

ORIGINAL ARTICLE

Occult Hepatitis B Virus (HBV) Infection: a Global Challenge for Medicine

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SUMMARY

Hepatitis B virus (HBV) is a serious risk as a disease that can be spread through blood transfusion. Occult hepatitis B infection (OBI) is defined in a patient with the presence of HBV-DNA but a lack of HBsAg in the serum and hepatocytes. OBI can be considered as a high potential risk factor for inducing post transfusion hepatitis (PTH), hepatocellular carcinoma (HCC), cirrhosis, and reactivation of the HBV. Recently, several investigations from various regions of the world have reported PTH as well as HCC and cirrhosis among blood recipients with diseases such as thalassemia and other disorders requiring regular hemodialysis. This form of hepatitis also causes complications for individuals that are co-infected with other viruses such as HCV and HIV. Because of its extreme disease potential, OBI can be considered a high risk for PTH, HCC, and cirrhosis. Therefore, an understanding of the prevalence of OBI among blood donors is a critical strategy in most transfusion services. This review addresses the recent information regarding the prevalence of OBI worldwide, with an additional focus on Iranian blood donors.

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KEY WORDS

Occult HBV infection, blood donors, post transfusion hepatitis

INTRODUCTION

Hepatitis B virus (HBV) is a major cause of human liver infections [1,2]. The most frequent clinical presentation of the hepatitis B is a change of the skin scleroproteins and nausea due to the increased bilirubin levels and dysfunction of liver cells [3,4]. Recent studies demonstrated that many individuals are suffering from the long term forms of HBV infection including chronic, asymptomatic, and occult (OBI) hepatitis B infection [5-7]. Although the majority of blood transfusion services are currently using ELISA techniques for the detection of HBsAg, to reduce the rate of transferring HBV infection, there are still reports of post transfusion hepatitis (PTH) [8-10]. OBI is a form of hepatitis B in which,

despite of absence of HBsAg in serum, HBV-DNA is present in both serum and hepatocytes [11]. Therefore, it seems that substantial passage of PTH is by transfusion of whole blood or its components contaminated with OBI. This is highly significant for permanent recipients of blood including those with thalassemia or requiring regular hemodialysis [12,13]. Due to the high rate of HBV infection through blood transfusion from donors carrying OBI, it is important to examine and understand the prevalence of OBI in blood donors. This information will better inform blood services and help them prepare suitable diagnosis and management plans for OBI. This review draws on current reports regarding the worldwide prevalence of OBI among blood donors with an additional focus on Iranian blood donors.

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Status of OBI prevalence among blood donors in different regions of the world

The prevalence of OBI among blood donors from different countries is addressed in the Table 1 and explained in more detail in the following sections.

Asia

There are several reports regarding the prevalence of OBI among Asian blood donors. For examples Yuen et al., [3], Liu et al., [14], and Chen et al. [15] reported OBI prevalence among Chinese blood donors was 0.11%, 0.13% and 0.19%, respectively. Other studies showed that the prevalence of OBI was between 0.001% [4] to 1.01% [16] among Japanese blood donors. Seo and colleagues from South-Korea revealed that 0.016% of the blood donors had contracted OBI [17]. Researchers also demonstrated that OBI prevalence among Pakistani [18] and Indian [19] blood donors was 0.005% and 0%, respectively. The prevalence of OBI among Saudi Arabian and Omani blood donors was also evaluated by Bamaga et al. [20] and Kaminski et al. [21], respectively. They revealed that the prevalence of OBI among Saudi Arabian blood donors is 0.83 %, while it is 0 % for Omani blood donors [20,21]. There are several reports regarding the epidemiology of OBI among Iranian blood donors and we have collated the reports to cover three regions as follows:

Status of OBI in the Northern region of Iran

There are several provinces that are located in the Northern part of Iran where the majority of the Iranian population is living but there is limited information regarding OBI status in blood donors. To the best of our knowledge there is one report by Amini et al. regarding the prevalence of OBI among blood donors from the Tehran blood transfusion services [22] and they have shown that 5 out of 2000 (0.15%) evaluated blood donors were infected by OBI [22]. Based on the fact that the largest population of Iranians is living in the Northern part of Iran, more studies regarding the prevalence of OBI in this region are urgently needed.

