Co-infection HBV and malaria: a striking association

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SUMMARY

Many geographical areas are highly endemic for infectious tropical diseases, although in disproportional fashion. Various infections often overlap in terms of presentation of various epidemiological and clinical manifestations that are linked to the mutual influence of pathogens. The epidemiological and clinical aspects of hepatitis B virus and malaria co-infection remain little known because there have not been many studies until recently. We performed a systematic search of the epidemiology of HBV/malaria co-infection, in particular, their overlapping clinical and histological features and their reciprocal conditioning. We examined published data regarding HBV and malaria. The data we obtained varied substantially. The interaction between malarial parasites and HBV viruses, both in chronic HBV hepatitis patients and in carriers, did not vary or change the clinical evolution of either infection. The diversity of epidemiological and clinical results depended both on the geographical areas in which the studies were carried out and on the various stages of the infections at the time of the study. Strategies to improve currently available diagnostic techniques, and studies dealing with vector control procedures and other operational tools and approaches are needed for better understanding of this health problem.

Keywords: malaria, hepatitis B, co-infection, epidemiology

■ INTRODUCTION

In terms of infectious and tropical diseases, many geographical areas [sub-Saharan Africa (SSA), Asia, Central and South America] are highly endemic, although with different epidemiological patterns for infections such as malaria parasites, hepatitis B virus, hepatitis C virus and human immunodeficiency virus. These pathologies sometimes present with the same route of transmission (blood-to-blood contact, shared needles and blood transfusions), such that it is not uncommon to have co-infections of several viruses, plasmodia and viruses [1].

Several epidemiologic findings have reported synergy of malaria co-infections with viruses, including with hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and human parvovirus B19. Nevertheless, there is a paucity of research, especially in industrialized countries, regarding the effects of malaria and viral co-infections on the affected host [2-4].

Epidemiological studies of HBV/malaria co-infection have been rare. The mutual interactions between HBV and malaria are poorly understood. In recent decades, thanks to studies carried out first in Brazil and subsequently in Sub Saharan Africa and Asia, there has been a greater awareness of the rates of this co-infection. Overlapping HBV/malaria may be more frequent than previously believed, with possible influence on the natural history of both diseases. The two pathogens share some development stages within the liver, a condition that could cause impaired clearance of

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the liver stages of the malaria parasite because of hepatocyte damage in HBV infection or exacerbation of HBV hepatitis [2-4].

The purpose of this review was to examine the epidemiology of HBV/malaria co-infection, the clinical and histological features of the overlap of these two pathogens, their clinical interaction and their reciprocal conditioning.

■ EPIDEMIOLOGY

Epidemiology of malaria infection
According to the WHO-World Malaria Report 2016, there were 212 million new cases of malaria worldwide in 2015. In the same year, an estimated 3.2 billion people were at risk of malaria, of whom 1.2 billion are at high risk. In high-risk areas, more than one malaria case occurred per 1000 population. The WHO African region accounted for most global cases (90%), followed by the South-East Asia (7%) and Eastern Mediterranean Regions (2%). Between 2010 and 2015, malaria incidence rates (new malaria cases) fell by 21% globally and in the WHO African Region. In 2015, there were an estimated 429,000 malaria deaths worldwide. Most of these deaths occurred in Africa (92%), followed by South-East Asia (6%) and the Eastern Mediterranean (2%). During this same period, malaria mortality rates fell by an estimated 29% globally and by 31% in the WHO African Region. Other regions achieved impressive reductions in their malaria burdens.

The risk of malaria infection is much lower in Europe, North America, Australia, where environmental remediation and disinfestation were performed long ago. In 2015, the European Region was indigenously malaria-free: all 53 countries in the region reported at least 1 year of zero locally-acquired cases of malaria. Infections currently present were almost exclusively imported from highly endemic countries without adequate prophylaxis. In recent decades, a great migratory flow has been occurring from countries highly endemic for infectious diseases to industrialized countries (mainly USA and Western-Europe), changing the epidemiological pattern and causing increases in infectious diseases (HIV, TB, viral hepatitis, and malaria). Approximately 7,000 cases of imported malaria are recorded in Europe annually [5].

