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Research article

ACIDOSIS IN HIV PATIENTS ON ANTIRETROVIRAL DRUGS

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ABSTRACT: A survey of one hundred and twenty HIV patients was carried out to evaluate a possible cause of acidosis in HIV patients using biochemical parameters such as Uric acid, Lactate dehydrogenase, Phosphate and Bicarbonate .The patients were drawn from Aba in Abia State. Fifty HIV positive and fifty HIV patients on antiretroviral drugs were tested respectively comprising of 30 females and 20 males. Twenty HIV negative subjects made of 10 females and 10 males served as control. Subjects were of age 20 -35 yrs, HIV patients were on antiretroviral drugs (triviro-LNS-Lamivudine, Nevirapine and Starvudine) 1-2 pills daily depending on the CD4 count. Moreso, have been on the drug for the duration of 2- 3 years. All the investigations were done with serum. The phosphate and uric acid was assayed using fortress diagnostic kit based on calorimetric assay, so also Lactate dehydrogenase. Bicarbonate was determined based on titrimetric method. The results of the study revealed that there was a significant increase in the serum levels of Phosphate and Uric Acid in HIV positive subjects not on drugs (phosphate level Control (mg/dL). 3.70 ± 1.54 vs 10.00 ± 4.00, uric acid level control (mg/dL) 4.61± 2.36 vs 7.60 ± 3.60 compared to HIV negative subjects and HIV infected subjects on Antiretroviral drugs. Inaddition the Bicarbonate level was significantly reduced in HIV positive subjects compared to the other two groups as well (control (mmol/L) 23.00 ± 6.19 vs 7.16 ± 3.50 ($P<0.05$) .The activity of lactate dehydrogenase was very pronounced in HIV positive patients on antiretroviral drug compared to the other groups($P<0.05$). Similarly, a significant increase in the serum level of Phosphate was obtained for HIV positive subjects on drugs compared to HIV negative subjects (control (mg/dL). 3.70 ± 1.54 vs 4.78 ± 1.80 $P<0.05$).The result indicated equally that HIV positive subjects on drugs exhibited slight decrease in the levels of Uric Acid and Bicarbonate compared to HIV negative subjects ($P<0.05$). This study is therefore supporting and encouraging HIV infected patients to take antiretroviral drugs to reduce the associated metabolic abnormalities.

Key words: Uric acid, Phosphate, Bicarbonate HIV, AIDS

INTRODUCTION

The HIV and AIDS epidemic in Nigeria remains a public health problem of enormous magnitude that must be given priority attention, Considering that an estimated 3.6 percent of the population is living with HIV and AIDS (UNGASS 2010).Unfortunately, approximately 220,000 people died from AIDS in Nigeria in 2009 (UNAIDS 2010). Worrisome however is that 80-95 percent of HIV infections in Nigeria are as a result of heterosexual sex (Curtis1992, Reeves and Doms, 2002, Ungass 2010). To date, there is no cure for HIV/AIDS disease. There is no cure primarily because there is no cure for most viruses. Our immune system does not yet know how to direct an attack on *only* those cells which are infected with the virus.

