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Immune thrombocytopaenic purpura: 11-year experience in Ile–Ife, Nigeria

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Summary

Immune thrombocytopaenic purpura (ITP) is believed to be rare in indigenous black Africans and people of African extraction in other parts of the world, compared to reports among the Caucasians. This paper is therefore aimed at investigating the incidence, clinical features and course of ITP managed at the Obafemi Awolowo University Teaching Hospitals Complex Ile-Ife over the past 11 years. The study was both retrospective and prospective. Case notes of patients confirmed to have ITP were retrieved and studied. Clinical, haematologic as well as management protocols and outcomes were evaluated. Diagnosis was based on the presence of haemorrhagic manifestations, thrombocytopaenia with normal or increased bone marrow megakaryocytes. Hospital incidence of the disease was computed from all hospital admissions in the period under review. There were eleven cases (7 females, 4 males), aged 10 to 55 (median, 21) years. Eight (72.7%) of the patients presented within one week of onset of symptoms. None of the patients had a history of any overt infection. Two patients (18%), both females were positive for lupus erythematosus (LE) test. Eighty percent of the patients presented with severe thrombocytopaenia (platelet count $<10 \times 10^9/l$), while 72% had severe anaemia (PCV $\leq$ 25%) requiring blood transfusion. Remission was induced within 4 weeks in 92% of patients, using oral prednisolone. Immunosuppressive treatment with cyclophosphamide was required to achieve remission in one patient. The overall prevalence rate is 0.005% of hospital cases. The review confirms rarity of ITP in this population and its female preponderance (F:M ratio 1.8:1). Although clinically severe, response to corticosteroid therapy is impressive. No patient underwent splnectomy.

Keywords: *ITP, clinical presentation, management outcome, Nigerians.*

Résumé

L'immuno-thrombocytopaenique purpura (ITP) est rare dans la population endigene d3es noirs Africains et les pemples ā racine africanine dans les antres prarties du anonde, compare an rapports chez les pengles Caucasiens. Ce document a pour but d'investiguer l'incidence, les effets cliniques et le cours d'ITP repertores an complexe du Centre Hospitalier Universitaire d'Ile-Ife a cours dess 11 dermeres annees.

Cette etude a ete a la fois retrospective et prospective. Les dossiers des patients confirmes avoir l'ITP ont ete edentifiés et etudies. Les protocols clinique, haematologique d'assistance amni que les resultants ont ete evalues. Le diagnostic était base sur la presence des manifestations hemornagiques, trombocytopaenia normal on avec augmentation megoidaryocytes de la moelle des os.

L'incidence Hospitalier de la maladie a ete calculee a partir du taux d'admission (des internes) an cous de la periode cousideree.

Ye y avait 11 cas (7 femmes, 4 hommes), ages de lo a 55 (mediane, 21) ans hint (72, 7%) des patients ont developers pendant une semaine des symptoms. Aucum des patients n'avait un passé avec infection. Deux patients (18%) tous deux femmes ont ete tertes positives an lupus erythematosus (LE). Quatre vingt pour cent des maladies presente avec une thrombocytopaenia severe (deconyste des platelets $< 10 \times 10^9$/e) alors que 72% avait une anemie severe (PCV = 25%) demandant une tranfusion sanojunne . Une remission a ete induite an courant de 4 semaires chez 92% des patients, en utilisant la prednisolone orale. Le traitement par immunosuppression avec la cyclophosphamide a ete demandee pour obtemir la remission chez l'un des patients. Le taux de prevalence total est de 0, 005% pour les cas des hopitaux. La revue confirme la rarete de l'ITP chez ces populations et sa preponderance femmine (F:H rapport est de 1, 8:1).

Bien que clinicallement sever, la reponse an traitement par corticosteroide est impressionante. Aucum patient n'a eu recours a la splnectomie.