Epidemiology of HBV infection
According to the WHO report 2015, an estimated 257 million people are living with hepatitis B virus infection (defined as hepatitis B surface antigen-positive) worldwide. In the same year, hepatitis B resulted in 887,000 deaths, mostly from complications (including cirrhosis and hepatocellular carcinoma). Hepatitis B prevalence was highest in the WHO Western Pacific and WHO African Regions, where 6.2% and 6.1%, of the adult population is infected, respectively. In the WHO Eastern Mediterranean, South-East Asia and European Regions, an estimated 3.3%, 2.0% and 1.6% of the general population is infected, respectively; whereas, only 0.7% of the population of the WHO Region of the Americas is infected. In 2015, 30 EU/EEA member states reported 24,573 cases of HBV infection, a crude rate of 4.7 cases per 100.000 population. Of these, 10.2% were acute, 63.5% were chronic, 19.4% were unknown, and 6.9% could not be classified. There continues to be a downward trend in the rate of acute cases, in accordance with global trends, reflecting the impact of national vaccination programs. By contrast, the rate of newly-diagnosed chronic cases continues to rise over time, and this increase is most likely related to changes in local testing and reporting practices [6]. In recent decades, migrants to many countries in Europe have come from countries with high rates of hepatitis B, and prevalence among some of these migrant groups is often high. Data from four north European countries with fairly complete reporting (Finland, Norway, the Netherlands and Sweden) indicate that a high proportion of newly-diagnosed infections were suspected to have been acquired in another country. A recent study on the epidemiological burden of hepatitis among migrant populations estimated the rate of infection among migrants, in relation to the overall number of chronically infected hepatitis B cases in Europe, to be around 25%. In 2015, of 7,924 (32.2%) patients with information on importation status, 4,814 (60.8%) were reported by 24 countries as imported; the majority (87.7%) were chronic. Data on importation status of cases remain incomplete; however, the impact of migration on reported cases of hepatitis B in Europe is striking, especially among chronic infections [7].

Epidemiology of co-infection HBV/malaria

Until recently, data were few and insufficient; however, this has changed and there is now considerable information regarding the epidemiological patterns of HBV-coinfected malaria. Initial studies came largely from Brazil, especially the Amazon region, a geographic area where HBV infection and malaria are highly endemic. Subsequently, other studies were conducted in SSA, Asia and among immigrant populations from developing countries to industrialized countries.

Souto et al. (2000) studied a population of 520 Brazilian miners, including data collected during a malaria survey in a large area including 16 gold mines. Previous malaria episodes were admitted by 517 (99.4%) of the miners, and *Plasmodium* spp. were detected in 106 (*P. falciparum*, 56; *P. vivax*, 47; and *P. malaria*, 3). Among the 517 participants, most with acute or occult malaria came from other Brazilian regions via internal immigration. Among those that had been exposed to HBV, 37 (7.1%) were HBsAg carriers and 431 (83.3%) had anti-HBc alone [8].

Braga et al. (2005) studied 605 individuals and found that the prevalence of antibodies against plasmodium antigens was 51.4% (311/605). The rate of HBsAg-positivity was 3.3% and total anti-HBc was 49.9%. The simultaneous presence of malaria antibodies and HBsAg was 1.8% (11/605), while the simultaneous presence with anti-HBc alone was 32.9% [4]. Subsequently, Braga (2006) studied another 545 patients with acute malaria, in which 333 (61.1%) presented with *P. vivax*, 193 (35.4%) with *P. falciparum* and 19 (3.5%) had mixed infections. The prevalence of co-infection of malaria and HBsAg positivity was 4.2% while the malaria/anti-HBc alone was 49.7% [9].

Andrade et al. studied 636 individuals who remained in the same geographical area. A total of 431 (67.8%) had malaria; 210 had febrile infections and 221 had asymptomatic malaria. Among those with acute malaria, co-infection with HBV active hepatitis was present in four (1.9%), while malaria co-infection and previous HBV infection (anti-HBs/anti-HBc or anti-HBc alone) was found in 51 (24.3%). Among individuals with asymptomatic malaria, co-infection with active HBV hepatitis was present in 28 (12.7%), while previous HBV was detected in 77 (34.8%) [10].

