, but usually have surprisingly few other abnormal physical or laboratory findings. The majority of children have acute disease and the thrombocytopenia resolves spontaneously within weeks to months of presentation (2). The risk of severe bleeding in patients with acute ITP is low. In one large international prospective study of over 1700 children, the incidence of intracranial hemorrhage (ICH) was less than 0.2% (2). However, several recent retrospective studies showed the incidence to be somewhat higher (3, 4). Because of the low risk of bleeding in children with acute ITP and the high likelihood of full resolution of symptoms, observation alone is often a viable treatment option (5-7). Therapy to raise the platelet count into a safe range may be reserved for patients with evidence of more serious bleeding symptoms.

Chronic ITP is immune thrombocytopenia which persists beyond 6 months duration (8). It is diagnosed in approximately 20-30% of children and in most adults who present with immune thrombocytopenia (2). Children with chronic ITP are at increased risk for serious bleeding and may have recurrent episodes of bruising, petechiae, epistaxis, gingival bleeding, and menorrhagia (9). More serious bleeding is uncommon

in chronic ITP as well, but when it does occur, the outcome for the patient can be devastating. The mechanisms which trigger ongoing platelet destruction beyond 6 months in patients with chronic ITP are not known.

Treatment for chronic ITP is focused on the prevention of serious or life threatening bleeding such as intracranial bleeding. First line therapy includes corticosteroids, intravenous immune globulin (IVIG) and anti-D immune globulin (anti-D). While the majority of children with chronic ITP will respond to standard therapy, the responses are not sustained and many patients require ongoing or more aggressive therapy (10). Patients on long term therapy may have serious side effects or develop refractory disease. Children, because they are still growing and developing, are particularly vulnerable to the side effects of therapy. Long term steroid therapy may interfere with normal growth or result in low bone density among other serious side effects. Other therapies require IV placement and must be given at frequent intervals.

In older children and adults, splenectomy is a therapeutic option and is curative in up to 80% of patients (11). However, splenectomy is not usually recommended for young children with chronic severe ITP because of the risk of overwhelming bacterial sepsis with encapsulated organisms (12, 13).

Up one quarter of patients with severe, chronic ITP requiring therapy, do not respond adequately to any standard therapy (14). Severe, refractory ITP is a difficult clinical problem for which there are no good therapeutic options. A variety of immunosuppressive and hormonal agents have been employed in patients with severe, refractory disease with varying efficacy including: rituximab, azathioprine, mercaptopurine, vincristine, danazol, cyclosporin, mycophenolate and cyclophosphamide

(15-22). Usually fewer than 50% of patients show a sustained response to any treatment and most of these agents have measurable toxicities. Newer agents, including the thrombopoietin mimetics, eltrombopag and romiplostim, have shown promising results in adults, but efficacy and safety in children has not been established (23-25).

Ultimately, treatment choice for patients with severe disease is largely arbitrary as there are no criteria which are helpful in predicting serious bleeding or response to therapy. Platelet count alone is not a reliable indicator for bleeding risk since the many children with chronic ITP have platelets under 20 $X10^9$/L, but no history of serious bleeding (26). Despite years of study, no parameters have been identified which predict disease development, severity or response to therapy.

Large numbers of pediatric patients with chronic ITP have not been well studied. The risk of chronic ITP in pediatric patients is also not clearly established. Many children with chronic ITP for 6 months have disease resolution by one year (2). When compared to adults with similar disease manifestations, pediatric patients with chronic ITP are more likely to have spontaneous remissions over time (27). Clearly, significant differences remain between adults and children with ITP and studies focused on children with disease are necessary.

Evans syndrome is a clinical syndrome of ITP and autoimmune hemolytic anemia with a positive direct antibody (Coombs) test (28-30). Some patients with Evans syndrome may also have other immune cytopenias (e.g., neutropenia) or evidence of a global autoimmunity. Evans syndrome has not been well studied and likely represents a heterogeneous group of patients (28, 31). The thrombocytopenia and anemia of Evans syndrome is thought to be more severe and refractory to that of either disease alone (17).

Bleeding symptoms have been reported to be more severe (29). However, large numbers of patients with Evans syndrome have not been studied to date.

