Epidemiology and Synergistic Hepatopathology of Malaria and Hepatitis C Virus Coinfection

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ABSTRACT: Malaria and hepatitis C virus (HCV) infections are very common causes of human suffering with overlapping global geographic distributions. With the growing incidence of HCV infections in malaria-endemic zones and malaria in areas with exceptionally high HCV prevalence, coinfections and syndemism of both pathogens are likely to occur. However, studies of malaria and HCV coinfections are very rare despite the fact that liver-stage plasmodiasis and hepatitis C develop in hepatocytes which may synergistically interact. The fact that both pathogens share similar entry molecules or receptors in early invasive steps of hepatocytes further makes hepatopathologic investigations of coinfected hosts greatly important. This review sought to emphasize the public health significance of malaria/HCV coinfections and elucidate the mechanisms of pathogens’ entrance and invasion of susceptible host to improve on existing or develop antiplasmodial drugs and hepatitis C therapeutics that can intervene at appropriate stages of pathogens’ life cycles.

KEYWORDS: Hepatitis C, liver disease, plasmodiosis, syndemism

Introduction

Globally, infectious diseases are major causes of human suffering. Among these pathogens, malaria and hepatitis C virus (HCV) infections have affected people in disproportional fashion. To date, several epidemiologic findings have revealed the synergy of malaria with other viral diseases; such as malaria and hepatitis B virus, malaria and human immunodeficiency virus, and malaria and human parvovirus B19 coinfections. However, there is a paucity of research focusing on the effects of malaria and HCV coinfections on affected hosts. It has been reported that approximately 180 million HCV-infected persons exist globally.⁵ Although the global HCV prevalence is <3%, there exist parts of the world where prevalence close to 15% have been reported.² For instance, epidemiologic data revealed that Egypt has prevalence of >14% (Figure 1).² Hepatitis C virus exists in different genotypes with varying global distribution. Hepatitis C virus genotypes 1a, 1b, 2a, and 3a are loosely called the epidemic subtypes because they are largely distributed and responsible for greater proportion of all HCV cases, particularly in the developed societies. These HCV genotypes were likely spread 3 to 4 decades ago by injection drug users and blood transfusion before the advent of pathogen sequencing technology.¹³⁴ However, the other genotypes called the endemic strains are relatively rare and have long been confined to specific regions such as Southern Asia, West and Central Africa, and Southeastern Asia.⁵⁷

Malaria transmission is a widespread issue that affects all the 5 World Health Organization regions. Approximately, 3.2 billion people are at risk of being infected with Plasmodium spp (Figure 2) and greater than 1:1000 chance of getting malaria per year.⁸ In 2015, the World Malaria Report revealed about 214 million cases of malaria and 438 000 malaria-related deaths, representing a downside in malaria cases and deaths by 37% and 60% within 15 years, respectively. The burden of malaria was mostly in the sub-Saharan African region, where about 90% malaria-associated deaths occurred. Two-thirds of these deaths were in children aged <5 years.⁸

Plasmodium spp and HCV, the causal agents of malaria and hepatitis C, respectively, share some similarities in their pathogenesis especially during their development within the liver cells.⁹¹⁰ Malaria and HCV coinfection is largely unstudied, but due to their epidemiologic similarities, it is possible that susceptible persons can contract both pathogens. In recent times, some studies have revealed that Plasmodium spp and HCV use 4 similar host receptors to gain entry into hepatocytes, namely, scavenger receptor B1 (SR-B1), heparan sulfate proteoglycans (HSPGs), apolipoprotein E, and CD81.⁹¹⁰ Considering the growing incidence of HCV infections in areas of high malaria transmission and vice versa, coinfections and syndemism are likely to occur. Thus, it is possible that simultaneous infections with both infections affect the replication and severity of either during their hepatic phases.

Spontaneous viral clearance occurs in 15% to 20% of all HCV-infected persons, whereas others progress to chronicity.¹¹ Chronic HCV infections are usually associated with the development of liver steatosis, cirrhosis, hepatocellular carcinoma, liver failure,
and ultimately, death.\textsuperscript{12} In the developed nations, as the incidence of HCV infections appears to decline, mortality secondarily associated with HCV infections will increase in the next 2 decades.\textsuperscript{13}

So, a good understanding of HCV infection is required to develop strategies to prevent new coinfections that may worsen the clinical presentation.