The most effective treatment against viruses is to develop a vaccine-which stimulates our own immune system to enable the immune system to fight the virus (CDC, 1987, Lang et al 1989, Dybul et al 2002, Heath et al, 2002 and Fultz et al 2004). The vaccine *per se* does not fight the virus, but instead causes an immune response specifically directed against the particular virus from which the vaccine is made - this response directly increases the number of specific B- and T-cells available to respond against a live virus infection encountered at some later time (Tindall and cooper, 199l). A single trial of the vaccine RV 144 published in 2009 found a partial efficacy rate of ~30% and has stimulated optimism in the research community regarding developing a truly effective vaccine. However, the fact that HIV is a retrovirus causes serious problems in vaccine development because the enzyme which generates RNA and DNA copies of the virus's RNA genetic material makes errors. These errors are sometimes not lethal to the virus, but instead result in a different strain of a given virus - a different "looking" virus. Our immune system's ability to recognize any foreign substance or agent depends *entirely* upon how the substance or agent "looks" with respect to the molecular shapes displayed. With these frequent mutations or changes, our immune system gets confused and is unable to recognize the new strains (Justice el, al 1989, Clesielski, et al ,1991). Though, the antiretroviral drugs use these days to reduce the progression of HIV to AIDS are not without side effects. Specific adverse events are related to the agent taken. Some relatively common adverse effects include: lipodystrophy syndrome, dyslipidemia, and diabetes mellitus especially with protease inhibitors. Other common symptoms include: diarrhea, an increased risk of cardiovascular disease. (Montessori et al, 2004 and Coovadia ,2004 and Laeyendecker et al 2006). Unfortunately, some chemotherapy can cause acidosis especially lactic acidosis. Hyperuricemia in HIV infected patients seems to occur. When considering the potentials pathophysiological mechanism of the frequent occurrence of Hyperuricemia in HIV infected patients it was suggested that it may result from multiple metabolic, immunologic and pathological abnormalities which characterized the disease progression from asymptomic infection to terminal illness. Infact, abnormal serum urate levels have been observed in a broad spectrum of pathologic situations often complicating the course of HIV disease such as prolong fever due to infections, neoplastic or autoimmune disorders, hypercatabolic states associated with fasting or cathexia, viremia and possibly HIV related loss of mononuclear cells (Rynes et al ,1988 ,Manfredi et al 1998).Hypouricemia has also be attributed to increased renotubular loss(Maesaka et al ,1990).Aside from HIV infection itself, serum urate levels could potentially be altered by antiretroviral drugs . However the use of Didanosine and Stavudine or the combination of the two drugs was associated with hyperuricemia (Lambert et al ,1990). Respiratory chain failure causes ATP depletion which increases urate production in the purine nucleotide cycle. Mitochondrial dysfunction may increase the formation of lactate which competes with urate for tubular excretion in the kidney. This mechanism is the basis for the hyperuricemia and other metabolic myopathies. And, may also provide an explanation for the association between dideoxynucleoside analogues (Stavudine and Didanosine) and elevated urate. Therefore hyperuricemia is multi factorial origin in HIV patients (Walker et al, 2006).

More recently, tubular disorders have been related to ARV drug toxicity .Acyclic nucleotide reverse transcriptase inhibitor and more particularly tenofovir despoil fumarate(TDF)has been involved in tubulopathy leading to Fanconi or Fanconi-like syndrome with or without acute renal failure .An impairment of renal proximal tubular function is characterized by decreased tubular handling of phosphate leading to hypophosphatemia and their relation to tubular reabsorption disorder in tenofovir treated patients remain uncertain(Chattha et al. 1993, Sunda et al 1997, Izzidine et al 2004 and Walker et al 2006,) . Also, It has been suggested that HIV patients have an increased lactate dehydrogenase (LDH) levels, However, in most of these cases, such increase has been associated to the presence of pneumonia by Pneumocystis carinii. The Lactate Dehydrogenase level may also increase in other lung infections and in a variety of extrapulmonary disorders (Valencia el, al 1994, Quist and Hill, 1995). Conversely, lactate dehydrogenase being an enzyme found in blood cells destruction of the blood cells will cause its elevation. We assessed the association of some biochemical variables uric acid and Lactate Dehydrogenase (LDH) with indicators of acidosis forinstance phosphate and bicarbonate. Our goals were to evaluate possible acidosis in HIV patients and to ascertain whether HIV infection was associated with lower plasma value of phosphate and high value of bicarbonate.

MATERIALS AND METHODS

A survey of one hundred and twenty HIV patients was carried out to evaluate a possible acidosis in HIV patients using biochemical parameters such as Uric acid, Phosphate and Bicarbonate .The patients were drawn from Aba in Abia State. Fifty HIV positive and fifty HIV patients on antiretroviral drugs were tested respectively comprising of 30 females and 20 males.

Twenty HIV negative subjects made of 10 females and 10 males served as control. Subjects were of age 20 -35 yrs, HIV patients were on antiretroviral drugs (triviro-LNS-Lamivudine, Nevirapine and Starvudine) 1-2 pills daily depending on the CD4 count. Moreso, have been on the drug for the duration of 2- 3 years. All the investigations were done with serum. The phosphate and uric acid was assayed using fortress diagnostic kit based on calorimetric assay. Bicarbonate was determined based on titrimetric method. While, lactate dehydrogenase was determined using Henry, cannon and winkelman, 1974 method. The statistical analysis used was the one-way analysis of variance ANOVA.

RESULTS AND DISCUSSION

The results obtained from the study revealed that there was a significant increase in the serum levels of Phosphate and Uric Acid in HIV positive subjects not on antiretroviral drugs compared to HIV negative subjects (Table-1). Similarly, the Bicarbonate level was significantly reduced in HIV positive subjects not on antiretroviral drugs as to those of HIV negative subjects ($P<0.05$). The activity of lactate dehydrogenase was very pronounced in HIV positive patients on antiretroviral drug compared to the other groups ($P<0.05$).