This study examines a large cohort of children with both acute and chronic ITP so that the natural history of this disease can be described and underlying risk factors for bleeding and other outcomes may be measured more accurately.

METHODS

Null Hypothesis

In patients with immune thrombocytopenic purpura, (ITP), the proportion that has severely low platelet counts is equivalent between those with chronic versus acute disease.

Specific Aims

The specific aims of the study were to 1) retrospectively collect data, including age, gender, bleeding type, bleeding severity, platelet counts and other laboratory tests, treatments, responses to treatments and outcomes in a cohort of children with acute and chronic ITP over a 12 year period; 2) perform descriptive and regression analyses to define possible risk factors for chronic disease and 3) analyze outcomes, including disease severity, treatment response, bleeding severity, intracranial hemorrhage and death.

Study Design

Retrospective cohort study

Research subjects

Research subjects were identified from the computerized clinical database of the Benign Hematology Program at Children's Hospital Boston (CHB). Medical records of all children 21 years and under with ITP seen at CHB between January 1990 and August 2003 were reviewed after approval from the Institutional Review Board. Children were

seen and treated for ITP in the outpatient setting (in the hematology clinic or in the emergency department) and on the inpatient ward. A total of 698 patients were identified from the hospital billing service via ICD-9 coding for ITP and thrombocytopenia and from the records of the hematology clinic. Records for 199 subjects were excluded due to diagnoses other than ITP (bone marrow failure, viral suppression, medication, congenital thrombocytopenia, other). One subject with ITP documented in the chart was eliminated due to undocumented laboratory evidence of thrombocytopenia. Of the 689 original records, 498 were reviewed for this study.

Human Subjects Protection

Consent was waived as this was a retrospective medical record review only. No contact was made with patients and no further information was obtained from patients. No further laboratory testing or data collection was attempted other than what was available in the medical record. Elements of the record were de-identified to protect patient confidentiality per HIPAA regulations. Database was kept on in a password protected research computer.

Data Collection

Medical records were reviewed and data collected into an Access database. Data collected included demographic information, laboratory information and outcomes measurements, including ITP diagnosis, age at diagnosis, gender, bleeding type and bleeding severity score, treatments, treatment responses, blood counts and other laboratory testing, such as direct antibody testing and antinuclear antibody testing.

Study Definitions

1. ITP category: Chronic ITP was defined as immune thrombocytopenia lasting at least 6 months with documented diagnosis by hematologist at CHB. Acute ITP was defined as all ITP other than chronic. This group included patients with disease that resolved within 12 mo of diagnosis. Patients who were diagnosed with acute ITP and did not have documented follow up after initial presentation were defined as 'acute ITP". Patients with chronic disease typically require ongoing follow up at tertiary care centers, so categorizing these patients as acute is likely to be accurate in the majority of cases. In addition, the analyses were done including and excluding this group of patients and the results were unchanged. Therefore this group was categorized with the 'acute ITP' group.
2. Bleeding score. The bleeding score was based on the one formulated by Buchanan and Adix (32) and describes 5 levels of bleeding severity: none, mild (cutaneous bleeding, bruising, petechiae), moderate (mucosal bleeding, epistaxis), severe (any bleeding requiring medical intervention), life-threatening (intracranial hemorrhage or any bleeding requiring emergent intervention). These scores were dichotomized into 2 clinically relevant levels for the analysis: not severe (none, mild, moderate) and severe (severe or life-threatening).
3. Response to therapy. Response to therapy was graded into four categories based on platelet measurements (number X 10^9/L). None (less than 20), minimal (20-50), partial (50-149), complete (150 or greater). The response categories were

dichotomized into 2 clinically relevant groups for the analyses: Responsive (partial and complete) and non-responsive (none or minimal).

