IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDHOOD*

A Follow-Up of Sixty-Two Cases

Yüksel Konakçı, M. D.**, Şinasi Özsoylu, M. D.***

and İzzet Berkel, M. D.***

Idiopathic thrombocytopenic purpura (ITP) in childhood is generally considered a self-limited condition with a good prognosis.[1,2] A follow-up of our patients with idiopathic thrombocytopenic purpura revealed that this classical belief does not always hold true since we encountered a number of cases which became chronic and presented certain problems.

The causes of thrombocytopenia are various as can be seen from Table 1. When the etiological factor cannot be found, the condition is labeled idiopathic thrombocytopenia.

In this paper we present 62 cases of ITP which were seen and followed at this hospital between July 1958 and March 1967.

Materials and Methods

Thirty girls and 32 boys with ages varying between three months and 14 years were seen because of bleeding into the skin and mucous membranes. Forty-seven of the 62 patients were in the acute phase and 15 were considered chronic at the time of their admission. Later nine patients from the first group became chronic. The criterion for differentiating the acute stage from the chronic was whether the disease lasted for a period of six months or longer. Twenty of these patients were seen and the prognoses of the others were learned through questionnaires at least six months after their first admission. Tables 2 and 3 summarize the age, sex and duration of symptoms of all patients on admission.

From Hacettepe University Faculty of Medicine, Department of Pediatrics, Ankara.

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** Senior Resident in Pediatrics.

*** Associate Professor of Pediatrics and Hematologist.

TABLE 1
CLASSIFICATION OF THROMBOCYTOPENIA

I. Idiopathic thrombocytopenic purpura
   1. Acute
   2. Chronic

II. Neonatal thrombocytopenia

III. Hereditary thrombocytopenia : Aldrich syndrome, thrombocytopenia with dominant inheritance

IV. Secondary thrombocytopenia

   1. Infections
      A. Viral : rubella, infectious mononucleosis, mumps, chicken pox, rubeola, cytomegalic inclusion disease
      B. Bacterial : sepsis
      C. Parasitic : malaria, toxoplasmosis
   2. Drugs
      A. By sensitization : sedormid, quinidine, quinine, acetazolamid, sulfisoxazole, chlorthiazide, phenylbutazone
      B. By direct action on platelets : ristocetin
      C. By bone marrow depression : chloramphenicol, streptomycin, quinacrine, nitrogen mustard, cyclophosphamide, vincristin sulfate, 6-MP, methotrexate, etc.
   3. Bone Marrow Infiltration : myelophthisic anemia, leukemia, lymphosarcoma, Letterer-Siwe disease
   4. Idiopathic aplastic anemia
   5. Hypersplenism
   6. Giant hemangioma
   7. Systemic lupus erythematosus
   8. Iron deficiency anemia
   9. Megaloblastic anemia
   10. Acquired hemolytic anemia
   11. Massive blood transfusions, exchange transfusions
   12. Thrombotic thrombocytopenic purpura
   13. Hemolytic uremic syndrome
   14. Congenital cyanotic heart disease
   15. Hyperglycinemia

TABLE 2
AGE AND SEX OF PATIENTS IN STUDY

	Age in Years on Admission							
	Acute					Chronic		
	Up to 2	2 to 5	5 to 10	10 to 15	Total	5 to 10	10 to 15	Total
Female	4	5	10	6	25	2	3	5
Male	2	11	4	5	22	7	3	10
Total	6	16	14	11	47	9	6	15

TABLE 3
SYMPTOMS OF THE DISEASE AT THE TIME OF ADMISSION

	Number of Cases	Percent
Petechiae, ecchymoses	56	91
Epistaxis	51	82
Hematuria	7	12
Splenomegaly	3	4.8

In each case a detailed history was taken and a complete physical examination was done. The following hematological tests were performed: hemoglobin (by cyanmethemoglobin method using Klett-Summerson photometer); hematocrit (by micromethod); platelet count (by Rees-Ecker[3] method and by estimating platelets on each blood smear); peripheral smear; bone marrow and leukocyte count; direct Coombs' test; L E cell preparation and throat cultures (by conventional methods[4]).

Twenty-eight cases of the acute type and nine cases of the chronic type had a hemoglobin level under 10 gm/100 ml. W.B.C. was under 5000 per cmm in two patients and was over 10,000 per cmm in 23 patients. The platelet counts are summarized in Table 4.

TABLE 4
PLATELET LEVELS *

First Counts on Admission			
Acute		Chronic	
Less than 40,000/cmm	40,00 - 80,000/cmm	Less than 40,000/cmm	40,00 - 80,000/cmm
18	21	7	6

* Platelet counts were done on 52 patients.

Bone marrow aspiration was done in each case and every patient had either a normal or an increased number of megakaryocytes. Nineteen marrow smears revealed eosinophilia, 21 presented normoblastic erythroid hyperplasia and seven had megablastoid changes. The L E cell preparation and Coombs' test were negative in every patient. Fourteen out of 47 patients with acute thrombocytopenia had a history of infection prior to the onset of the disease. Beta hemolytic streptococci were cultured from the throat of two and six cases among acute and chronic ITP cases respectively.

Therapy

Acute Cases : Forty-five out of 47 patients were given prednisolone (1 - 3 mg per kg of the body weight) for a period of at least two weeks. Twelve patients received oral iron and ten were transfused for their anemia.

The time required from the beginning of therapy until the normal platelet count was reached was one week in six patients, two weeks in one patient and two to eight weeks in four patients. The platelet count rose over 100,000 per cmm in 15 patients, but never attained normal levels. There was no response to therapy in 18 patients and 11 of these were given another course of corticosteroid therapy. Half of these 18 became chronic and the rest were lost in the follow-up. A complete remission was obtained in one case with cyclophosphamide treatment (5 mg/kg) in ten days who has been in remission since then. A trial of plasma (30 cc per kg of body weight) transfusions in eight patients failed to raise the the platelet count.

