Thrombocytopenia in Children Infected with the Human Immunodeficiency Virus: Prevalence among Nigerian Igbo Children

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SUMMARY

Background: Human immunodeficiency virus (HIV) infection is associated with a myriad of hematopoietic abnormalities, of which thrombocytopenia (TP) is a common complication. The condition could predispose to life-threatening hemorrhage.

Objectives: To determine the prevalence of thrombocytopenia among HIV- infected children presenting to the Paediatric HIV Unit of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Southeast Nigeria, and to determine the effect of HAART on HIV-associated TP.

Methods: This is a cross-sectional descriptive prospective study. Inclusion criteria were confirmed HIV infection (age>18 mo) and presumptive diagnosis (<18mo). Patients were consecutively recruited, demographic data collected and baseline hematological and relevant laboratory indices obtained. Clinical Staging and Immunological Staging were obtained. Adherence counselling and ARV therapy were commenced as indicated. All patients were duly followed up.

Results: Two hundred and thirty-three HIV infected children were seen in the unit between July 1, 2003 and June 30, 2005. Ages ranged from 6 months to 15 years. There were 126 males (54.1%) and 107 females (45.9%). According to WHO Clinical Staging, 41 (17.8%) were in stage 1, 79 (33.8%) stage 2, 82 (35.2%) stage 3, & 31 (13.2%) in stage 4. The CDC Immunological classification showed that 32(13.3%) had no suppression, 71(39.5%) had moderate suppression and 130(56.2%) were severely suppressed. One hundred and sixty-eight (71.9%) children were on antiretroviral (ARV) therapy. Twelve children had thrombocytopenia (platelet count < 100,000 cells/mm^3) giving a prevalence of 5.2%. Only one patient among these (8.3%) presented with one of the clinical signs of thrombocytopenia (epistaxis) and needed to be transfused. Most of the patients who had thrombocytopenia were within WHO Clinical Stages 3 & 4 and had severe immunosuppression. However, their platelet counts improved with ARV therapy, which was monitored for varying durations.

Conclusion: Highly active ARV therapy (HAART) is effective in correcting HIV-associated TP. Due to the possibility of life-threatening hemorrhage attendant on thrombocytopenia, routine platelet estimation is advocated as part of the initial laboratory evaluation of all HIV-infected children. It is suggested that severe thrombocytopenia should qualify for recruitment into antiretroviral therapy even when all the usual criteria are not present.

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INTRODUCTION

Thrombocytopenia (TP) is defined as platelet count less than 100 x 10^9/L (100,000 cells/mm^3) (1). It is a relatively frequent complication in patients infected with HIV. Several pathogenetic mechanisms have been advanced. In most recently infected patients, TP is due to accelerated platelet destruction. In these patients platelet sequestration is splenic, and splenectomy is usually effective in correcting the TP[1].

TP may also be due to increased amounts of anti-platelet antibodies and consequent immune complex platelet destruction [2,3]. This mechanism is said to be antagonized by Zidovudine[4,5]. Defective megakaryopoiesis is another mechanism for HIV-associated TP[2], especially in patients with advanced disease[6]. Additionally, at an earlier stage of platelet development, HIV may inhibit megakaryopoiesis at multiple stages of pluripotent CD34+ progenitor stem cell differentiation possibly contributing to decreased levels of platelets in circulation[7].

Thrombotic thrombocytopenic purpura (TTP) is quite common among patients with HIV infection. HIV-1 infection has been reported to account for at least a third of cases of thrombocytopenic purpura-hemolytic uremic syndrome [6,8-13]. The risk of microangiopathy has declined in the post-HAART era. Although no controlled studies comparing HIV-related TTP with classical TTP has been conducted, HIV-related TTP is generally thought to be associated with a milder course and a better response to therapy than classical TTP[14]. A study from Washington, USA, reported immune thrombocytopenic purpura (ITP) occurring in as many as 40% of patients infected with HIV[15]. Consequent upon the diverse clinical variants of thrombocytopenia observed among HIV patients, Landonio *et al*[16] have proposed the term "HIV-related thrombocytopenia" to include more than one kind of TP: "Acute ITP-like" TP, "Chronic ITP-like" TP, "pooling" TP, and "hypoplastic" TP, which have to be evaluated differently for pathogenesis, clinical manifestations and treatment.

This study aims at determining (a) the prevalence of TP in HIV-infected children presenting at the Paediatric HIV Unit of the Nnamdi Azikiwe University Teaching Hospital, Nnewi, southeast Nigeria, (b) the effect of highly active antiretroviral therapy (HAART) on HIV-associated TP.