Data Analysis

Continuous demographic and clinical variables are reported as mean±SD. The univariate associations between ITP diagnosis (acute vs. chronic) and presenting platelet count, age at diagnosis, sex, bleeding severity, and response to treatment were examined using un-pooled t-tests for continuous variables and Chi-square tests for categorical variables. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of chronic ITP. Two sample t tests and Chi-square test were also used to identify demographic and clinical predictors for splenectomy. Further, among patients with chronic ITP, similar analyses were performed to find predictors of Evans syndrome. In all tests, statistical significance was achieved with a 2 sided p-value < 0.05. Analyses were performed by the SAS software, Versions 9.1 and 9.2 of the SAS System for Windows (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Four hundred and ninety-eight children and adolescents met the inclusion criteria and their medical records were reviewed for this study (Table 1). One hundred and seventy six patients were diagnosed with chronic disease; ITP lasting greater than 6 months. Most subjects were under 10 years of age (mean 7.1 ± 5.2) with a slight male preponderance (51.2 versus 48.8 %). The youngest patient was 3 months and the oldest was 20 years. While the mean low platelet count was 14.7 ± 17.0 X 10^9/L, more than 50% of patients had platelets less than 10 X 10^9/L at presentation. Despite this low presenting platelet count, the overall incidence of severe or life-threatening bleeding was low (7.8%). There were no intracranial hemorrhages or ITP related deaths. The majority of subjects (85%) received some form of therapy at presentation with an overall response rate to the first recorded therapy of 80.3%. The most common therapy was corticosteroids (35.3%), but IVIG (25.1%) and anti-D (22.7%) were also popular therapeutic interventions. Fifty one patients underwent splenectomy (10.2%) with an 84% overall response rate.

Chronic versus acute ITP

Of the 498 patients, 176 (35.3%) had persistent ITP for more than 6 months and were defined as having chronic ITP. The other 233 patients were defined has having acute disease. These patients had either documented normalization of their counts or had no further follow up and were presumed for the purposes of the study to have acute disease. The two groups were compared to identify features that were associated with the

development of chronic disease. One hundred two (20.4%) of patients underwent bone marrow evaluation with no abnormal results. No diagnoses were altered based on bone marrow results.

The following characteristics were analyzed: age at presentation, platelet count at presentation, gender, bleeding severity and response to first documented therapy (Table 2). Acute ITP patients had significantly lower platelet counts compared to patients with chronic ITP (mean 12.8 vs. 18.2X 10^9/L), however there was significant overlap based on the standard deviations for the 2 groups. Patients with chronic ITP presented at a significantly older age, with a mean of 9.6 years (SD 5.1) compared to patients with acute disease, who presented with a mean age of 5.8 years (SD 4.8). The age range at which ITP presented was similar for both groups, 3 months to 20 years for acute ITP and 6 months to 18 years for chronic ITP.

A univariate analysis was performed for the association between chronic ITP and the five risk factors (Table 3). At the 5% level, there was evidence of an association between chronic ITP and a platelet count of greater than 10 X 10^9/L and age older than 10 years. Patients with severe or life threatening bleeding were at increased risk for chronic disease, but this association was not statistically significant with a p-value of 0.1012. The incidence of severe bleeding in both groups was low, therefore, the sample size may not have been adequate to detect a statistically significant difference. Female gender and response to therapy were not associated with disease outcome.

The association between chronic ITP and presenting low platelet count was analyzed using multivariate regression to control for confounding (Table 4). At the 5% significance level, platelet count and age at diagnosis were associated with chronic ITP.

The odds of chronic disease were higher in patients with more severe bleeding, but this association was just over the 0.05 significance level. Neither gender nor response to therapy was associated with the development of chronic disease.

Splenectomy

Overall, 51 patients (10.2%) underwent splenectomy (Table 5). The majority of patients who were treated with splenectomy had chronic disease (94.1%). Only 3 patients who had acute disease underwent splenectomy. All three patients had received multiple therapies before splenectomy. Patients who underwent splenectomy were older, had lower platelet counts and were more likely to have had severe or life threatening bleeding than those who did not have splenectomy. Splenectomy patients were more likely to have refractory disease but this association was not statistically significant at the 5% level. The majority (84%) of patients who had splenectomy had a partial or complete response. There were no recorded post-splenectomy deaths or cases of overwhelming bacterial sepsis.