Introduction

Immune thrombocytopaenic purpura (ITP) is an autoimmune disease that can occur in children and adults. It is characterized by low platelet count with normal or elevated bone marrow megakaryocytes and bleeding from mucous membranes [1,2]. The shortened platelet survival is due to anti-platelet antibodies which are directed at platelet glycoproteins (gp) IIb/IIIa and/or gp Ib/IX [2,3]. In view of the detection of specific auto-antibodies against platelet gp and the therapeutic effect of the administration of immunoglobulin concentrates [4,5] the less precise description term 'idiopathic' is being replaced by 'immune' thrombocytopaenic purpura.

ITP has distinct clinical manifestations in children and adults [6]. In children, Immune thrombocytopaenic purpura is typically abrupt in onset and self-limited in its course with higher spontaneous remission rate (> 80%) [7]. Boys and girls are equally affected. In adults, ITP is more indolent in its onset and the course is persistent often lasting many years; spontaneous remission is very unusual [7]. Most adult patients are young women. ITP is more common in Caucasians in Europe and the United States of America than in Africans [8].

The management of ITP is designed to prevent life-threatening complications such as intracranial haemorrhage (ICH) [9]. Therapy, especially in adults, may include single or combination therapy with corticosteroids, intravenous immunoglobulin (ivIg), anti-D and splenectomy.

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Immunosupressive drugs such as vinca alkaloids, azathioprine and cyclophosphamide may be employed in resistant cases [10]. Immuno-ablation by high dose chemotherapy, followed by autologous peripheral stem cell transplantation (PBSCT) is another form of therapy currently under investigation [11]. Oral therapy with prednisolone or other glucocorticoids suffices in most childhood ITP [12].

The aim of this study is to outline the pattern of clinical presentation and to evaluate the effectiveness of therapy available to patients presenting with ITP in this environment.

Patients and methods

The medical records of patients diagnosed as suffering from ITP at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria, between January 1988 and December 1998 were analysed. In each case, the following variables were noted: demographic data, presenting clinical features and date of onset, haematological parameters and physical findings at presentation, type of therapy and outcome. Diagnosis of ITP was based on the presence of muco-cutaneous bleeding and thrombocytopaenia in the absence of any other pathology that may cause low platelet count. Bone marrow aspiration slides of each patient was also reviewed. Patients were classified as either acute or chronic depending on whether on not they remitted within 6 months of presentation.

Results

Eleven cases of ITP were managed in the unit during the 11-year period under review. Ages of the patients ranged from 10 to 55 years with a median of 21 years. There were 7 females and 4 males (F:M ratio 1.8:1). The haemorrhagic manifestations presented with are as shown in Table 1.

Table 1: Presenting blending sites in ITP, Ile-Ife, Nigeria

	Bleeding manifestation	No of cases
1	Gingival bleeding	9 (81.8%)
2	Purpura	4 (36.4%)
3	Haematuria	3 (27.3%)
4	Epistaxis	3 (27.3%)
5	Haematemesis	1 (9.1%)
6	Menorrhagia	1 (9.1%)

\+ *present or positive*
\- *absent or negative.*

Eighty-two percent of patients presented with gingival bleeding, purpuric skin lesion occurred in 4 (36.4%) cases, followed by haematuria and epistaxis in three (27.3%) patients each. Excessive menstrual flow and gastrointestinal bleeding occurred in one patient each. Three patients had positive family history of similar illness, but none had any antecedent history of overt infection. Eight (72.7%) patients presented within one week of onset of symptoms. Severe (PCV < 0.25) to moderate (PCV 0.25-0.30) anaemia were seen in 54.5 % and 36.4% of the patients, respectively. Only 1 (9%) patient had mild anaemia (0.35) (Table 2). Nine of the patients had packed cell transfusion for symptomatic anaemia. Correlation analysis shows a significant positive relationship between haematocrit and time of presentation ($r = 0.6$; $P < 0.05$). Two patients (18.2%) had mild splenomegaly (< 10 cm) below the costal margin. Chronic malaria, concomitant occult infections or even anaemia may be responsible for the higher frequency of splenomegaly in our series compared to the patients from the non-malarious temperate population.

