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Original Research Article

Clinical and laboratory predictors of chronic immune thrombocytopenia in children: A study of 25 cases and review of literature

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Abstract

Background: Childhood immune thrombocytopenia (ITP) is a rare autoimmune bleeding disorder. Most children recover within 6 to 12 months, but in individual course is difficult to predict. We performed a systematic review and meta-analysis of data and literatures to identify predictors of chronic ITP in 25 patients.
Methods and Material: Clinical and laboratory data of 25 cases of chronic ITP collected and analyzed to determine predictors of development of chronic ITP. We included observational cohort studies with newly diagnosed ITP patients by studying the relationship among clinical, therapeutic, laboratory and genetic parameters at time of diagnosis and development of chronic ITP after 1 year.
Result: Females developed chronic ITP significantly more often Patients who developed chronic ITP were older, and the mean difference was 2.68. Five articles studied the onset of disease and found significant more chronic ITP in patients with an insidious onset of ITP. The correlation between the absence of bleeding symptoms at diagnosis and a chronic course of ITP was studied, and both did not find this to be a risk.
Discussion: There was acute and abrupt onset in our cases. The bleeding manifestations of thrombocytopenia were mucocutaneous petechiae, ecchymotic patches to hematuria and melena. Petechiae, purpura, and easy bruising are usually expected in ITP. Less common are epistaxis, gingival bleeding, and menorrhagia. Uncommon findings are melena, gross hematuria and intracranial hemorrhage. It is important to note that the clinical manifestations of thrombocytopenia vary with patient age. Older patients have more severe and rare bleeding manifestations, such as GI bleeding and possibly intracranial hemorrhage. In children clinical manifestations are more mucocutaneous and usually self limiting.
Conclusion: The following are predictors of chronic ITP: female gender, older age at presentation (age ≥11 years, absence of preceding infection or vaccination, insidious onset, higher platelet counts at presentation ≥20 × 10^9/L, positive ANA titers and treatment with a combination of steroid and IVIg. Mucosal bleeding at diagnosis and treatment with IVIg seem to protect against development of chronic ITP.
Keywords: Chronic ITP, Thrombocytopenia, Steroid, Bleeding disorder, Acute ITP.

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1. Introduction

Idiopathic thrombocytopenic purpura (ITP) is defined by low platelet count (thrombocytopenia) of unknown cause (idiopathic). It is also known as immune thrombocytopenic purpura because most cases are due to antibody against platelets. Majority are asymptomatic, very low platelet counts can lead to a bleeding and purpura [1]. ITP is a disorder that affects the count of blood platelets rather than their function. The normal platelet level in adults is between 150,000 and 450,000/mm^3. Platelet counts below 50,000 mm^3 increase the risk of dangerous bleeding from trauma and major surgery ; counts below 20,000/mm^3 increase the risk of spontaneous bleeding and chance of

spontaneous bleeding is maximum when count is < 10,000/mm^3 [2]. ITP may be either acute or chronic. The incidence of ITP is 50-100 new cases per million per year, with children accounting for more than half of cases. Most often these antibodies are against platelet membrane glycoproteins IIb-IIIa or Ib-IX, and are of the immunoglobulin G (IgG) type. [4] The coating of platelets with IgG renders them susceptible to opsonization and phagocytosis by splenic macrophages. Recent evidence suggests that the stimulus for autoantibody production in ITP is due to abnormal T helper cells reacting with platelet antigens on the surface of antigen presenting cells. [5]

Childhood ITP is a rare autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count < 100,000/mm^3 in the absence of other causes that may be associated with thrombocytopenia. Most children present with sudden development of purpura, petechial rashes and mucosal bleeding, often after a mild viral infection. Management of newly diagnosed ITP consists of careful observation, regardless of platelet count. Severe bleeding, occurring in only 3% to 5% of children, requires treatment with corticosteroids, intravenous immunoglobulin (IVIg), or anti-Rhesus-D immunoglobulin, either alone or in combination and, if life threatening, also with platelet transfusions [5,6].

Chronic ITP is currently defined as thrombocytopenia< 100,000/mm^3 lasting for >12 months. About 20% to 25% of children with newly diagnosed ITP will develop chronic disease. In this study, we systematically analyzed the clinical and laboratory data of 25 cases of ITP to determine the evidence for clinical, therapeutic, laboratory, and genetic predictors for development of chronic ITP in children.