Two studies from SSA both involved potential blood donors. Aernan et al. (2011) in Nigeria screened for HBV/malaria co-infection in 337 individuals. Malaria screening involved standard laboratory methods (thin and thick films); one-step HB surface antigen test strips were used for HBV diagnosis; it was not possible to differentiate those with hepatitis HBV from inactive carriers. An overall co-infection rate of 40.7% (137/337 subjects) was observed among the donors [11].

Freimanis et al. (2012) screened pre-transfusion samples in a Ghanaian cohort of 117 blood transfusion recipients to study associations between HBV and *Plasmodium*. Parasite density was stratified according to HBV status in all samples. A total of 42% had evidence of active HBV infection, seven of which were occult HBV infections with detectable HBV DNA (OBI) and 48% had anti-HBc alone without detectable HBV DNA. *Plasmodium* genome prevalence was 50%. Among the patients with active HBV infection, 25/42 (59.5%), and 4/7 (57.1%) with OBI-infected individuals exhibited parasitemia; therefore, co-infection of HBV/malaria was observed in 59.2% of those with an active HBV infection. Fifty-six had anti-HBc alone and 24 (42.8%) had co-infection with malaria [12].

Omalu et al. (2012) reported a co-infection rate of 7.8% in pregnant Nigerian women [13]. Dabo et al. and Sharif et al. reported HBV/malaria co-infection rates of 4.5% [14, 15]. In various studies on Nigerian populations, Kolawole et al. (2018), observed that 11/200 (5.5%) subjects screened had co-infection with HBV/malaria. It was not always possible to differentiate forms of active hepatitis from simple carriers [16].

In Asia, there have been only two complete studies regarding overlapping HBV/malaria. These studies produced conflicting results, probably because of the different types of screening. Barcus et al. (2002) retrospectively investigated HBV infection among 324 adult Vietnamese patients hospitalized for severe *P. falciparum* malaria. Sera from patients were assayed for hepatitis B surface antigen (HBsAg). The overall prevalence of HBsAg was 23.7% (77/324); this rate was higher than reported estimates (9.8%) of prevalence in the general catchment population of the hospital in the study [3].

Completely different results were obtained by Shrestha et al. (2009), who conducted a multi-trial study to determine the prevalence of HBV and malaria in Nepalese blood donors. Screening of malaria and hepatitis B surface antigen (HBsAg)

was done in 1200 blood samples. Among the samples, 1% (12/1200) were HBsAg positive; while only 0.33 % (4/1200) samples were positive for malarial parasite. Co-infection HBV/malaria was not observed during the entire study, covering the major blood banks in the country [17].

In industrialized countries, even in those with high HBV infection prevalence, there are no cases of HBV/malaria co-infection. This is unusual, considering the significant increase in immigration from regions where both diseases are endemic. This scarcity of data may be linked to absence of evidence of epidemiological patterns in immigrants with HBV/malaria co-infection. McCarthy et al. and Barnett et al. (2013) examined pathologies presented by 8,000 immigrants and found a significant number of cases of HBV or malaria mono-infections, but neither mentioned possible overlap between the two pathogens [18, 19]. Our research group, Malcangi et al. (2009), using nucleic acid sequence-based amplification (NASBA), assessed the prevalence of possible asymptomatic infections with *Plasmodium* species in a cohort of 195 immigrants with no clinical signs of malaria. Sixty-two study subjects (31.8%) were positive for *Plasmodium* species and 24/62 (38%) had *P. falciparum* gametocytes. Subsequently, in subjects with malarial infection, we evaluated the prevalence of HBV infection; HBV/asymptomatic malaria co-infection was found in 46/62 (74.2%) patients; 15/46 (32.6%) individuals had concurrent HBV hepatitis. There was simultaneous asymptomatic malaria and anti-HBc alone in 31/46 (67.4%) patients [20].