MATERIALS AND METHODS

This is a cross-sectional, prospective and descriptive

study spanning from July 1, 2003 to June 30, 2005. Two hundred and thirty-three HIV-infected children presented at the Paediatric HIV Unit. These children were recruited from four sources:

- Patients presenting to the Children's out-patient clinics and Children Emergency Room of NAUTH, who were screened on suspicion by the attending physicians;
- Referrals of HIV-positive children from private clinics, primary and secondary level health facilities, and HIV/AIDS Support Groups and Non-Governmental Organizations within Anambra State and beyond;
- Referrals of HIV-positive progeny of patients attending the Adult HIV Clinics of NAUTH;
- Symptomatic babies of HIV-positive mothers on follow-up in the PMTCT (Prevention of Mother to Child Transmission of HIV) programme in NAUTH.

Patients were consecutively recruited. Inclusion criteria were confirmed HIV infection in children aged e" 18 months or a presumptive diagnosis of HIV infection in symptomatic children <18 months, (World Health Organization [WHO] criteria for symptomatic HIV infection), who showed evidence of immunosuppression (low CD4 count for age). The WHO clinical case definition for Paediatric AIDS (17) and the U.S. Centers for Disease Control and Prevention (CDC) Immunological classification[18] were applied for all patients.

On enrolment, a pre-coded proforma was completed. Presenting features, demographic data, family history, HIV status of parents and siblings and immunization status of each child, among other data were filled in. A complete physical examination and baseline laboratory investigations were carried out. These included an HIV screening test, Confirmatory test (Western Blot or Double Elisa), CD4 lymphocyte count, complete blood count including platelet count, liver function tests, urine analysis, serum electrolytes/urea/creatinine and chest x-ray, when indicated. Child-parent/guardian pairs had post-test counselling (since they usually came with a positive test result). All referred patients had a repeat HIV screening test done after an informed consent was obtained from the parent/guardian.

Initial screening was done with Genscreen®plus (Bio-Rad laboratories) for antibodies to HIV I and II. Confirmation was done initially with New-Lav blot I (Bio-Rad Lab) until September 2004, when the U.S. PEPFAR (Presidential Emergency Program For AIDS Relief) program supplied Rapid test screening kits (Capillus and Genie II) for confirmation. A sample was considered HIV antibody-positive if the serum was reactive in both tests. Where discordance occurred Determine rapid test kit was used as a tie breaker. Automated complete blood counts were performed with Sysmex KF 21 machine. CD4 lymphocyte counts were carried out with the Dynal CD4 kit, Manual Coulter counter CD4 kit (in March 2005), and from April 2005, Partec Cyflow machine. Strict compliance with manufacturer's instructions on usage and storage of reagents was adhered to.

At follow up visits, new complaints, findings on physical examination, adherence counseling for ARV drugs were addressed. Those who qualified for ARV drugs received HAART – a combination of 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and 1 Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). The NRTIs included Zidovudine 240mg/m^2 body surface area twice daily; Lamivudine 4mg/kg body weight twice daily; Stavudine 1mg/kg body weight twice daily. In the NNRTI group were Nevirapine commenced once daily for the first 14 days, then maintained on 7mg/kg twice daily for age < 8 years, and 4mg/kg twice daily for age e" 8 years; Efavirenz for age > 3 years (especially for those on concomitant anti-tuberculosis therapy) as a single daily dose as follows: 10 - <15kg 200mg, 15 - <20kg 250mg, 20 - <25kg 300mg, 25 - <33kg 350mg and 33 - <40kg 400mg. Stavudine and Zidovudine were not used together. Hematological laboratory profiles were obtained every 3 months or earlier if necessary.

Data analysis was aided by the SPSS version 11.5 software.

RESULTS

Of the 233 HIV-infected children aged 6 months to 15 years, there were 126 males (54.1%) and 107 females (45.9%). According to the WHO Clinical Staging 41 (17.8%) were in Stage 1, 79 (33.8%) Stage 2, 82 (35.2%) Stage 3, and 31 (13.2%) in Stage 4. The CDC Immunological classification showed that 32 (13.3%) had no immunological suppression, 71 (30.5%) had moderate suppression, and 130 (56.2%) were immunosuppressed. One hundred and sixty-eight children (71.9%) were placed on ARV drugs.

Twelve children had thrombocytopenia (platelet count < 100,000 cells/mm^3), giving a prevalence of 5.2%. Only one patient among these (8.3%) presented with a clinical sign of thrombocytopenia (in this case epistaxis) that necessitated blood transfusion. All the patients were treatment-naïve. No bone marrow aspiration was performed. No case of thrombotic thrombocytopenia with renal or neurologic symptoms was observed in this study, as was reported elsewhere (8-10, 12-14).

Most of the patients who had thrombocytopenia were within WHO Clinical Stages 3 and 4 and had severe immunosuppression (see Table 1). However, their platelet counts improved when placed on HAART for varying periods.

