The Liver in HIV/AIDS Infection: The Import of Liver Function Tests

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ABSTRACT

Human immunodeficiency virus (HIV) is a recognized foe, a public and private health concern that has, with some help from less publicized foes, achieved international fame. As it spreads its deadly tentacles through its human prey, the mighty liver is not left out of its death toll among organs. A minute retrovirus stands accused here, convicted for waging war on the immune system of the unwary host. This silent killer has no ounce of decency, for various organs lay waste in its attempt to claim sovereignty. This paper reviews its effects on the liver and the role of liver function tests in assessing the damage to this valiant organ in an oft-repeated battle that ends the way Napoleon Bonaparte, the famous 19th century French general "... accepted peace like he had been defeated".

INTRODUCTION

HIV infection is a pandemic and statistics abound everywhere to discount any atom of doubt on this. Globally, it is estimated that every second, one person dies of AIDS and about six to nine people are infected with HIV somehow somewhere. The scourge of HIV has a terrible effect on life expectancy and has considerably reduced the quality of life of people, especially those in Sub-Saharan Africa. The prevalence is quite high for it is estimated that over 90% of the affected people are in sub-Saharan Africa, with pronounced effects in countries such as Zimbabwe, Botswana and Mozambique. HIV/AIDS has been a public health issue of import for a while now and so it is not surprising that great emphasis is placed on it and its associated problems.

HIV infection has a multi-systemic effect, either directly through its destructive effect on CD4 cells or its indirect action by giving privilege to opportunistic infections because of a defective specific and non-specific immune response. With no claim to decency, its ability to precipitate neoplastic growths from unregulated proliferation of immuno-active cell lines and its promotion of STI organisms such as the Human papilloma virus is reminiscent of the shine on the poisoned apple. Various systems are affected ranging from the central nervous, lymphomyeloid, cardiovascular, respiratory to the gastro-intestinal.

THE ANATOMY OF THE LIVER

The liver is the largest gland in the body in terms of weight. It is located in the right upper quadrant of the abdomen and proudly holds patents to both exocrine and endocrine function. The entire liver is lined by the Glisson capsule. Macroscopically it is divided into two lobes each of which are further subdivided into segments. To commemorate its importance, it is fed by two major vessels; the hepatic artery contributes about 20% and the portal vein makes up the remaining 80%.

Microscopically, it is a compound tubular gland organized into functional units called lobules surrounded with connective tissue. Within the lobule are the portal triads, the hepatic cell plate and the centrilobular vein. Nature loves variety and the lobules are filled with different shapes of cells such as the stellate cells which elaborate the connective tissue matrix and the oval cells that are bipotential and play a role in compensatory regeneration of the liver following hepatectomy.

The involvement of the liver in HIV infection can be classified into infective, neoplastic and infiltrative. Now, suppose a retroviral positive patient with low CD4 cell counts in full-blown AIDS presents in the ward with jaundice, haematemesis, right hypochondriac pain and abdominal swelling. Upon examination there is massive hepatomegaly with tenderness and ascites. Liver function tests (LFTs) fortify the evidence of compromise.

The old school method of taking a detailed history is perhaps the most critical element in the evaluation of this patient with evidence of liver damage, while a physical examination may provide valuable evidence in support of chronicity, which in this case is ascites. Occasionally the aetiology may be suggested by LFTs. Biochemical laboratory tests may help to identify the abnormal functions of the liver such as enzymatic, excretory and synthetic activities that are important in metabolic processes. Liver functions are assessed by measuring certain parameters that are indicators of the different activities of the liver. These parameters, referred to as liver function tests (LFTs), are important tools for assessing the medical/surgical needs of a

patient either by aiding diagnosis or assisting with the monitoring of a disease process or the effect of administered drugs. In HIV-1 infection, LFTs are essential for the assessment of the extent of liver damage by the virus itself or other microorganisms (e.g. bacteria, other viruses, fungi, protozoa) that may cause opportunistic infections (OIs) before treatment; and adjustment of doses of antiretroviral agents (ARVs) when there is associated hepatotoxicity or drug-drug interactions.

LIVER FUNCTION TESTS

Abnormal LFTs are common in HIV-1 infection and may be due to acute or chronic viral hepatitis, adverse drug reactions, sclerosing cholangitis, infiltrative liver disease (i.e. tuberculosis or Kaposi's sarcoma), bacillary angiomatosis, and steatohepatitis. Elevation in the transaminases and bilirubin indicate hepatocellular damage, but raised alkaline phosphatase with or without increase in bilirubin indicates cholestasis or infiltrative liver disease. Many medications used in HIV infection such as cotrimoxazole, pentamidine, isoniazid, rifampicin, pyrazinamide, paraaminosalicylic acid and ketoconazole cause abnormal LFTs. If the LFTs remain abnormal after discontinuing the offending agent, the pattern of hepatocellular injury should be evaluated to rule out viral hepatitis due to A, B, C, and D, *cytomegalovirus*, *Epstein-Barr virus* and *herpes simplex virus*. Evidence of cholestatic liver disease should be evaluated with ultrasound to exclude bile-duct obstruction, gallstones, focal mass lesions and fatty liver. Endoscopic retrograde cholangiography should be used to diagnose AIDS cholangiopathy. If serologic and radiologic examinations are inconclusive, a percutaneous liver biopsy may be performed.