Considerations
In terms of the prevalence of co-infected subjects from various geographical areas, we observed that the data were significantly different, mostly related to the hosts, had varied epidemiological patterns of two pathogens and different clinical features. Common features of the studies included predominance of male (~75%) and young patients (average ~26 years). Both gender and personal data probably represent the typology and geographical origin of the subjects. HBsAg-positivity (active hepatitis) occurred primarily in young adults, while subjects with anti-HBc alone/malaria co-infection were over 50 years old.

A large proportion of co-infected individuals, both for chronic B hepatitis and for anti-HBc (45-50%) were observed in two studies conducted in SSA. However, in these countries, a significant decrease in the prevalence/incidence of co-infection was also observed within a few years (2011-2015), probably due to better prophylaxis against the two pathologies, as reported by the WHO.

The rates of co-infection, both in the general population and in the at-risk subjects in various Brazilian studies were extremely variable. Co-infection has been highlighted in both forms of HBV infection (active infection or carriers) and malaria (febrile or asymptomatic illness); while the prevalence of co-infection among anti-HBc subjects was quite high, the rate among subjects with active hepatitis was very modest.

A completely different aspect, probably linked to local factors, was described in Asia where, in two geographically distant regions, the prevalence of co-infection was quite different (Vietnam 23.8%, Nepal 0%). It is unclear if this was because of different epidemiological patterns or different screening methods.

In industrialized countries, even those with high levels of immigration from at-risk areas, the problem appears to be completely unknown. Indeed, there are no completed or ongoing studies regarding cases of HBV/malaria co-infection, even though numerous studies regarding diseases linked to immigration have been carried out.

Among malarial patients, although numerically very small, our results are between those observed in the studies mentioned above, albeit closer to the ones conducted in Africa. However, most of the patients we examined were immigrants from SSA.

■ HISTOLOGICAL PICTURES

Histological liver features of malaria infection
The predominant histopathological changes in malarial liver reveal the activation of cells of the mononuclear phagocyte system, Kupffer's cells in particular, with the presence of brown-black "malarial pigment" granules and iron deposits, also known as "hemozoin" and congestion along with minor effects on hepatocytes. Substantial hepatic damage is present in patients with proven *P. falciparum* malaria with jaundice. The most consistent histological findings are reticulo-endothelial cell hyperplasia, pigmentation in Kup-

ffer's cells, presence of swollen hepatocytes, sinusoid; portal infiltration by mononuclear cells, fatty change and cholestasis are other prominent features. During electron microscopy, hepatocyte swelling, Kupffer's cell hypertrophy, sinusoidal macrophage hypertrophy along with changes in endoplasmic reticulum/mitochondria, loss of microvilli and damage to canalicular membranes have been seen. These changes may be non-specific but the presence of centrizonal necrosis and hyperplastic Kupffer cells loaded with malarial pigment is a strong indicator of hepatic damage. The characteristics of malarial hepatitis are usually described in patients with *P. falciparum* infection, and only in some cases of infection with *P. vivax* [21-22].

Histological liver features of HBV infection
Acute hepatitis B is characterized by lobular disarray, ballooning degeneration, numerous apoptotic bodies, Kupffer cell activation and lymphocyte-predominant lobular and portal inflammation. In chronic hepatitis B, there is a varying degree of predominantly lymphocytic portal inflammation with interfacing hepatitis and spotty lobular inflammation. Inflammation is minimal in the immune-tolerant and inactive carrier phases but is prominent in the immune-reactive phase. Bridging necrosis is identified as inflammation connecting portal tracts to one another or to central veins. Confluent necrosis, as the name implies, affects several contiguous hepatocytes. Inflammation is typically associated with scarring, varying from mild portal expansion to periportal fibrous strands, bridging fibrosis and cirrhosis [23].

Considerations
The two pathologies exhibit some different and peculiar histologic hepatic features linked to the action of the virus or protozoa. The interaction of the two pathogens has been the subject of studies by some researchers and, as both infections share an intra-hepatic stage in their life cycles, have been hypothesized to occur at both immunological and cellular levels. Intriguingly, both pathogens might also utilize common receptors during hepatocyte invasion: heparin-sulphate proteoglycans (HSPGs). Individually, malaria infection causes changes in haematological parameters while HBV infection causes changes in liver function indices.

