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Research Article

Evaluation of Interleukin 6 and Interleukin 12 and C-reactive protein in hepatitis B and C subjects co-infected with HIV attending specialist Hospital Owerri

*Ihionu Chidozie.[1], Harrison Nwanjo [2] and Nwosu Dennis [3]

[1,2,3] Department of Medical Laboratory Science, Imo State Universiy Owerri

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Corresponding author:** ***Ihionu Chidozie.
Department of Medical Laboratory Science, Imo State Universiy Owerri

Abstract
This study examined the mean levels of C-reactive protein (CRP), interleukin-12 (IL-12), and interleukin-6 (IL-6) in hepatitis B virus (HBV) patients who were also infected with HIV in comparison to healthy controls. Standard immunoassay methods were used to test serum samples from age-matched healthy controls and HBV/HIV co-infected people. With t-values of 14.23 and 11.52, respectively (p = 0.000 for both), the results showed that the HBV/HIV group had considerably higher levels of IL-6 (18.06 ± 0.81 pg/ml) and IL-12 (9.93 ± 2.21 pg/ml) than the control group (IL-6: 5.01 ± 2.11 pg/ml; IL-12: 2.10 ± 0.65 pg/ml). Likewise, the co-infected participants' CRP levels were significantly higher (7.2 ± 0.48 mg/L) than the controls' (3.04 ± 0.26 mg/L), with a t-value of 4.325 (p = 0.000). These results underline the possible significance of these biomarkers in disease development and monitoring by pointing to a higher pro-inflammatory state in HBV/HIV co-infection.

Keywords: *Hepatitis B and C, HIV, IL-6, IL-12, CRP, Co-infection.*

INTRODUCTION
Viral hepatitis is a systemic disease that mostly affects the liver. It is caused by five distinct hepatitis viruses (A, B, C, D, and E) and is a prevalent public health concern in the African Region. Liver cancer and cirrhosis, a condition in which the liver becomes irreparably scarred after a protracted infection with hepatitis B and C, are the primary causes of death, despite the fact that all five hepatitis viruses can cause serious sickness. Most cases of acute viral hepatitis in children and adults are caused by the following viruses: hepatitis A virus (HAV), which is the etiologic agent of viral hepatitis type A (infectious hepatitis); hepatitis B virus (HBV), which is linked to viral hepatitis B (serum hepatitis); hepatitis C virus (HCV), which is the agent of hepatitis C (common cause of post transfusion hepatitis); hepatitis D (Delta Virus); and hepatitis E virus (HEV), which is responsible for enterically transmitted hepatitis [1]. Significant similarities between the hepatitis B virus (HBV) and the hepatitis C virus (HCV) include global distribution, hepatotropism, similar modes of transmission, and the ability to produce chronic infection that may lead to liver cirrhosis and hepatocellular carcinoma. Sexual activity, sharing needles for drug injections, and receiving blood transfusions are common ways for the hepatitis B and C viruses to spread. Co-infection with both HBV and HCV should be linked to higher rates of morbidity and mortality as well as an impact on the utilization of medical resources, since both viruses are known to cause the aforementioned illnesses. [2] Co-infections between HBV and HCV in individuals with HIV are very dangerous due to the underlying consequences, such as hepatological problems associated with both viruses, which have been shown to reduce the life expectancy of HIV-positive patients. The frequency of these co-infections in sub-Saharan Africa is now unknown [3]. Because of the advantages of early detection and treatment, it is essential to measure the levels of interleukin 6 and interleukin 12 as well as C-reactive protein in hepatitis B and C subjects who are also co-infected with HIV patients of HBV and HCV. [4, 5] Especially in regions where hepatitis B and C viruses are widespread, this is done to develop public health strategies and increase awareness of the significance of knowing one's hepatitis status. This study could be used by health managers and planners to target particular populations, examine risk factors that are associated to them, assign resources, set priorities, and offer the right diagnostic, therapeutic, and preventative services.

MATERIALS AND METHODS

Study Area

The study was carried out in Imo State University, Owerri, Imo state, Nigeria. Owerri is the capital of Imo State in Nigeria, set in the heart of Igboland. It is also the state's largest city.

Study Population/Sample Size

The study was conducted in Owerri Imo State of Nigeria; the climate of the study area has two main regimes; dry (November- February) and rainy or wet (March-October) seasons. Rainfall in the study area is between 1800 - 2700 mm and average temperature of 28±2oC. The study area has inhabitants who are predominantly farmers, traders, civil servants, cyclist riders and students.