Direct antihuman globulin test (DAT) was negative in all the patients but lupus erythematosus (LE) test was positive in two (18.2%) of the affected women. Neither anti-platelet antibody tests nor HLA typing were performed in any of the patients. Most (82%) of the patients presented with severe thrombocytopaenia (platelets <10 x 10^9/l), however no patient had platelet count more than 40 x 10^9/l at presentation (Table 2). Nine (82%) were transfused with blood due to severe symptomatic anaemia (PCV<0.25). With the exception of one patient who discharged himself against medical advice after receiving blood transfusion, all of the others received cortico-steroid as initial therapy with only one requiring addition of immuno-suppressive therapy (cyclophosphamide) due to intractable thrombocytopaenia (Table 3). No patient underwent splenectomy.

There was significant improvement in platelet count (platelet >50 x 10^9/l) at the time the haemorrhagic symptoms ceased in 6 patients. It is,however, interesting to note that despite persistent thrombocytopaenia in some of these patients (platelets < 50 x 10^9/l), bleeding ceased on or before 7 days in 5 (50%) of those who had prednisolone 14 days in another 30%, the other 2 bled for between 21 and 28 days before remission (Table 3). The period of follow-up post-remission ranged between 0.25 and 54 months. Seven of the 10 patients that received steroid continued to be in remission until they were lost to follow-up while the other 3 had recurrent episodes of bleeding. None of the patients sustained intracranial haemorrhage and no death was recorded.

Discussion

The eleven cases reviewed in this report were seen over a period of eleven years, giving an average of 1 case per year. During the same period, a total of 217, 422 new patients were seen in this hospital, giving a prevalence of 0.005 percent hospital cases. A similar prevalence rate (0.01%) was obtained in Nigerian children at Ibadan by Lewis and Essien in 1975 [12]. In some other parts of Africa, the same pattern was demonstrated, 4 cases per year was reported by Badri and Abebe [13] in a twelve-year review from Ethiopia, whereas only 2 cases were reported from Togo over a 16-year period [8]. However in the United States of America, between 14,000 and 16,000 new cases are reported yearly [14] while Doan *et al.* (1960) reported an incidence of 0.18 percent from a population of another 132,235 Caucasian patients [15]. The difference between Doan's figure and ours was statistically significant ($P = 0.00001$, $P^2 = 319$). This wide disparity in the occurrence of ITP between the Caucasian and black populations is in support of the view that ITP, and indeed autoimmune disorders generally, are rare in indigenous Africans [8,12]. The reason for this rarity has been linked with widespread infections, especially chronic malaria infection, which impairs host's T-cell immunity [16-18].

Our patients presented with known haemorrhagic manifestations of ITP [8,12,13,19] (Table 1), including gingival bleeding (81.8%) cutaneous bleeding (36.4%), epistaxis (27.3%), haematuria (27.3%), gastrointestinal bleeding (9.1%) and menorrhagia (9.1%). This pattern of thrombocytopaenic bleeding is similar to what Lewis and Essien [12] reported in children. This is however unlike the pattern of presentation seen in Caucasian populations where cutaneous bleeding (purpura) is far more common, accounting for over 70 % [15,19]. We agree it might be partly related to difficulty in

Table 2: Cinical and Haematological Parameters of ITP at Presentation.

	Age (yrs)	Sex	DOBP (days)	Platelets x10⁹/l	PCV (%)	Spleen	FHx	DAT	LE Cell	Infection
1	10	M	3	<10	13	-	-	-	-	-
2	13	M	3	<10	25	+	-	-	-	-
3	16	F	4	<10	23	-	+	-	-	-
4	19	M	5	<10	21	-	+	-	-	-
5	20	M	6	<10	28	-	-	-	-	-
6	21	F	6	<10	24	-	+	-	-	-
7	27	F	35	<10	35	-	-	-	-	-
8	27	F	10	18	17	-	-	-	+	-
9	38	F	3	<10	25	-	-	-	-	-
10	43	F	60	<10	30	+	-	-	+	-
11	55	F	3	37	18	-	-	-	-	-

Key: *DOBP - duration of bleeding before presentation*
FHx - family history of similar bleeding.
LE cell - Lupus erythematosus cell test.
DAT - direct anti-human globulin test.

