AFLATOXIN CONTRIBUTION TO LIVER CANCER BURDEN IN NIGERIA: A MINI REVIEW

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Abstract
The quality of stable food items consumed in Nigerian communities is bedevilled by high aflatoxin content. This mycotoxin is the nexus between hepatocellular carcinoma, poor food storage and agricultural practices. The proportion of histologically diagnosed hepatocellular carcinoma (HCC) cases in liver biopsies, range from 20.3% to 33% in different parts of Nigeria. Aflatoxin B_1 adducts in the liver cells promotes mutagenesis by inducing mutation at the third position of codon 249 of p53 gene. Synergistic action between hepatitis B virus infection and aflatoxin in the pathogenesis of HCC is established. There is data gap on the direct contribution of aflatoxin to the burden of hepatocellular carcinoma diagnosed in Nigeria.

Key words*: Liver, cancer, hepatocellular carcinoma, aflatoxin, mycotoxins.*

Introduction

Hepatocellular carcinoma (HCC), the common liver cell cancer, is the 6th most common cancer worldwide[1]. High figures of histologically confirmed HCC cases have been reported from different parts of Nigeria. And these include 20.3% of liver biopsies in Jos[2], 27% in Kano[3], 33% in Lagos[4] and 24.6% at Enugu[5]. Apart from aflatoxin and hepatitis B virus infection, other aetiological factors for HCC include hepatitis C virus infection, dietary iron overload, non–alcoholic steatohepatitis, chronic alcoholism and liver cirrhosis. Mycotoxin contamination of food products is an established nexus linking ineffective agricultural practices with carcinoma of the liver[6]. The literature is presently deficient on the relative contribution of aflatoxin B_1 (AFB_1) to histologically diagnosed cases of HCC in Nigeria.

Aflatoxin in food items

Aflatoxin is a mycotoxin produced mainly by the aspergillus species prevalent in hot humid climates and may contaminate a variety food items. Aspergillus flavus and parasiticus produce the most important isomers of aflatoxins, B_1 and B_2. Other toxins of less importance include citrinin, ergot alkaloids, deoxynivalenol, ochratoxin, fumonisins, trichothecenes, zearalenone, patulin, etc[6].

Makun et al studied the occurrence of fungal contaminants on food products obtained from several markets in Niger and Kogi states in Nigeria. *Aspergilus flavus* was found to be the major contaminant of maize while *Fusarium* species was more common in dried yam chips (commonly called amala). The amount of AFB_1 in the beans and wheat were much higher than the level accepted by national and international regulatory standards[7]. Akano and Atanda reported aflatoxin B_1 levels between 37 – 455 µg kg-1 in groundnut cake (also called kulikuli). Among all the samples studied, groundnut had the highest level of aflatoxin B_1.The reason why the incidence of aflatoxin is more frequent in groundnut than in other agricultural commodities is not fully understood[8,9]. In Nigeria, the following aflatoxin B_1 levels have been published for the following food items: sorghum, 30.2-211.2ug/kg[10], yam chips, 4-186ug/kg[11] and groundnut, up to 2000ug/kg[12]. In contrast, low sorghum toxin level (0-25ug/kg) occurred in South Africa, compared to figures from other African countries[13].

Pathogenesis

Epidemic outbreaks of toxicity resulting from acute exposure to AFB_1 have been reported[14]. Hepatic metabolism involves CYP3A4 and CYP1A2 enzymes catalyzed biotransformation to the exo-8,9, eposide [15]. This binds avidly to guanine in DNA forming AFB1-N7-Gua adduct. This adduct promotes mutagenesis by the formation of guanine

(a purine) to thymine (a pyrimidine) transversion mutation at the third position of codon 249 of p53 gene[16]. The aflatoxin B1 formamidopyrimidine adduct (AFB1-FAPY) has tremendous mutagenic capacity and has been demonstrated by Smela et al to be six times more like to induce transversion mutation[17].

Contribution of aflatoxin to HCC diagnosis

There is a vast volume of literature, articles and monographs written on mycotoxins[6]. In Nigeria and most of sub-Sahara Africa, there is an apparent gap in the literature of the proportion of histologically diagnosed cases of hepatocellular carcinoma directly attributable to aflatoxin. What appears to be a statistical illusion is perhaps, caused by the overlap created by the synergistic actions of both HBV and aflatoxin and the fact that the regions with the worst records of aflatoxin contamination of food items also parallel that of hepatitis B virus endemicity. The synergistic interaction between aflatoxin and hepatitis B virus in the aetio-pathogenesis of HCC has been established in the primary literature[18]. And a meta-analyses performed by Liu et al (2012) concluded that in areas of high aflatoxin exposure and chronic HBV infection, aflatoxin exposure and HBV has a nearly perfectly multiplicative relationship in increasing HCC risk[19]. The slow smothering effect of chronic exposure to the toxin in foods consumed daily in Nigeria may have a vast mutagenic impact on the population and thus, deserves greater attention from researchers. About 25% of the 600,000 new cases of HCC reported annually worldwide were estimated by Liu and Wu (2010) to be attributed to aflatoxin exposure[20]. Igetei et al, in a case-control study, evaluated 79 Nigerian HCC patients using cell free DNA in plasma for p53 gene codon 249 G – T mutation. In this study, none of the control individuals had this mutation while six (7.6%) of the HCC cases turned out positive[21]. A similar work was done in India by Murugavel et al directly demonstrated aflatoxin in the liver cells by employing immunohistochemical techniques. The group evaluated 31 liver biopsy cases of HCC for the presence of AFB1 using in-house immunoperoxidase test directly on the paraffin embedded tissue sections and found 18 (58.1%) to be positive. Thirteen of the biopsies were positive for HBV surface antigen and 6 (46.1%) were also positive for AFB_1[22].