2. Methods and Material

Clinical and laboratory data of 25 cases of chronic ITP collected and analyzed to determine predictors of development of chronic ITP. Data were collected from department of hematology and pathology of tertiary medical institutes.

We included newly diagnosed ITP patients up to 16 years old patients and studied the relationship among clinical, therapeutic, laboratory, or genetic parameters at time of diagnosis and development of chronic ITP after 1 year. We have children (aged 3 years to 16 years) with newly diagnosed ITP. The primary outcome was development of chronic ITP. As per definition of chronic ITP, we used the definition (platelet count <100 × 10^9/L lasting >12 months. We used all available clinical, therapeutic, laboratories, or genetic parameters studied in patients with newly diagnosed ITP for possible association with chronic disease.

3. Result

Demographics, Clinical and laboratory data of study population was (n= 25): Male 18(72%), female 7 (28%). Mean platelets at admission 12,600/cm, preceding illness:acute Gastroenteritis6(25%),upper Respiratory Tract Infections 8 (33%), fever 2 and without apparent preceding illness 9(36%). Clinical Presentations :Petichiae 10 (40%), bruises and ecchymotic patches5 (20%), epistaxis 4 (16%) and others have Gastrointestinal bleed and hematuria (Table1). In our study only two patients developed chronic ITP.

Table 1: Clinical and hematological parameters of patients

Case	Gender M:Male F:Female	Platelet Count /Cm	Preceding Illness	Clinical Presentation	Bone Marrow	Age In Years
1	M	20,000	Cold	Petechiae	Stimulated Megakaropoiesis	5
2	M	<10,000	Cold & Cough	Nasal And Gum Bleeding	Do	8
3	F	15,000	Pain Abdomen	Ecchymotic Patches	Do	4
4	M	8	Cold	Nasal And Cutaneous	Not Done	3
5	F	15	No Preceding Symptom	Petechiae And Ecchymotic	Stimulated Megakaryopoiesis	15
6	M	6	URTI	Gum And Nasal Bleed	Stimulated Megakaryopoiesis	10
7	M	10	NO	Bruising Around Nipples	Normal Megakaryopoiesis	8
8	M	7	Pain Abdomen	Hematuria	DO	16
9	M	12	Cold	Melena	Do	14
10	F	18	No	Petechiae	Normal megakaryopoiesis	10
11	M	5	Cold	Mucocutaneous	Normal megakaryopoiesis	4
12	M	20	Loose Motion	Hematuria	Normal Megakaryopoiesis	12
13	M	10	Cough	Petechial Rashes	Not done	9
14	F	8	Vomiting	Do	Normal megakaryopoiesis	14
15	M	11	No	Ecchymotic Patches	Stimulated Megakaryopoiesis	13
16	M	13	Nausea	Gum Bleeding And Petechiae	Do	5
17	M	25	No	Bruising	Do	8
18	M	11	No	Petechiae	Do	5
19	F	15	Cold And Cough	Hematuria	Do	10
20	M	12	No	Petechia	Do	12
21	M	10	Fever	Ecchymotic	Do	15
22	M	9	No	Melena	Do	9
23	M	22	Fever	Nasal Bleed	Do	10
24	F	10	Pain Abdomen	Petechiae	Do	11
25	F	12	No	Petechiae	Not Done	5