Status of OBI in the Center region of Iran

There is not enough information regarding OBI prevalence in the Center of Iran and only two studies by Sofian et al. and Pourazar et al. were reported [23,24]. Sofian et al. evaluated 531 blood donors in the Arak blood transfusion services [23]. Their studies demonstrated that there were no HBV-DNA⁺ samples in the anti-HBc isolated (anti-HBc⁺/anti-HBs⁻) HBsAg negative blood donors [23]. On the other hand, our previous study on 545 blood donors from Isfahan province showed that 5 contributors (0.9%) had HBV-DNA despite of absence of HBsAg [24]. Therefore, it seems that the range of OBI prevalence in the North and Central regions of Iran is between 0 to 0.9%.

Status of OBI in the Southern region of Iran

In contrast to the Northern and Central regions of Iran, more studies were performed in the Southern region. For example, our previous study on 270 blood donors attending the Rafsanjan blood transfusion service (a city of the Kerman province) from 2007 to 2008 revealed that 4 (1.48%) donors were infected with OBI [25]. Interestingly, our next study on a larger population (3700 cases) of Rafsanjanese blood donors showed that 1.54% of the HBsAg negative blood donors had detectable HBV-DNA [2]. Furthermore, another study by Behbahani et al. has shown a high prevalence of OBI in the blood donors from Shiraz (center of the Fars province) [26]. They evaluated 2000 HBsAg and anti-HCV negative samples and in relation to the anti-HBc antibody they found that 6.55% were anti-HBc positive [26]. Behbahani et al. have shown that 16 out of 131 (12.2%) anti-HBc positive samples were infected with HBV-DNA indicating they were OBI patients [26]. In conclusion, Behbahani et al. demonstrated that 0.083% of the blood donors in Shiraz were infected with OBI [26]. In addition, Sharifi and colleagues performed a study on the general population of Zahedan (center of the Sistan and Baluchestan province) [27]. They reported that 3 out of 512 cases suffered from OBI [27]. Based on the fact that blood donors were derived from the general population, it could be concluded that the prevalence of OBI in the Sistan and Baluchestan provinces is 0.58%. Based on these reports, it seems that the OBI is more prevalent in Iran than other Asian countries. Some possible reasons are as follow: a) Iran is in an intermediate region (2 - 5%) of HBV prevalence [28], b) more studies were done in Iran than other countries, c) the type of HBV genotype may have an effect on the clinical presentation of hepatitis B (the common HBV genotype in Iran is type D) [29], d) differences in the studied populations in terms of genetic background, and e) PCR techniques are not used for screening of the Iranian blood donors and ELISA is used exclusively allowing the further spread of OBI. Additionally, it seems that the prevalence of post transfusion hepatitis B transmission (PTH) is different in permanent Iranian blood recipients, including thalassemic, hemophilia patients, and those undergoing regular hemodialysis [30-32]. It seems that more studies regarding the prevalence of OBI in the Asian countries is urgently needed for transfusion services to be able to formulate an informed strategy to restrict the spread of PTH through the use of blood and its products.

Europe

Investigation in European countries showed that the OBI prevalence in Poland [33,34], Italy [34,35], Spain [34, 36], Germany [34], and Switzerland [37] were 0.0001 - 0.006%, 0.007 - 0.63%, 0.00005 - 0.05%, 0.0006%, and 0.001%, respectively. Based on the reports, it can be concluded that OBI prevalence in European countries is very low.

Table 1. The prevalence of OBI among worldwide blood donors.