Evans Syndrome

Twenty four patients (4.8%) were diagnosed with Evans Syndrome; chronic ITP with autoimmune hemolytic anemia evidenced by positive direct antibody (Coombs) test. Evans syndrome patients were compared to patients with chronic ITP alone and the 2 groups were found to be similar. The mean platelet count and age at diagnosis were not statistically different at the 5% level. Interestingly, patients with Evans did not

experience more serious bleeding and were not more refractory to treatment than patients with chronic ITP.

DISCUSSION

Previous studies of pediatric ITP have shown that most children with ITP present with acute disease, have no significant bleeding and recover with or without treatment in weeks to months. In 10-30% of patients, the ITP persists beyond 6 months and becomes chronic. Fortunately, most children with chronic disease do not have serious bleeding either, but, some children require ongoing therapy to treat symptoms. A small minority of children with chronic ITP have disease that is severe and refractory to most standard therapy. Disease that is severe and refractory is very difficult to manage and often toxic or experimental therapy must be used to present life threatening bleeding. To date, there are no characteristics or risk factors in patient presenting with ITP that predict the development of chronic disease, risk of severe bleeding or response to therapy. Information about children with ITP is needed so that the disease can be more clearly defined, clinically and biologically, in order for optimal treatment to be initiated.

In this study of a large cohort of children with ITP, the incidence of chronic disease was 35%, somewhat higher than in most other reports. It is likely that this finding is related to the status of Children's Hospital Boston as a major tertiary care and referral center. Patients with chronic disease are more likely to be referred to such a center. Children with chronic ITP presented at an older age and with higher platelet counts than children whose disease resolved spontaneously. Severe and life threatening bleeding was unusual among patients with either acute or chronic disease. There were no cases of intracranial hemorrhage. Accordingly, the incidence was less than that reported from a recent prospective study (0.2%). There were no ITP related deaths. Most of the children responded well to some form of therapy. Disease characteristics which were

associated with the development of chronic disease included platelet count above 10 x 10^9/L at presentation and age over 10 years. Our results suggested that a history of severe bleeding is associated with the development of chronic disease. However, severe bleeding was an uncommon event, and the study may not have had sufficient power to detect a difference. Splenectomy was a successful treatment in children with ITP and there were no splenectomy related deaths or sepsis events in the study.

In this cohort, the diagnosis of Evans syndrome was not associated with increased bleeding risk or refractoriness to therapy. Disease characteristics, such as presenting platelet count, age, gender were similar in patient with Evans syndrome and chronic ITP alone.

While chronic ITP can be a devastating disease in patients who have severe and refractory disease, the outcome in most children is favorable. Few children have serious bleeding and most respond to some form of therapy. A minority of patients has chronic, severe or refractory ITP with more serious symptoms of bleeding requiring frequent hospitalization for treatment. Because of disease heterogeneity, it is important to have an individualized approach to the treatment of chronic ITP in childhood. Particular attention must be paid to clinical findings, as platelet count alone is not helpful to determine bleeding risk. Consideration must be given to treatment toxicity and mode of administration to limit patient side effects and discomfort.

Prospective studies are necessary to evaluate the efficacy and toxicity of new agents, but must also examine the biology of the disease so that drug development may be targeted at the underlying cause.

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TABLES

Table 1. Patient Characteristics

Characteristic	
ITP Diagnosis, n (%)	
Acute	**322 (64.7)**
Chronic	**176 (35.3)**
Low Platelet Count (X 10^9/L)	
Mean ± SD	**14.7 ± 17.0**
Median (range)	**8 (1-109)**
Age at Diagnosis (years)	
Mean ± SD	**7.1 ± 5.2**
Median (range)	**5.8 (0.26-20)**
Platelet Count (%)	
< 10 x10^9/L	**275 (55.8)**
≥ 10 x10^9/L	**218 (44.2)**
Gender, n (%)	
Female	**243 (48.8)**
Male	**255 (51.2)**
Bleeding, n (%)	
Severe-life-threatening	**38 (7.8)**
Mild-Moderate	**485 (92.2)**
Treatment Response, n (%)	
Responder	**302 (80.3)**
Non-responder	**74 (19.7)**
Treatment Type, n (%)	
None Recorded	**72 (14.5)**
Anti-D	**113 (22.7)**
IVIG	**125 (25.1)**
Corticosteroids	**176 (35.3)**
Other	**12 (2.4)**
ITP Related Deaths	**0**
Intracranial hemorrhage	**0**
Splenectomy, n (% responders)	**51 (84%)**