However, hepatic involvement in severe \textit{plasmodiasis} is often a major cause of diseases and death in humans. Jaundice usually denotes a certain degree of hepatic damage in malaria-infected persons. Malaria caused by \textit{Plasmodium falciparum} has been reported to be responsible for jaundice in 2.5\% to 5.3\% of infected persons in endemic countries.\textsuperscript{14} Although hepatic dysfunction is unusual in malaria, yet, more cases are being increasingly reported in patients with falciparum plasmodiasis. The extent of liver dysfunction ranges from mild abnormal liver function tests (LFTs) results in liver failure.\textsuperscript{15} Patients with malaria with various grades of liver dysfunctions are at higher risks of developing complications in HCV coinfections.

This review sought to emphasize the public health significance of malaria/HCV coinfections and elucidate the mechanisms of pathogens’ entrance and invasion of susceptible host to improve on existing or develop antiplasmodial drugs and hepatitis C therapeutics that can intervene at appropriate stages of pathogens’ life cycles.

**Modes of Transmission of Malaria and HCV Infections**

Malaria has been known to be transmitted through the bite of female \textit{Anopheles} mosquito, which occurs mainly between dusk and dawn.\textsuperscript{16} Other relatively rare routes for transmission include blood transfusion, congenitally acquired disease, organ transplantation, and sharing of contaminated needles.\textsuperscript{16} Whereas, HCV is a blood-borne virus that is mostly transmitted between injection drug users through sharing of HCV-infected equipment, transfusion of HCV-infected blood products, and the reuse of inadequate sterilized medical equipment in health care settings. Sexual and congenital transmissions are other means of contracting HCV infections; however, these are less common.\textsuperscript{17}

In 2015, global estimates obtained from mathematical modeling suggest that 1.75 million new HCV infections (ie, 23.7 new cases per 100 000 people).\textsuperscript{17}

**Hepatopathology of Malaria and HCV Infections**

Liver involvement of malaria parasitemia is mainly seen in severe falciparum plasmodiasis. The clinical features of jaundice usually denote certain degree of hepatic damage.\textsuperscript{15} The liver stage is a crucial part of \textit{Plasmodium}’s life cycle. Less often, \textit{Plasmodium} spp migrate to the liver where it begins the exoerythrocytic phase.\textsuperscript{18}

Sporozoites enter hepatocytes via SR-B1, CD-81, and HSPGs; these are similar receptors used by HCV during its
pathogenesis. Once in the liver cells, the sporozoite replicates which leads to the bursting of hepatocytes, releasing infective merozoites. The merozoites continue the erythrocytic cycle of *Plasmodium* infection.

Because HCV is a blood-borne virus, it reaches the liver through the circulation system. The entry of HCV into hepatic cells requires the host cell–derived factors. Consequently, CD-81 on host cell surfaces acts as the viral receptor. This binds with the virus and facilitates its entry into hepatocytes.

E2 is an HCV envelope protein that binds to the major extracellular loop of CD8. However, HCV shows multiple binding sites and could also bind with other cellular molecules such as the receptor for low-density lipoprotein and the dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN). E2 has been revealed to be the most variable viral protein and exhibits strain-specific interactions with CD81. E2 has 2 hypervariable regions known as HVR-1 and HVR-2 which undergo frequent mutations, possibly due to HCV-specific cytolytic T lymphocytes and virus-neutralizing antibodies. Hepatitis C virus replicates and simultaneously causes cell necrosis by several mechanisms which include immune-mediated cytolysis and insulin resistance, oxidative and stress hepatic steatosis. The lack of proof-reading ability of HCV RNA-dependent RNA polymerase makes it to exhibit high mutation rate. Consequently, HCV exists in several distinct but related virus species within an infected person.

Because the life cycles of both *Plasmodium* and HCV require the liver as an important stage for parasitic and viral development, it is important to note that coinfections with both will affect the replication and promote the disease severity of either.

**Prevention of Malaria and HCV-Associated Hepatopathy**

Prompt and accurate treatment is the mainstay of prevention or minimizing severe consequences of coinfections. Till today, no single antimalarial drug can eradicate all forms of the parasite's life cycle. Therefore, 1 or more of the 4 classes of drugs are often given at the same time to synergistically combat malaria. In addition, treatment regimens are dependent on the geographic location of malaria, the *Plasmodium* spp, and the severity of disease. Malaria-related hepatitis often resolves after the clearing of the parasite from the body, and serum bilirubin levels usually recede 3 days after starting treatment. However, this may delay in persons having coinfections or comorbidity.