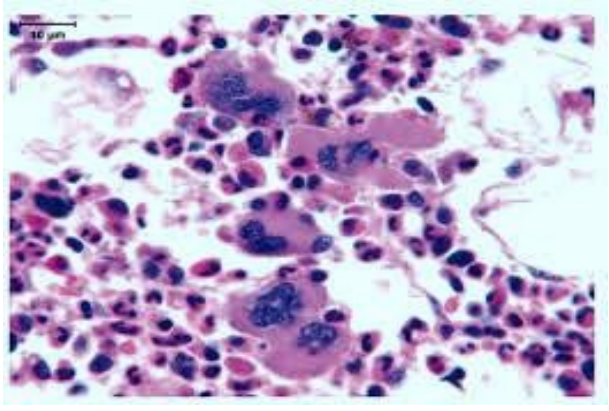

Figure 1: Smear shows stimulated megakaryopoiesis

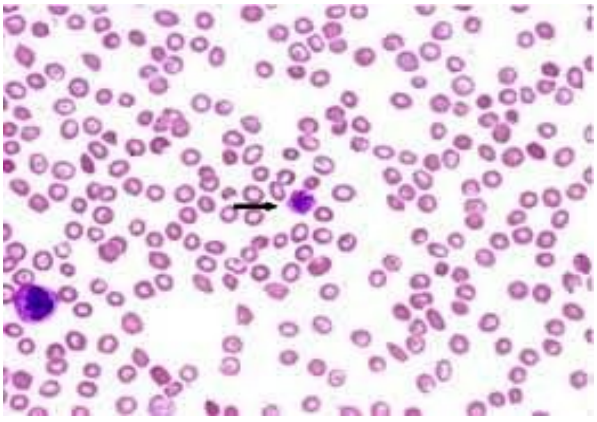

Figure 2: PBS shows occasional giant platelet

3.1 Clinical and laboratory Predictors and review of literatures

Patients who developed chronic ITP were older. Five articles studied the onset of disease and found significant more chronic ITP in patients with an insidious onset of ITP.

The correlation between the absence of bleeding symptoms at diagnosis and a chronic course of ITP, and both did not find this to be a risk.

Four articles reported clinical course of ITP in relation with treatment at diagnosis with high-dose methylprednisolone (15-30 mg/kg per day) and 13 articles studied the effect of standard-dose methylprednisolone (SDMP; 1-2 mg/kg per day) No significant differences were found. Fourteen studies analyzed the influence of treatment with IVIg and found significantly less chronic ITP in patients treated with IVIg. In 4 studies, the effect of treatment with anti-Rhesus-D immunoglobulin was analyzed, but no significant differences were found. Observational management versus any medical treatment was studied in 10 articles, but no significant differences were found. In 5 studies, combination therapy with SDMP and IVIg was analyzed. A significantly higher risk for chronic ITP was found in patients treated with a combination of IVIg and SDMP.

The mean platelet count at time of diagnosis was calculated. A significantly higher platelet count at diagnosis was found in patients who developed chronic ITP, with a mean difference 5.27 (95% CI 2.69-7.86). Four articles calculated a median platelet count, and one found significantly higher median platelet counts at diagnosis in patients who developed chronic ITP. Significantly more chronic ITP was found in children with a platelet count ≥10 × 10^9/L (6. Thus more platelet count at time of diagnosis is positive predictor of chronic ITP

We found a significant higher MPV in patients who developed chronic ITP. Giant platelets were more common who developed chronic ITP. Hb level did not detect a significant difference.

3.2 Anti-nuclear antibody (ANA) positivity (>1:80)

ANA positivity was studied. Two studies analyzed the presence of platelet antibodies, and both did not find a significant difference Nielsen *et al* analyzed the presence of anti-glycoprotein antibodies and found significant less frequent anti-glycoprotein antibodies in patients who developed chronic disease. Yildirmak *et al* studied the percentage of platelet-associated immunoglobulin M and immunoglobulin G and found a significantly lower percentage of platelet-associated immunoglobulin M in patients who developed chronic ITP**.** They also analyzed the mean percentage of platelet surface antigens but found no significant differences.

3.3 Bone marrow parameters

Bone marrow findings were available in 22 cases. Five patients showed normal megakaryopoiesis and rest revealed stimulated megakaryopoiesis. Number of megakaryocytes did not predict course of ITP especially development of chronic ITP.

Alexander *et al* found no differences in the amount of megakaryocytes in bone marrow but did find significantly higher percentages of eosinophilic granulocytes in bone marrow of patients developing chronic ITP. Ding *et al* reported a higher presence of human cytomegalovirus in bone marrow of patients developing chronic ITP

4. Discussion

There is marked variability in the clinical presentation of ITP. There was acute and abrupt onset in our cases. The bleeding manifestations of thrombocytopenia were mucocutaneous petechiae, ecchymotic patches to hematuria and melena (Table 1). Petechiae, purpura, and easy bruising are usually expected in ITP. Less common are epistaxis, gingival bleeding, and menorrhagia. Uncommon findings are melena, gross hematuria and intracranial hemorrhage [2]. It is important to note that the clinical manifestations of thrombocytopenia vary with patient age. Older patients had more severe and

rare bleeding manifestations, such as GI bleeding and possibly intracranial hemorrhage [2].