Inaddition, a slight increase in the serum level of Phosphate was obtained for HIV positive subjects on drugs compared to HIV negative subjects ($P<0.05$). However, a relative increase in the serum level of Phosphate was obtained for HIV positive subjects on drugs compared to HIV negative subjects. ($P<0.05$).

Table- 1: Serum Levels of Uric Acid, Phosphate, Bicarbonate and Lactate Dehydrogenase of HIV Negative, HIV Positive not on Drugs and HIV Positive Subjects on Drugs.

Parameters	Phosphate (mg/dL).	Uric Acid (mg/dL)	Bicarbonate (mmol/L).	LDH (U/L)
HIVNegative Subjects (control)	3.70±1.54	4.61±2.36	23.00+6.19.	184.00±4.50
HIV Positive Subjects not On drugs	10.00.± 4.00**	7.60± 3. 60 **	7.16±3.50**	439± 10.5 *
HIV Positive On drug	4.78. ± 1.80*	5.16 ± 2.47 *	20.72±5.8.*	450.00± 15.00**

* Significant difference at $P < 0.05$.

The significant increase observed in serum levels of Phosphate and Uric Acid in HIV positive subjects compared to HIV negative subjects and the decrease in bicarbonate level in HIV positive subjects compared to those of HIV negative subjects may be as a result of metabolic abnormalities that arose due to the presence of HIV, particularly, the high uric acid level seen in HIV subjects not on drugs. This tends to conform to the study of (Chattha et al. 1993, Sunda et al 1997, Datta, et al 2001, Walker et al 2006.)Where, it was postulate that the higher uric acid level is due to the oxidative damage to cells causing an increase in cell turnover and muscle wasting (Wayner, 1987). This shows that HIV infection is associated with increase cell turnover as suggested by (Walker et al, 2006).Most antiviralretroviral drugs cause mitochondrial toxicity leading to increase lactate formation, which competes with urate for tubular secretion in the kidneys leading to hyperuricaemia. The decrease in phosphate levels observed in patients used in this study showed that hypophosphataemia is found in HIV infection independent of the use of antiretroviral drugs (Badiou et al, 2006). Conversely the high phosphate and low bicarbonate levels is compensatory mechanism to regulate the body's p^H. Also, it has been suggested that HIV patients have an increased lactate dehydrogenase (LDH) levels, however, in most of these cases, such increase has been associated to the presence of pneumonia by Pneumocystis carinii. The Lactate Dehydrogenase level may also increase in other lung infections and in a variety of extrapulmonary disorders (Valencia et al 1994, Quist and Hill, 1995). Consersely, lactate dehydrogenase being an enzyme found in blood cells, hepatocytes and other tissues. Destruction of the blood cells or any effect on the hepatocytes will cause its elevation.

This study is therefore supporting and encouraging HIV infected patients to start early with antiretroviral drugs to enable their immune system to build up defense and reduce the viral load and the associated metabolic abnormalities.

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REFERENCES

Badiou Stephanie, De Boever Corinne Merle, Terrier Nathalie, Barlat Vincent, Cristol Jean-Paul ,Reynes Jacques (2006). Is Tenofovir involved in hypophosphatemia and decrease of tubular phosphate reabsorption.Journal of Infection.52:335-338.

CDC. (2003). Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987; 36:1-15S. Food and Drug Administration. Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

Chattha G, Arieff AI, Cummings C, and Tierney LM Jr: (1993): Lactic acidosis complicating the acquired immunodeficiency syndrome. Ann Intern Med 118: 37–39, 1993.

Ciesielski CA, Fleming PL, Berkelman RL. (1991). Changing trends in AIDS-indicator diseases in the U.S. -- role of therapy and prophylaxis? (Abstract 254). 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 141.

Coovadia, H. (2004). "Antiretroviral agents—how best to protect infants from HIV and save their mothers from AIDS". N. Engl. J. Med. 351 (3): 289-292. PubMed.

Curtis, T. (1992). ″The origin of AIDS″. Rolling Stone (626): 54-59, 61, 106, 108

.6. Datta, D Mandalia, S Morlese, JM Moyle, G Asboe, D Gazzard BG. (2001) Biochemical abnormalities associated with hyper lactataemia in HIV-1positive patients .BHIVA Conf Apr 27-29;7:P13.