■ INTERACTION BETWEEN HBV AND MALARIA

In the last few years, there have been both experimental and clinical studies regarding how the interaction of the two pathogens can or cannot determine mutual influence on the pathogenesis of clinical evolution of the two infections. This could happen, as stated above, especially at the hepatic level, and their interaction has been hypothesized to occur at both immunological and cellular levels. Indeed, HBV induces a robust pro-inflammatory type 1 immune response (Th1) that is important for *Plasmodium* clearance but is also implicated in HBV disease severity. Moreover, in some cases, it has been shown that the mutual influence could also manifest in extra-hepatic locations.

Impact of malaria on HBV
In an interesting study, Pasquetto et al. (2000) described immunological features of HBV/malaria co-infection. They showed that the hepatic stage infection appeared to trigger an early T cell-independent cytokine response along with a delayed cytokine response that was simultaneous with infiltration of T cells. Intrahepatic HBV replication and gene expression were inhibited in mice infected by *P. yoelii*. In fact, the infection with this parasite determined an intrahepatic inflammatory response characterized by influx of natural killer cells, macrophages, and T cells, and the induction of IFNγ, IFNα/β, TNFα, and iNOS in the liver. These cytokines probably inhibit HBV replication, because it appears that IFNγ and IFNα/β are essential for suppression of HBV gene expression and replication in the liver. The antiviral effect of malaria is likely to be triggered principally by phagocytosis of infected erythrocytes by Kupffer cells, leading to their activation and production of chemokines that recruit NK cells, NKT cells and malaria-specific T cells, all of which produce inflammatory cytokines that eliminate HBV from the hepatocytes [24]. Some human studies confirm this hypothesis; a study from Brabin et al. (1989) investigated the interactions in the co-infection and found that patients with higher states of malaria infection had low prevalence of hepatitis B infection [25]. Barcus (2002) showed that Vietnamese patients admitted with cerebral malaria had a slightly greater risk of registering positive for HBsAg relative to other manifestations of severe malaria [3].

By contrast, other groups concluded that HBV and malaria did not significantly affect one another, and that HBV infection evolved independently. Indeed Braga (2006) and Sharif (2015) observed that patients with HBV/malaria presented no clinical differences with respect to only HBV infection, neither did co-infection have a profound effect on the level of serum protein and liver enzyme activities in the serum [9,15]. HBV DNA load was not significantly different in parasitemic and non-parasitemic individuals. Dabo (2015) observed that HBV/malaria interaction had no profound effect on the haematological parameters [14]. Our study (Scotto et al., 2018), comparing co-infected vs. HBV mono-infected subjects, showed that coexistence with Plasmodium did not significantly affect the clinical course of HBV infection [26]. In fact, the numerical data of the two groups of subjects showed that 24.2% of co-infected vs. 19.8% of mono-infected subjects presented a similar clinical picture of chronic hepatitis.

Whereas these studies appeared to indicate a positive or indifferent influence of plasmodium on HBV infection, others highlighted how malarial infection could cause negative progression of HBV infection.

In Thailand, Brown et al. (1992) verified that chronic asymptomatic malaria falciparum may be accompanied by sustained periods of HBV reactivation [2]. Thursz (1995) studied Gambian co-infected children with severe malaria and highlighted observations of significantly increased HBV viral load in those who were parasitemic compared to HBV-only infections, suggesting that increased viremia in individuals with severe malaria was likely due to decreased HLA expression [27].

Andrade (2011) showed that co-infected Brazilian individuals presented higher levels of HBV viremia [10].

Freimanis (2012) in Ghana showed that median HBV viral load was higher in parasitemic than in non-parasitemic individuals, although the difference was not significant [12].

Finally, data from a small investigation highlighted that acute falciparum malaria modulated HBV viremia in patients with chronic HBV infection causing an exacerbation of hepatitis B [4,28].

The authors who presented the latter results suggested that the amount and type of intrahepatic inflammatory cytokines, induced and/or secreted by activated macrophages and the inflammatory cells they recruit into the liver during malaria infection, might play a pivotal role in the negative outcome of coexisting HBV infection (exactly the opposite of what was proposed by the proponents of an improvement in HBV infection in co-infected subjects).