Study Population and Sample Size

The study was a hospital based type conducted within the period of February, 2023 to July, 2024. The study population included 500 HIV patients on Highly Active Antiretroviral Therapy (HAART) who attended Specialist Hospital Umuguma Owerri during the period of the study.

3.4. Ethical Approval

The study was approved by the Ethical and Research Committees of the Hospitals used in the study. Informed consent was also obtained from all participating patients. For subjects under 18 years, parental consent was sought and obtained.

Collection of Blood Samples

Blood samples were collected aseptically by venopuncture, using a 5ml sterile disposable syringe and needle from all the subjects and was then dispensed into a labeled plain dry specimen container. The samples were centrifuged at 3,000pm for 5 minutes after clotting to separate and to obtain the serum. The sera were extracted using a Pasteur pipette and put into appropriate specimen container, and stored at -20^{o}C prior to use.

Laboratory Procedures

All reagents were commercially purchased and the manufacturer's standard operational procedure (SOP) was strictly followed.

Determination of C Reactive protein using ELISA Method. Serum concentrations of IL-6 and IL-12 were determined with the Human Cytokine/Chemokine Panel I Merck Millipore (Cat. No. MPXHCYTO-60K, Millipore Corporation, Billerica), according to the manufacturer's instructions on the Luminex fully automated analyzer.

Statistical Analysis

All data generated in this study was subjected to statistical analysis using SPSS version 23. Mean and standard deviation, student t-test and correlation were determined. The level of significant will be taken at $p<0.05$.

RESULTS

Table 4.1. The mean standard deviation of the levels of IL6 and IL12 and CRP in hepatitis B subjects co-infected with HIV and Control

Parameters	HBV/HIV	control	t- value	p value
IL6 (pg/ml)	18.06±0.81	5.01±2.11	14.23	0.000
IL12 (pg/ml)	9.93±2.21	2.10±0.65	11.52	0.000
CRP (mg/L)	7.2 ± 0.48	3.04 ± 0.26	4.325	0.020

Table 4.2. The mean standard deviation of the levels of IL6 and IL12 and CRP in hepatitis B subjects co-infected with HIVand HBV coinfected HIV on therapy

Parameters	HBV/HIV	HBV/HIV on T	t-value	p value
IL6 (pg/ml)	18.06±0.81	13.98±2.78	4.91	0.0271
IL12 (pg/ml)	9.93±2.21	7.20±2.31	2.52	0.0410
CRP (mg/L)	7.2 ± 0.48	5.37 ± 0.05	4.41	0.0233

Table 4.3. The mean standard deviation of the levels of IL6 and IL12 and CRP in hepatitis C subjects co-infected with HIV and control

Parameters	HBV/HIV	control	t-value	p value
IL6 (pg/ml)	17.00±0.72	5.76±2.11	12.74	0.020
IL12 (pg/ml)	8.54±2.00	2.00±0.76	10.33	0.007
CRP (mg/L)	9.1 ± 2.06	4.25 ± 1.11	11.25	0.030

Table 4.4. The mean standard deviation of the levels of IL6 and IL12 and CRP in hepatitis C subjects co-infected with HIV and HBV/HIV on therapy

Parameters	HBV/HIV	HBV/HIV on T	t-value	p value
IL6 (pg/ml)	17.00±0.72	15.00±2.22	4.03	0.020
IL12 (pg/ml)	8.54±2.00	6.90±2.01	2.64	0.047
CRP (mg/L)	9.1 ± 2.06	6.11 ±1.13	2.49	0.031

Discussion

The results of the study showed that the hepatitis B and C participants who were also co-infected with HIV and the control group had significantly different levels of IL6 and IL12 as well as CRP. These results provide valuable insights into the physiological processes behind variations in CRP levels among populations and environments. [6] Evidence for the long-standing association between inflammation and HIV coinfections is provided by the noticeable difference in CRP levels between hepatitis B and C participants who were also co-infected with HIV and the control group. The higher mean CRP level in the HIV-coinfected hepatitis B and C participants compared to the control group suggests that there is a substantial systemic inflammatory response in those who have HIV coinfection. This is consistent with other research [7]. High CRP levels are the outcome of tissue damage brought on by the immune system's response to pathogenic microorganisms. HIV coinfection occurs when viral infections initiate an inflammatory cascade that triggers immune cell activation and the release of many pro-inflammatory mediators, such as CRP [8]. These variations in CRP levels in HIV coinfections may be caused by modifications in virulence factors, pathogen-host interactions, and immune responses brought on by specific hepatitis species. However, compared to patients who were previously diagnosed, those receiving therapy had a significantly lower CRP [9].