In contrast to these high convincing figures establishing AFB_1 as an important risk factor for HCC, Atalla et al examined 46 HCC patients in Egypt for AFB_1 in their plasma using quantitative thin layer chromatography. Surprisingly, the results of this study showed that

HCC was highly correlated to viral hepatitis C (HCV), viral hepatitis B (HBV) and anti-bilharzial antibodies. However, all patients and their relatives, unexpectedly, showed negative AFB_1 in their blood[23]. There are pertinent questions yet still left unanswered. What is the relative contribution of aflatoxin, acting alone, to the occurrence of hepatocellular carcinoma in sub-Sahara Africa, a region where most staple food items are aflatoxin contaminated?

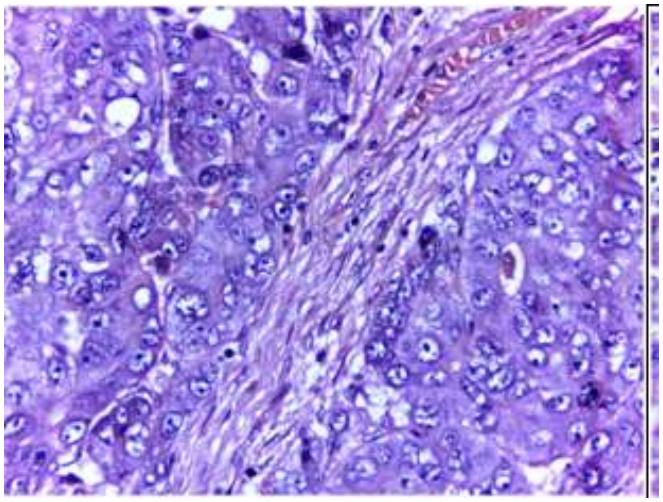

Figure : Hepatocellular carcinoma arising on a background of liver cirrhosis.

Aflatoxin control and HCC Prevention

Several modalities are being employed to reduce aflatoxin food contamination worldwide. Some countries effect control by insisting that imported grains meet pre-set standards. The aflatoxin food minimum level permitted by control standards in Japan is 10µg/kg, United States, 20µg/kg and European Union 2µg/kg[24]. Nigeria is yet to establish a minimum level of aflatoxin content of imported and locally produced food items. As part of control, the farming population especially in rural communities are made increasingly aware of the implications of poor storage practices. And occurrence in foods and feeds may be reduced by a variety of procedures, improved farm management practices, more rapid drying and controlled storage[24].

Data on the relative proportion of HCC caused by aflatoxin is pivotal to effective control of this malignancy in Nigeria. Some efforts have been made to quantify the contribution of this toxin in

some population studies elsewhere, conjuring a picture of how this situation might look like in the absence of contamination of foods. One of such study is the analysis by Chen et al of HCC in a Taiwanese population as described in Liu et al (2012). These researchers postulated that HCC in the study population could be reduced by about 10% (2.5–12%) if dietary aflatoxin exposures in this population were reduced such that aflatoxin-albumin adduct levels were below 0.01 fmol/µg which was the detection limit in this study. This indirectly implied that the toxin was responsible for up to ten percent of the cases of hepatocellular carcinoma[19,25].

Similarly, Qian et al demonstrated that HCC in a study population in Shangai males could be reduced by about 9% if aflatoxin levels were reduced to below 6ng/kg/day[26]. These figures are encouraging in the sense that with good agricultural practice, a significant proportion of HCC will be prevented from occurring. Relatively consistent observations have been noted even when the presence of viral hepatitis is factored into the picture. Liu et al conducted a meta-analysis of population attributable risk of aflatoxin related HCC and concluded that if it were possible to reduce aflatoxin to below detectable limits in the geographical regions studied, HCC incidence could be reduced by 14–19%[19].

The histological sub-types of this cancer reported in Nigeria include the pseudoglandular or acinar, trabecular, mixed, clear cell and fibrolamellar variants[2,27]. The literature appears to be silent on any association between aflatoxin B_1 adducts and a particular sub-type of hepatocellular carcinoma.

Conclusion

Aflatoxin, the nexus connecting poor agricultural practice and cancer of the liver, is a contaminant of most staple food items in Nigeria. Data on the population-attributable risk and relative contribution of aflatoxin to histologically diagnosed cases of hepatocellular carcinoma will go a long way in the planning of effective control strategies.

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