DISCUSSION

Table 1: Clinical details of HIV-infected thrombocytopenic children

Patient Clinical Details				Pre-Treatment Platelet count/mm³	Post-Treatment Platelet count/mm³
Age	Sex	WHO Clinical Stage	CDC Immunologic Class		
9 yr	M	3	Severe	90,000	176,000 [5 mo on HAART]
4 yr	F	3	Severe	51,000	137,000 [9 mo on HAART]
10 yr	F	3	Severe	41,000	460,000 [8 mo on HAART]
5 yr	M	3	Moderate	36,000	430,000 [6 mo on HAART]
13 yr	F	3	Severe	78,000	290,000 [5 mo on HAART]
9 yr 9 mo	F	2	Severe	42,000	103,000 [5 mo on HAART]
13 yr	F	3	Severe	89,000	250,000 [9 mo on HAART]
14 yr 7 mo	F	4	Severe	38,000	132,000 [5 mo on HAART]
1 yr 7 mo	M	3	Moderate	53,000	360,000 [4 mo on HAART]
10 yr	F	4	Severe	94,000	175,000 [6 mo on HAART]
5 yr	M	3	Severe	68,000	252,000 [5 mo on HAART]
7 yr	M	3	Severe	66,000	148,000 [7 mo on HAART]

In this study, a TP prevalence of 5.2% was observed. This seems to be slightly higher than 2.5% reported among children in Lagos, southwest Nigeria[19] and less than 10% noted among an adult cohort in Port Harcourt, south-south Nigeria[20]. Elsewhere, among different American paediatric populations TP had a prevalence of 8-13% [21,22]. These are higher rates than what is obtainable in Nigeria. The difference may be attributable to more sophisticated diagnostic armamentarium.

The efficacy of HAART in reversing HIV-associated TP is also borne out in other reports. HAART seems to be effective in improving platelet counts in the setting of HIV-associated ITP, enhancing CD4+ cell counts and reducing HIV viral loads (15). HAART has been found to induce a sustained platelet response in HIV-associated severe TP, an undetectable plasma HIV viraemia induced by HAART being necessary for severe TP recovery[11]. HAART is also efficacious in TTP not responsive to plasmapheresis[23].

For completeness mention will be made of other treatment modalities employed in HIV-associated TP. In TTP plasmapheresis (plasma exchange) has remained the initial therapy[6,8,12,14]. Zidovudine monotherapy was employed before the advent of HAART[3,4]. Zidovudine increases the platelet count without correlation with its antiviral effect. In animal models and HIV patients, this enhancement of platelet count appears to be due to a stimulation of platelet production, the precise mechanism of which remains unknown[4].

Continuous low dose interferon-alpha therapy has been found beneficial in HIV-related ITP, especially in the milieu of failure of response to zidovudine monotherapy[24]. Corticosteroids have also been used with good effect[3,22], but with the underlying potential for further immune suppression.

In HIV-related acute and chronic ITP high dose intravenous gamma globulins have also produced a favorable outcome[3,22,25]. Surgery (splenectomy) has been employed as a last resort in severely symptomatic ITP in hemophiliacs resulting in enduring respite[4,26].

In conclusion, highly active ARV therapy (HAART) is effective in correcting HIV-associated TP. Due to the possibility of life - threatening hemorrhage attendant on thrombocytopenia, routine platelet estimation is advocated as part of the initial laboratory evaluation of all HIV-infected children. It is suggested that severe thrombocytopenia should qualify for recruitment into antiretroviral therapy even when all the usual criteria are not present.

REFERENCES

1. Najean Y., Rain J. D. The mechanism of thrombocytopenia in patients with HIV infection. *J Lab Clin Med* 1994; **123 (3)**: 415 – 20.
2. Ballem P. J., Belzberg A., Devine D. V., Lyster D., Spruston B., Chambers H., Doubroff P., Mikulash K. Kinetic studies of the mechanism of thrombocytopenia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992; **327 (25)**: 1779 – 84.
3. Blockmans D., Vermylen J. HIV-related thrombocytopenia. *Acta Clin Belg* 1992; **47 (2)**: 117 – 23.
4. Louache F., Vainchenker W. Thrombocytopenia in HIV infection. *Curr Opin Hematol* 1994; **1 (5)**: 369 – 72.
5. Zidovudine for the treatment of thrombocytopenia associated with human immunodeficiency virus (HIV). A prospective study. The Swiss Group for Clinical Studies on the Acquired Immunodeficiency Syndrome (AIDS). *Ann Intern Med* 1988; **109 (9)**: 718 – 21.
6. Sloand E. Hematologic complications of HIV infection. *AIDS Reviews* 2005; **7**: 187 – 96.
7. Sundell I. B., Koka P. S. Thrombocytopenia in HIV infection: impairment of platelet formation and loss correlates with increased c-MpI and ligand thrombopoietin expression. *Curr HIV Res* 2006; **4 (1)**: 107 – 16.
8. de Man A. M., Smulders Y. M., Roozendaal K. J., Frissen P. H. HIV-related thrombotic thrombocytopenic purpura: report of 2 cases and a review of the literature. *Neth J Med* 1997; **51 (3)**: 103 – 9.