In children clinical manifestations are more mucocutaneous and usually self limiting. Clinically important bleeding does not appear to occur in these patients unless the platelet count is less than 10,000/cu mm. However, usual practice among many physicians is to initiate treatment in adult patients with ITP when the platelet count is less than 20,000/cu mm [4]. Childhood ITP is considered to be a heterogeneous disease regarding both pathogenesis and clinical course. In this study, we have systematically reviewed and analyzed all clinical, laboratories, therapeutic, and genetic predictors for the outcome of childhood ITP.

Among treating physicians, there is a great need for reliable predictors for the outcome of childhood ITP at the time of diagnosis as well as after initial therapy. This would help clinicians to provide patients and their parents with specific information about the expected clinical course, which may help to minimize anxiety and the impact of the disease on daily life. Furthermore, it could guide the decision on therapeutic management of the disease, especially if treatment would prevent development of chronic disease [4-6].

The results show that predictors that were thought to be related to the course of childhood ITP, like age, gender, preceding infection, duration of symptoms, bleeding tendency, and platelet count at diagnosis, are indeed supported by a considerable level of published evidence. Furthermore, our review adds some new possible predictors, like leukocyte count, ANA positivity, and treatment with a combination of corticosteroids and IVIg. Remarkable is the apparent protective effect of IVIg treatment against development of chronic disease. The question is whether this is a true effect of IVIg or is based on confounding factors. It might be that IVIg has beneficial long-term immunomodulatory effects (e.g., down regulating of the autoimmune response). [6,7] It has been shown that IVIg causes an increase in the number and function of regulatory T cells [9]. Regulatory T cells contribute to the maintenance of peripheral immune tolerance.[12] Several studies have shown lower frequencies and/or impaired function of regulatory T cells in adults as well as in children with ITP.[10,11]

Although the exact mode of action remains unclear, IVIg treatment might restore the immunologic balance by inducing proliferation and function of regulatory T cells. In children with lower platelet counts and higher bleeding tendency, both associated with a lower rate of chronic disease, treatment is instituted more often than in children with higher platelet counts or a low bleeding tendency. On the other hand, the higher rate of chronic disease in children who received a combination of steroids and IVIg in some cases seems to contradict this explanation, because the regular reason to give this combination is severe bleeding with low platelet counts as well. There is an estimated 25% incidence of chronic disease. We found 8% incidence of chronic disease, perhaps all patients treated with high dose methylprednisolone. However, future prospective studies, preferably randomized and combined with laboratory studies, are needed to find out if IVIg really protects against the development of chronic ITP and, if so, by what mechanism this effect is caused and if treating all children with IVIg would be cost effective, clinically effective, and tolerable[13-15]. However, limitation of our study was small data size.

5. Conclusion

The following are predictors of chronic ITP: female gender, older age at presentation (age ≥11 years, absence of preceding infection or vaccination, insidious onset, higher platelet counts at presentation $\geq 20 \times 10^9$/L, positive ANA titers and treatment with a combination of steroid and IVIg. Mucosal bleeding at diagnosis and treatment with IVIg seem to protect against development of chronic ITP. The possible protective effect of IVIg treatment needs confirmation in prospective randomized studies. Based on our review, new prediction scores can be generated and tested in large cohorts of patients. To be able to compare prognostic risk factors, in future studies, all predictors should be strictly defined and be recorded at time of diagnosis of ITP. In this way, we might be able to identify patients at higher risk of developing chronic ITP who may benefit from treatment to prevent a chronic course of ITP.

The initial treatment of ITP includes: (1) Treatment should be restricted to those patients with moderate or severe thrombocytopenia who are bleeding or at risk of bleeding; (2) treatment should be limited in duration unless it is demonstrated that symptomatic thrombocytopenia persists; and (3) patients with mild, asymptomatic thrombocytopenia, discovered incidentally on a routine blood count, should not be treated. Still bone marrow examination is important investigation to confirm ITP and rule out other causes of thrombocytopenia.

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