Table 3: Clinical and Haematological Indices in ITP Patients at Remission

	Age (yrs)	Sex	Therapy	Platelet x10⁹/l	DBR (days)	PCD%	LFU(mth)	CC
1	10	M	Bld Tx Pred.	251	14	30	6	A
2	13	M	Bld Tx Pred.	<10	5	34	6	A
3	16	F	Bld Tx Pred.	75	7.	28.	6.	A.
4.	19	M	Bld Tx	-	-	-	-	DAMA
5	20	M	Bld Tx Pred.	<10	6	29	0.25	A
6	21	F	Bld Tx Pred. Cyclo.	115	14	27	54	C
7.	27	F	Bld Tx Pred.	20	2	37	2	A
8.	27	F	Bld Tx Pred.	64	6	34	42	C
9.	38	F	Bld Tx Pred.	<10	21	28	0.75	A
10	43	F	Pred	85	28	28	1.5	A
11	55	F	Bld Tx Pred	173	10	34	42	C

Key: *Bld Tx – blood transfusion*
DBR - duration of bleeding before remission
CC - Clinical course (acute A chronic C)
Pred - prednisolone
DAMA – Self discharge
LFU- Period of follow-up (months)

recognizing tiny purpuric spots in dark skin [12]. However, a genetic predisposition to mucous membrane bleeding in Africans may also be responsible as 81.8 percent of our patients presented with platelet count of less than 10 x 10⁹/l, (Table 2) yet only 36.4% had purpuric lesions at presentation. In this series, there were 7 females and 4 males. This female preponderance is in keeping with reports from other workers [6,12,13]. Oestrogen has been implicated [20] as the factor responsible for the sex bias in autoimmune disorders. However, how it exerts its effect on lymphocytes or macrophages is unknown. Massive splenomegaly (spleen = 10cm) was very uncommon, only 2 (18.2%) had palpable mild to moderate splenomegaly.

Three of our cases had history of similar bleeding tendencies in family members. Immune thrombocytopaenic purpura in multiple members of the same family have been reported [21], and like other autoimmune disorders which are known to be human leucocyte antigen (HLA) – linked, the possibility of ITP also being HLA – linked has been suggested [22-23].

All the patients had bone marrow aspiration (BMA) at presentation and none was found to have any malignancy or other secondary causes of thrombocytopaenic bleeding. This may justify the view [24] that BMA is unnecessary in classic ITP. However, in an environment where no other tests [3,25-27] are available, BMA may continue to be a useful exclusion test. Megakaryocytes were either normal or elevated in all the patients.

The first line of therapy in all cases was oral prednisolone which has been shown to be effective in patients with moderate to severe ITP [12,28,29]. The majority of our patients had severe thrombocytopaenia (platelet count <10 x 10⁹/l). This review has shown the effectiveness of prednisolone as haemorrhagic symptoms ceased within 7 days in 5 patients (50 %), within 14 days in 3 (30%), while the remaining 2 patients remitted within 28 days. It is however interesting to note that despite persistent thrombocytopaenia of $\leq 20 \times 10^9$/l in some of these patients, the enhanced platelet function ("stress platelets") in ITP [30-32] compared with platelets found in hypomegakaryocytic thrombocytopaenia, may partly account for the remission of symptoms in these patients.

The average time between the commencement of prednisolone and ceasation of haemorrhagic symptoms was 11.3 days (range 2 – 28 days). This time interval was much longer than the mean of 2 days (range = 1-4) obtained in children [12], thus confirming the more acute nature of ITP in children, and the greater tendency to spontaneous remission compared to adults [6]. Follow-up period of patients, post

primary remission, ranged between 0.25 and 54 months (median, 6 months). While 7(70 %) continued to be in remission, 3 (30 percent) continued to have recurrent "bleeding attacks" for more than 6 months. Two of these 3 patients remitted on further use of prednisolone, while the third remitted only after the addition of cyclophosphamide.

This review has revealed that ITP is not a common cause of hospital admission in this environment. It is equally interesting to note that 6 of the nine adult patients had acute ITP which is more common in children. However the mode of presentation, clinical course and response to therapy are similar to what obtains in other part of the world.

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