9. Chu Q. D., Medeiros L. J., Fisher A. E., Chaquette R. F., Crowley J. P. Thrombotic thrombocytopenic purpura and HIV infection. *South Med J* 1995; **88 (1)**: 82 – 6.
10. Cruccu V., Parisio E., Pedretti D., Villa A., Confalonieri F. HIV-related thrombotic thrombocytopenic purpura (TTP) as first clinical manifestation of infection. *Haematologica* 1994; **79 (3)**: 277 – 9.
11. Carbonara S., Fiorentino G., Serio G., Maggi P., Ingravallo G., Monno L. *et al*. Response of severe HIV-associated thrombocytopenia to highly active antiretroviral therapy including protease inhibitors. *J Infect* 2001; **42 (4)**: 251 – 6.
12. Sood R., Rakkar A. S., Carmosino L., Mir T., Khan F. A. Thrombotic thrombocytopenic purpura in HIV infection: a report of two casae. *AIDS Patient Care STDS* 1996; **10 (6)**: 349 – 52.
13. Ranzini A. C., Chavez M. R., Ghigliotty B., Porcelli M. Thrombotic thrombocytopenic purpura and human immunodeficiency virus complicating pregnancy. *Obstet Gynecol* 2002; **100 (5 Pt 2)**: 1133 – 6.
14. Rarick M. U., Espina B., Mocharnuk R., Trilling Y., Levine A. M. Thrombotic thrombocytopenic purpura in patients with human immunodeficiency virus infection: a report of three cases and review of the literature. *Am J Hematol* 1992; **40 (2)**: 103 – 9.
15. Aboulafia D. M., Bundow D., Waide S., Bennet C., Kerr D. Initial observations on the efficacy of highly active antiretroviral therapy in the treatment of HIV-associated autoimmune thrombocytopenia. *Am J Med Sci* 2000; **320 (2)**: 117 – 23.
16. Landonio G., Nosari A., Spinelli F., Vigorelli R., Caggese L., Schlacht I. HIV-related thrombocytopenia: four different clinical subsets. *Haematologica* 1992; **77 (5)**: 398 – 401.
17. World Health Organization: Guidelines for the Clinical Management of HIV infection in Children. *WHO,* Geneva, 1993; 1.2 – 1.3.
18. Centers for Disease Control and Prevention: Revised Classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morbidity and Mortality Weekly Reports* 1994; **43 (RR – 12)**: 1 – 10.
19. Adetifa I. M., Temiye E. O., Akinsulie A. O., Ezeaka V. C., Iroha E. O. Haematological abnormalities associated with paediatric HIV/AIDS in Lagos. *Ann Trop Paediatr* 2006; **26 (2)**: 121 – 5.
20. Erhabor O., Ejele O. A., Nwauche C. A., Buseri F. I. Some haematological parameters in human immunodeficiency virus (HIV) infected Africans: the Nigerian perspective. *Niger J Med* 2005; **14 (1)**: 33 – 8.
21. Rigaud M., Leibovitz E., Quee C. S., Kaul A., Nardi M., Pollack H., *et al*. Thrombocytopenia in children infected with human immunodeficiency virus: long-term follow-up and therapeutic considerations. *J Acquir Immune Defic Syndr* 1992; **5 (5)**: 450 – 5.
22. Ellaurie M., Burns E. R., Bernstein L. J., Shah K., Rubinstein A. Thrombocytopenia and human immunodeficiency virus in children. *Pediatrics* 1988; **82 (6)**: 905 – 8.
23. Gruszecki A. C., Wehrli G., Ragland B. D., Reddy V. V., Nabell L., Garcia-Hernandez A., Marques M. B. Management of a patient with HIV infection-induced anemia and thrombocytopenia who presented thrombotic thrombocytopenic purpura. *Am J Hematol* 2002; **69 (3)**: 228 – 31.
24. Northfelt D. W., Charlebois E. D., Mirda M. I., Child C., Kaplan L. D., Abrams D. I. Continuous low-dose interferon-alpha therapy for HIV-related immune thrombocytopenic purpura. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; **8 (1)**: 45 – 50.
25. Bussel J. B., Haimi J. S. Isolated thrombocytopenia in patients infected with HIV: treatment with intravenous gamma globulin. *Am J Hematol* 1998; **28 (2)**: 79 – 84.
26. Leissinger C. A., Andes W. A. Role of splenectomy in the management of hemophilic patients with human immunodeficiency virus-associated immunopathic thrombocytopenic purpura. *Am J Hematol* 1992; **40 (3)**: 207 – 9.