Dybul, M., Fauci, A. S., Bartlett, J. G., Kaplan, J. E., Pau, A. K. (2002). Panel on Clinical Practices for Treatment of HIV"Guidelines for using antiretroviral agents among HIV-infected adults and adolescents″. Ann. Intern. Med. *137 (5 Pt 2): 381-433.* PubMed.

Fultz PN. (2004). HIV-1 superinfections: omens for vaccine efficacy?" AIDS 2004 Volume 18 Number 1.

Heath, K. V., Singer, J., O'Shaughnessy, M. V., Montaner, J. S. and Hogg, R. S. (2002). "Intentional Nonadherence Due to Adverse Symptoms Associated With Antiretroviral Therapy". J. Acquir. Immune Defic. Syndr. 31 (2): 211-217. PubMed

Justice AC, Feinstein AR, Wells CK (1989) :. A new prognostic staging system for the acquired immunodeficiency syndrome. N Engl J Med; 320:1388-93.

Izzedine,H,Izzard,B.C.,Hulot,J,S.Vittecoq,D Chen,A,Jais,C.CK et al, (2004). Renal safety of tenofovil in HIV treatment experienced patients.AIDS; 18:1O7

Laeyendecker O, Li X, Arroyo M et al, (2006). The Effect of HIV Subtype on Rapid Disease Progression in Rakai, Uganda" 13th Conference on Retroviruses and Opportunistic. Infections (abstract no. 44LB).

Lambert,J.S.,Seidlin,M,Reichmann,R.C.,Plank,C.S., et al, (1990). 2′,3′-dexynosine in patients with AIDS or AIDS related complex.A phase 1 trial. N Engl. J.Med; 322:1333-40.

Lang W, Perkins H, Anderson RE, Royce R, Jewell N, Winkelstein W (1989). Patterns of T lymphocyte changes with human immunodeficiency virus infection: from seroconversion to the development of AIDS. J Acquir Immune Defic Syndr 2:63-9.

Maesaka.J.K, Cusano, A.S., ThesH.L. Siegal, F.P, (1990). Hypourricemia in acquired immune deficiency syndrome.A.M,J.Kidney,15:252-57.

Manfredi,R, Mastroiami .A, Coronado.O.V,Chiodo.F (1996). Hyperuricaemia and progression of HIV disease .J.Aquired immune. Defic. Syndr.Hum.Retroviral; 12:318-19.

Montessori, V., Press, N., Harris, M., Akagi, L., Montaner, J. S. (2004). "Adverse effects of antiretroviral therapy for HIV infection." CMAJ 170 (2): 229-238. PubMed.

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Perrin L, Kaiser L, Yerly S. (2003). "Travel and the spread of HIV-1 genetic variants". Lancet Infect Dis. PubMed *3* (1): 22-27.

Reeves, J. D. and Doms, R. W (2002). "Human Immunodeficiency Virus Type 2". J. Gen. Virol. 83 (Pt 6): 1253-1265.

Quist; A. Ross Hill, (1995). Serum Lactate Dehydrogenase (LDH) Pneumocystis carinii Pneumonia Tuberculosis, and Bacteri

Pneumonia Free CHEST.August ;108(2):415-.418.

Rynes,R.I, Gold, D.L, Glacomo, R.,Oslon,R ,Husain, M ,Vaezey,J(1988). Acquired immune Defic Syndro Associated arthritis, J. Med 84:810-16

Sundar K, Suarez M, Banogon PE, Shapiro JM (1997): Zidovudine-() induced fatal lactic acidosis and hepatic failure in patients with acquired immunodeficiency syndrome: Report of two patients and review of the literature. Crit Care Med 25: 1425–1430.

Tindall B, Cooper DA (1991): Primary HIV infection: host responses and intervention strategies. AIDS; 5:1-14.

UNAIDS (2010) 'UNAIDS report on the global AIDS epidemic'

UNGASS (2010) 'UNGASS Country Progress Report: Nigeria'

Valencia ME, Laguna F, Camacho J, Castejón A, Soriano V, Adrados M, González Lahoz J.(1994) .Serum activity of the lactate dehydrogenase enzyme in patients with human immunodeficiency virus infection.]. An Med Interna. 1994 Dec; 11(12):580-3

Walker UA et al (2006.). High serum urate in HIV-infected persons: the choice of the antiretroviral drug matters. AIDS 20: 1556 – 1558