Impact of HBV on malaria
Whilst intriguing, little is known of the effects of HBV on the clinical presentation of malaria. Indeed, at present, the data are few, and in this case, largely conflicting. Some of the early studies concerning HBV/malaria co-infected subjects reported the concentrations of anti-RESA antibodies and their variations in cases of co-infection. Ring-infected erythrocyte surface antigen (RESA/Pf155) is a specific antigen derived from *P. falciparum* during intra-erythrocytic infection. It is deposited in red blood cell membranes shortly after merozoite invasion and disappears after the parasite matures. Antibodies to RESA have been associated with protection from malaria, Indeed, Berzins et al. (1991) demonstrated, in monkeys immunized with human antibodies, that anti-RESA inhibits merozoite invasion *in vitro*. For a time, this antigen was thought to be a potential vaccine candidate [29].

Selected epidemiological data from human studies identified associations between levels of anti-RESA and protection against malaria morbidity and mortality *in vivo*. Petersen et al. (1990) prospectively studied 118 adult Liberians for one year with monthly blood examinations for malaria parasites. Antibodies against the Pf155/RESA antigen were measured in two surveys 8 months apart; they observed that high RESA-responders presented lower parasite densities during study follow-up than did low RESA-responders, suggesting that high titres of antibodies to RESA may play a role in protection against malaria [30]. The same conclusion was reached by Migot et al., Achidi et al., and Al-Yaman et al. [31-33].

Dutra Souto et al. (2002) studied 520 sampled subjects, 517 (99.4%) of whom admitted previous symptomatic malaria; 82.9% had HBV markers and 7.1% were HBsAg-positive. Anti-RESA titres were significantly lower in HBV carriers than in those with resolved HBV infection, suggesting that the anti-RESA immune response could be supressed by HBV carrier status, thereby representing a more severe course of malarial disease.

However, immune deficient responses to both infections may take place in some subjects, causing concomitant lower anti-RESA concentration and incapacity to clear HBV [34].

Barcus, who studied samples collected in the setting of a therapeutic trial, suggested that acute hepatitis B infection might exacerbate falciparum malaria [3]. The authors did not highlight the mechanism of this apparent increase in susceptibility; however, they suggested that perhaps immune response caused by HBV infection would be less efficient at limiting parasite multiplication. Nevertheless, Freimanis observed that parasitemia levels were similar among three groups of patients (HBsAg positive, OBI and anti-HBc alone) with lower parasitic loads [12]. On the other hand, Andrade enlisted 636 Brazilian patients and found that HBV infection was associated with decreased intensity of malaria infection [10]. They proposed that this effect was due to cytokine balance and control of inflammatory ripostes. Braga observed that HBsAg-reactive subjects presented lower parasitic loads and higher antibody titres, although without statistical significance [4,9]. This suggested the possibility that immune responses in co-infected individuals were differentiated and led to variations in parasite load and antibody production.

■ CONCLUSIONS

HBV/malaria coinfection is present worldwide, especially in regions with high-endemic patterns for both pathogens. The problem is severe in developing countries, especially in Africa and Latin America. In industrialized countries, because of vaccine prevention (HBV) and environmental control (malaria), the epidemiological pattern of the two infections is sporadic. However, the epidemiological and clinical aspects of this co-infection remain little known, because there have not been many extensive studies until recently. The results of this review, examining data from the entire world, are obviously very varied. The diverse epidemiological and clinical data depend both on the different geographical areas in which the studies were carried out, and on the various stages of the two infections at the time of the study, as well as from the characteristics of the co-infected subjects. This could explain, at least in part, the differentiation of the impact of the virus or pro-

tozoa on the other pathogen, in cases of microbial overlap. In industrialized countries, the problem has not yet been tackled; however, it cannot be denied that the problem cannot arrive there as well, given immigration especially from sub-Saharan Africa. We believe that this review is the first to examine this health problem in Europe. Strategies to improve diagnostic techniques, studies of therapeutic and prophylactic agents and protocols, vector control procedures, and other operational tools are needed.

Conflict of interest
None

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