Table 2. Characteristics by ITP Diagnosis

Variable	Acute n=322	Chronic n=176	p value*
Mean Low Platelet Count, X 10^9/L (SD)	**12.8 (14.8)**	**18.2 (20.2)**	**0.0024**
Mean Age at Diagnosis, yrs (SD)	**5.8 (4.8)**	**9.6 (5.1)**	**<0.0001**
Platelet Count ≥ 10 x10^9/L, n (%)	**126 (39.4)**	**92(53.2)**	**0.0032**
Age 10 yr or greater, n (%)	**64 (20.3)**	**72 (48.7)**	**0.0001**
Male, n (%) **Female, n (%)**	**172 (53.4)** **150 (46.6)**	**83(47.2)** **93 (52.8)**	**0.1818**
Severe bleeding, n (%)	**20 (6.3)**	**18 (10.5)**	**0.1012**
Refractory to treatment, n (%)	**49 (18.6)**	**25 (22.3)**	**0.4016**

* Distributions of variables were compared between ITP groups using unpooled t test for continuous variables and the Chi square test for categorical variables.

* Statistical significance was achieved with a 2 sided p-value < 0.05

Table 3. Univariate Analysis for the association between chronic ITP and five risk factors

Variable	OR	CI	p value*
Platelet Count ≥ 10 x10^9/L	**1.75**	**1.20-2.54**	**0.003**
Age ≥ 10 yr	**3.73**	**2.44-5.70**	**<0.0001**
Male Female	**1.28**	**.89-1.86**	**0.182**
Severe bleeding, %	**1.76**	**0.89-3.38**	**0.105**
Refractory to treatment	**1.26**	**0.73-2.17**	**0.402**

* Distributions of variables were compared between ITP groups using unpooled t test for continuous variables and the Chi square test for categorical variables.

* Statistical significance was achieved with a 2 sided p-value < 0.05

Table 4: Multivariate Analysis of chronic ITP with significant risk factors

Variable	β	SE	OR	CI	p value*
Intercept	**-1.61**	**0.18**			**<.0001**
Platelets > 10 X 10^9/L	**0.71**	**0.22**	**2.04**	**1.33-3.12**	**0.0011**
Age ≥10 yr	**1.33**	**0.22**	**3.77**	**2.42-5.86**	**<.0001**
Severe bleeding, %	**0.65**	**0.38**	**1.91**	**0.90-4.05**	**0.0925**

Table 5. Characteristics of Splenectomy Patients

Variable	No Splenectomy (n=447)	Splenectomy (n=51)	p value
Total, n (%)	**447 (89.8)**	**51 (10.2)**	
Acute ITP	**319 (71.3)**	**3 (5.9)**	**<0.0001**
Chronic ITP	**128 (28.6)**	**48 (94.1)**	
Mean Low Platelet Count, X 10^9/L (SD)	**15.2 (13.6)**	**10.5 (13.6)**	**0.034**
Mean Age at Diagnosis, yrs (SD)	**6.8 (5.2)**	**9.0 (5.5)**	**0.029**
Platelet Count ≥ 10 x10^9/L, n (%)	**205 (46.2)**	**13 (26.5)**	**0.009**
Age ≥ 10 yr, n (%)	**119 (27.7)**	**17 (48.6)**	**0.009**
Male, n (%)	**227 (50.8)**	**28 (54.9)**	**0.577**
Female, n (%)	**220 (49.2)**	**23 (45.1)**	
Severe bleeding, n (%)	**29 (6.6)**	**9 (18.8)**	**0.003**
Refractory to treatment, n (%)	**63 (18.5)**	**11 (30.6)**	**0.084**

* Distributions of variables were compared between ITP groups using unpooled t test for continuous variables and the Chi square test for categorical variables.
* Statistical significance was achieved with a 2 sided p-value < 0.05