In this investigation, HBV/HCV coinfected individuals with HIV had considerably lower levels of cytokines, particularly interleukin-6 (IL-6), an induced acute-phase reactant that is mostly produced in the liver, compared to the control group. The creation of CRP and its release into the bloodstream are triggered by IL-6, which is released when immune cells are activated during infections. The cytokine interleukin-6, sometimes referred to as IL-6, plays a complex role in both inflammation and the immune system [10]. It has both pro- and anti-inflammatory properties and impacts several cellular functions. IL-6 is involved in both the innate and adaptive immune responses and affects the activation and differentiation of B and T cells. It also regulates the production of acute-phase proteins such C-reactive protein (CRP) and fibrinogen [11].

IL-6 is a crucial modulator of the immune system that influences the development of both innate and adaptive immunity. IL-6 is a key player in the inflammatory response as both an anti-inflammatory myokine and a pro-inflammatory cytokine. It is a strong inducer of the hepatic acute phase response by encouraging the creation of acute-phase proteins such as fibrinogen and CRP.
IL-6 affects the production and development of blood cells.
The B and T cells' activation: It encourages the activation and differentiation of B and T cells.
IL-6 is one of the components that causes fever [12].
IL-6 is connected to certain mental health conditions even though it has neuroprotective effects on the brain. IL-6 in Health and Illness: Since high IL-6 levels are associated with a number of autoimmune diseases, inhibiting IL-6 is being researched as a possible therapeutic target.
Rapid production of IL-6 during infections and tissue injury aids in host defense.
IL-6 is implicated in the development and spread of certain cancers [13].
Elevated IL-6 levels are linked to cardiovascular disease and diabetes.
In addition to being linked to conditions including depression, schizophrenia, and bipolar disorder, elevated physiological IL-6 signaling can also have neuroprotective effects.
IL-6 Analysis:
An IL-6 test is a blood test used to quantify inflammation.
It may be recommended to monitor inflammatory responses, evaluate diabetes and heart disease, or guide treatment [14].
It can be ordered in addition to or after a CRP test, but it is not a standard test.

IL-6, a pleiotropic cytokine, has a number of functions in both health and disease. Its significance in inflammation, immunological response, and other physiological processes makes it a crucial molecule to study and possibly target in a range of circumstances.
IL-6 in Inflammation, Disease, and Immunity
IL-6 serves as a mediator to alert people when an urgent occurrence takes place. IL-6 is produced by an infected lesion, like hepatitis [14, 15].

In HBV and HCV coinfected individuals with HIV, interleukin 12 was markedly elevated in comparison to both the control group and those receiving treatment. This is consistent with the findings of (), which showed a considerable impact on IL 12 [16]. The immune system depends on interleukin 12 (IL-12), particularly when it comes to fighting infections and cancer. It is primarily produced by antigen-presenting cells such dendritic cells and macrophages. The presence of IL-12 activates and multiplies T cells and natural killer (NK) cells, which are critical for immunological responses. IL-12 stimulates NK cells and CD8+ T lymphocytes, which are vital for identifying and destroying sick or cancerous cells [17]. In response to IL-12, NK cells and T cells generate interferon-gamma (IFN-γ), which is essential for the development of Th1-type immune responses, which are required to fight intracellular infections and cancers. IL-12 inhibits angiogenesis, or the development of new blood vessels, which may slow the spread of cancer.

IL-12 can be utilized to boost vaccination effectiveness by enhancing immune responses [18].
Despite being studied as a potential cancer treatment, IL-12's therapeutic efficacy at appropriate concentrations has not been well established. IL-12 is essential for the body's defense against a number of diseases.
Consequently, the observed variations in CRP, IL 6 and IL 12 levels, the extent of tissue damage, and the pathogenicity of the viral infection involved may all be attributed [19].

Conclusion

This study's findings showed that CRP levels in hepatitis B and C subjects co-infected with HIV and control group, differed significantly. The systemic inflammatory response brought on by hepatitis and tissue damage is reflected in the higher CRP levels in HIV coinfection. CRP levels show that immunological responses fluctuate at various developmental stages. Additionally, changes in pathogen virulence and host immune responses are reflected in CRP levels across different categories of bacterial growth. These results help us understand the physiological processes behind the inflammatory response in HIV coinfections and offer important new information for clinical therapy and further research. HIV coinfected with hepatitis A and B infections are associated with significant increase in IL-6 and IL-12. These findings suggest that IL-6 and IL-12 could be used as a laboratory indicator to assess the severity of HIV coinfected with Hepatitis B and C, and its tendency to form scars, aiding in disease prognosis.

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