OPPORTUNISTIC INFECTIONS [OIS]

There is no doubt that the use of antiretroviral therapy (ART) has reduced the prevalence of OIs. Prior to treatment however, infection by HIV-1 causes destruction of cell-mediated immunity (CD4+ lymphocytes) which ultimately results in acquired immunodeficiency syndrome (AIDS) that renders the infected person susceptible to opportunistic infections. Such infections include candidiasis, *Herpes* infections, *cytomegalovirus*, *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Pneumocystis Jirevocii* pneumonia (PJP; formerly known as *pneumocystis Carinii* pneumonia, PCP), toxoplasmosis, non-typhoid salmonella septicaemia, and extrapulmonary cryptococcosis, coccidiodomycosis, toxoplasmosis and histoplasmosis. In the advanced AIDS disease *Mycobacterium avium intracellulare* is the most frequent bacterial infection agent while *Mycobacterium tuberculosis* is often diagnosed in less immunocompromised patients. The diagnosis of these infections can be made by examining sputum, body fluids and lymph nodes when necessary.

Viral Hepatitis and HIV infection

Viral hepatitis [A, B, C, D] is more often diagnosed in HIV-infected patients than in non-infected individuals. The prevalence of hepatotrophic viruses has been reported to be on the increase (Sulkowski et al, 2000), therefore all HIV patients should be screened for hepatitis A, B, and C and D. Non-immune patients should be vaccinated against hepatitis A and B. The prevalence of hepatitis C among blood donors and HIV patients at OAUTHC, Ile-Ife is low as found after eight years of caring for HIV-infected patients. Elsewhere, co-infection with HCV is relatively common, particularly among haemophiliacs and intravenous drug users. HIV infection has been found to worsen the course of HCV infection but not vice-versa.

Liver Tumours and HIV infection

HIV infection is made more sinister by neoplastic diseases .Commonly associated ones include Kaposi's sarcoma, non-Hodgkin lymphoma, the nodular type of Hodgkin lymphoma, CNS tumours and cervical cancer. These can secondarily metastasize to the liver with marked damage to the liver function. Liver biopsy reveals involvement and confirms the clinical diagnosis.

Antiretroviral agents and drug-drug interaction

Antiretroviral agents (ARVs) available in the market are classified into four categories namely; nucleoside reverse transcriptase inhibitors (NRTIs); non- nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); and fusion inhibitors. Many of these medications are metabolized by the liver and an assessment of the liver function is essential before the choice of drugs in any given regimen is made. Hypersensitivity reactions that are unpredictable have been reported for abacavir (ABC) and nevirapine (NVP), therefore they are commenced at a lower dose than is recommended for maintenance therapy.

The CYP450-mediated cytochrome system is an important mechanism among factors responsible for drug-drug interactions. Both PIs and NNRTIs are extensively metabolized mainly by CYP450 isoenzymes (CYP3A4 and 3A5) and many clinically relevant interactions occur via this pathway. A drug may interact with CYP450 enzymes in one of three

ways: as a substrate (PIs); as an inhibitor (PIs) or as an inducer (non-nucleoside reverse transcriptase inhibitor; NNRTIs, rifampin). A physician should have understanding of the potential for inhibition and induction in a given drug regimen. For example, efavirenz (EFV) is an inducer, but ritonavir however is a potent inhibitor of the CPY3A4 pathway. The dose of EFV should be adjusted when given in combination with other drugs metabolized by the liver that induce this pathway i.e. rifampin, ketoconazole, clarithromycin, ethinyl estradiol (oral contraceptive pills), carbamazepine, phenobarbitone, methadone, warfarin and statins. When ritonavir is combined with PIs, it increases the bioavailability of PIs, thus boosting their activities, but EFV however will reduce the plasma levels of amprenivir (APV), atazanavir (ATV), fosamprenavir (FPV), indinavir (IDV), saquinavir (SQV) and Kaletra (lopinavir/ritonavir). Tenofovir (TDF) when co-administered with Kaletra may reduce lopinavir levels and increase TDF concentration thus increasing the risk of TDF-associated kidney toxicity. Zidovudine (ZDV) levels may be lowered by rifampicin and rifabutin, but lamivudine (3TC) and emtricitabine (FTC) are remarkably free of drug-drug interactions although they should never be used together.

Conclusion

Liver function tests are essential indicators in the assessment, monitoring and evaluation of individuals living with HIV infection before and during antiretroviral therapy. It is not uncommon to find abnormal liver function tests in an AIDS patient, however, when found necessary action should be taken to establish the diagnosis and give the appropriate treatment.