Hepatitis C virus infections have long been treated and patients become less susceptible to cirrhosis or hepatocellular carcinoma and in some instances successfully cleared HCV from their body systems. However, some patients show poor response to antiviral pegylated interferon alfa and ribavirin-based therapy. It was reported that 40% to 50% of HCV genotype 1–infected persons and 80% infected by HCV genotypes 2 and 3 achieve sustained virologic response (SVR) with pegylated interferon and ribavirin regimen. In recent times, the use of direct-acting antiviral molecules resulted in more significant improvement of SVR rates in persons infected with HCV genotype 1.

Other comorbidities such as alpha-antitrypsin deficiency and iron overload may promote the progression of chronically HCV-infected persons to liver cirrhosis. Hence, the only effective prevention of chronic liver diseases for such people is treating the underlying conditions.

### Risk Factors of and Indications for HCV Testing In Persons with Malaria Parasitemia

Malaria is a parasitic infection with global distribution and especially endemic in developing and tropical countries. Hence, people living in or traveling to malaria-endemic parts of the world are at risk for contracting malaria. If infected with malaria, laboratory testing for HCV could be needful for persons with risk factors and/or clinical symptoms associated with HCV infection. History taking of persons by considering risk factors of contracting HCV will help to determine whether HCV screening is needful. However, whenever obvious clinical features of HCV infections are present, even in the absence of a declared risk factor, HCV test(s) is important. Acute hepatitis, cirrhosis, and abnormal LFT results increase the clinical suspicion of HCV infection.

There are many clinical conditions where HCV test may also be needful. These include health care workers who perform exposure prone procedures, persons in an occupational exposure, contact tracing of blood exposure of potentially infected person, or in situations where diagnosis of another infection with similar mode of transmission such as human immunodeficiency virus is made. It has been reported that >80% of existing and about 90% of all new HCV infections exist in people who have history of injection drug use (IDU). Hence, persons with history of IDU and blood transfusions should be considered for HCV testing.

### Diagnosis of Liver Diseases in Malaria and HCV Infections

Routinely, single-slide microscopy may not be sufficient to pick up the diagnosis of liver dysfunction due to malaria. Because the list of differential tests for liver diseases is long, LFTs and ultrasonography are crucial, but liver biopsy is not needful. However, long-term idiopathic jaundice may warrant the need for liver biopsy.

In the case of malaria/HCV coinfection, molecular diagnostic tests play key roles in prompt and accurate diagnosis of HCV infections. Nucleic acid amplification tests (NATs) is the gold standard for the detection of acute HCV viremia. Hence, NAT is largely useful in the diagnosis of acute infections. This is so because HCV RNA is detectable as early as days after being infected. However, in resource-limited settings, the diagnosis of HCV infection is done with antibody screening such as enzyme-linked immunosorbent assays followed by HCV NAT for confirmation.
Looking to the Future: Malaria and HCV Vaccines Development

Despite several decades of rigorous research, no single commercially licensed malaria and HCV vaccines are licensed for public use.

With respect to HCV vaccine, several setbacks halted the availability of effective preventive or therapeutic vaccines. These include considerable genetic heterogeneity of HCV isolates within and between geographic areas, evolution of quasispecies in an infected individual, poorly defined immunologic correlates of protection, lack of suitable cell or organ culture system, and animal models for efficient in vitro propagation of HCV. However, malaria vaccines are difficult to develop because of the existence of several species and poorly defined immunologic correlates of protection.

Despite these obstacles, vaccines for both malaria and HCV are underway and toward last phases of clinical trials. Conclusion

Malaria and HCV coinfection is of significant global health concern. In the pathogenesis of Plasmodium and HCV, liver is an important organ for parasitic and viral development. Hence, it is important to note that malaria and HCV coinfections will affect their replications and promote the disease severity of either. In view of these, there is need to test/diagnose patients with either type of infection especially when there are strong indications and risk factors of coinfections. This could help in improving on the existing antiplasmodiasis and hepatitis C therapeutics to minimize or halt the replication of these pathogens.

Author Contributions
IAN conceptualised the study design, literature search and conducted the review processes as well as developed the initial draft manuscript. SY and JOM gave input into the design, literature search and critically revised the manuscript before publication. All authors read and approved the final manuscript.

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