Chronic Cases : This group comprises 24 patients including the nine who became chronic during the follow-up. Twenty-two of these patients were already being given corticosteroids, nine of them for a period of two weeks. Eight of them had a second course with prednisolone.

For their anemia, seven patients were given blood transfusions and eight were treated with oral iron. Splenectomy was performed on 12 patients. All of the splenectomized patients were given corticosteroids previously.

Five patients were cured following splenectomy with normal platelet counts and disappearance of symptoms. In two cases, platelets were raised to a normal level postoperatively, but later their

number was again decreased. In these two patients another course of prednisolone therapy brought the platelet level to normal.

In three patients, the platelets were not increased following splenectomy. One of these was treated with Purinethol[R] (6-mercaptopurine, 2.5 mg per kg) but died from cerebral hemorrhage at the ninth postoperative week. In three, cyclophosphamide was given without any benefit. In two patients, the platelet count rose to 112,000 and 312,000 per cmm respectively following splenectomy. However, thrombocytopenia recurred in one case in a few weeks and seven months after the operation in the other.

Plasma transfusions (30 cc per kg) in four chronic cases (two preoperatively and two postoperatively) failed to raise the platelet counts.

A follow-up of twelve chronic cases who did not have splenectomy revealed that in three platelet levels were between 80,000 and 100,000 per cmm and presented no symptoms. They were considered improved. In eight patients there was no improvement in symptomatology and one died at home.

The overall results are summarized in Table 5.

TABLE 5
OVERALL RESULTS *

Type of case	Cured	Improved	Unchanged	Died	Unknown	Total
Acute	18				20	38*
Chronic	7	4	11	2		24*
Total	25	4	11	2	20	62

* Since nine of the acute cases became chronic, the follow-up of those cases are included in the chronic group.

Comments

Many theories have been proposed for the pathogenesis of ITP. The spleen has some relation to thrombocytopenia in this condition, whether it elaborates an abnormal humoral factor which decreases platelet formation by inhibiting megakaryocytic function or destroys the thrombocytes after their selective sequestration. While there is some evidence in favor of splenic sequestration, other findings suggest the role of splenic humoral factors.[5, 6] Harrington and co-workers have demonstrated that an immunologic mechanism is responsible for the low platelet count in many patients with ITP,

both in adults and in newborn babies.[7, 8] In terms of this concept, the spleen is involved in pathogenesis by removing sensitized platelets and producing thrombocyte agglutinins in variable amounts. However in ITP cases in childhood, platelet agglutinins are shown in only the minority of cases. The survival of platelets in normals is nine to 11 days[9] and is markedly decreased in cases of ITP.[10]

Preceding upper respiratory infections have some role in the pathogenesis of ITP. In some large series, 53 to 62 per cent of a history of this kind of infection was obtained one or two weeks prior to the development of thrombocytopenia.[11, 12] Although there are various theories, the precise manner in which infection, presumably bacterial or viral, affects platelets is unknown. In only 36 per cent of our cases with acute ITP was the preceding history of upper respiratory system infection obtained.

The patients in whose throats beta hemolytic streptococci were cultured were given penicillin treatment for ten days.

Because in acute ITP the prognosis is better in the group with preceding acute infection, this history should be carefully investigated.

Chronic ITP in adults occurs more frequently in females.[13, 14] In children, 40 per cent of the chronic ITP cases were reported in girls by Newton and Zuelzer[11] and 33 per cent of our cases with chronic ITP are also girls.

In general, the spleen is not enlarged in ITP. In three of our cases the spleen was one cm below the left costal margin which might be seen in ten per cent of children.[15]

The value of corticosteroids in the treatment of ITP in childhood is disputable.[16] However, it might decrease the bleeding tendency in this condition by the capillary effect. Usually we do not use this treatment more than two weeks.

In patients who have not responded to corticosteroids or who do not go into spontaneous remission, use of plasma transfusions and cytotoxic drugs might be attempted. Although there are a few reports in favor of plasma transfusions in ITP cases,[17, 18] in general the results are not so good as ours. A megakaryocyte-stimulating substance in normal human plasma is shown.[19] Human and animal plasma thrombopoietic activity seems more obvious in splenectomized rats,[20, 21] although in 12 patients of ours who were given plasma following splenectomy, no response was observed.

All seven patients who showed megaloblastoid changes in the bone marrow examination received folic acid (50 - 500 mcgr/day for at least three days) without any reticulocyte or platelet response. Thrombocytopenia due to iron deficiency anemia has been reported.[22] Altogether 20 patients received oral or parenteral iron treatment for their accompanying iron deficiency anemia without any significant changes in platelet counts under the treatment.

Recently some good results were observed with cytotoxic drugs in the treatment of chronic ITP cases.[23, 24] In one acute ITP case, a remission was obtained with cyclophosphamide and prednisone combination, but this might have been a spontaneous remission.

Although we have not observed any complications, splenectomy has some potential hazards in childhood such as producing severe infection and manifesting systemic lupus erythematosus earlier.

Among 25 of our acute ITP patients for whom we have a follow-up, nine became chronic; from the 12 splenectomized chronic ITP patients, only seven were cured. These results indicate that one should be more concerned about the prognosis of ITP.

Summary

From this study we may conclude that the incidence of chronic thrombocytopenic purpura in childhood is higher than it is thought to be and that one must be careful in making a prognosis to the parents on acute and chronic cases of thrombocytopenic purpura.

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