Continent	Country	Region (city)	Prevalence of OBI %	Prevalence %			Author	References
				Anti HBc	Anti HBs	HBs Ag		
Africa	Egypt		1.26	10.9	ND	1.1	El Zayadi et al.	[41]
	Ghana		1.7	ND	ND	1.5	Zahn et al.	[39]
	South Africa		0.004	ND	ND	ND	Allian et al.	[9]
	Sudan		0.99	ND	56	36	Mahgoub et al.	[40]
America	Brazil		0.13	3.6	1.1	2.6	Almeida et al.	[43]
	Canada		0.012	0.53	ND	2.2	Chevrier et al.	[45]
			0.52	1.13	ND	ND	O'Brien et al.	[46]
		Inuit	2.87	ND	ND	ND	Minuk et al.	[42]
	Venezuela		0%	ND	ND	ND	Gutierrez et al.	[44]
Asia	China		0.11	0.1	0.07	ND	Yuen et al.	[3]
			0.13	ND	ND	ND	Liu et al.	[14]
			0.19	ND	ND	ND	Chen et al.	[48]
	India		0	ND	ND	ND	Duseja et al.	[19]
	Japan		0.001	ND	ND	ND	Yoshikawa et al.	[4]
			1.01	0.6	ND	ND	Satake et al.	[16]
	Oman			20.5	ND	5.5	Kaminski et al.	[21]
	Pakistan		0.005	4.16	ND	2.16	Bhatti et al.	[18]
	Saudi Arabia			ND	ND	ND	Bamaga et al.	[20]
South Korea		0.016	13.5	12.2	ND	Seo et al.	[17]	
Europe	Germany		0.0006	ND	ND	ND	Candotti et al.	[34]
	Italy		0.007- 0.63	ND	ND	ND	Candotti et al.	[34]
				4.85	ND	ND	Manzini et al.	[35]
	Poland		0.0001-0.006	ND	ND	ND	Brojer et al., Candotti et al.	[49] [34]
	Spain		0.00005-0.05	ND	ND	ND	Candotti et al.,	[34]
			ND	ND	0.05	Gonzalez et al.	[50]	
Switzerland		0.001	0.008	ND	0.007	Stolz et al.	[37]	

Table 1 illustrates OBI, anti-HBc, anti-HBs and HBsAg prevalence among assessed countries. ND: Not determinant.

Table 2. The prevalence of OBI among Iranian blood donors.

Region (city)		Prevalence %	Prevalence of OBI %			Author	References
			Anti HBc	Anti HBs	HBs Ag		
North	Tehran	0.15	11.5	8.95	ND	Amini et al.	[51]
Center	Arak	0	2.1	ND	ND	Sofian et al.	[23]
	Isfahan	0.9	8	31.8	0.4	Pourazar et al.	[24]
South	Rafsanjan	1.48	5.18	1	ND	Jafarzadeh et al.	[25]
		1.54	9.51	ND	ND	Arababadi et al.	[2]
	Shiraz	0.083	6.55	ND	ND	Behbahani et al.	[26]
	Zahedan	0.58	21.5	ND	3.3	Sharifi-Mood	[27]

Table 2 illustrates OBI, anti-HBc, anti-HBs and HBsAg prevalence among Iranian blood donors. ND: Not determinant.

Africa

Africa is determined as having a high prevalence of HBV infection [38]. Therefore, it would be expected that the prevalence of OBI is also high among African blood donors and several investigations have confirmed this. For instance, Zahn et al. showed that 1.7% of the blood donors from Ghana are infected with OBI [39]. Allian and colleagues have evaluated 1149507 samples regarding OBI infection and they have shown that 54 (0.004%) of the evaluated blood donors were classified as OBI in South-Africa [9]. Another study in the Sudan demonstrated that 6 out of 404 anti-HBc positive blood donors were infected with HBV-DNA, while they were HBsAg negative [40]. Therefore, it seems that the prevalence of OBI among Sudanese blood donors is 0.99% [40]. OBI was also detected in 9/712 (1.26%) of the blood donations in the Egyptian population [41].

Based on these studies it appears that the prevalence of OBI is similar to that of Asia. Once again, more studies in the different countries within Africa would help give a more accurate picture of the prevalence of OBI in Africa.

American

Investigations from the Americas also revealed that OBI prevalence was not significantly different from other regions such as Asia and Africa. For example, Minuk et al. reported that HBV-DNA was detected in 14/487 (2.87%) Inuit people (Canada) [42]. Brazilian investigators showed that 2 of 1536 (0.13%) blood donors were infected with OBI [43]. Interestingly, Gutierrez et al. from Venezuela revealed that no OBI cases were found in 2,075 screened blood samples [44]. Studies from Canada demonstrated that the prevalence of OBI among the blood donors was 0.012 [45] to 0.52% [46]. Additionally, Kleinman et al. revealed that the rate of OBI prevalence among the USA population is as low as the Canadian population [47]. They have evaluated 231 blood donors and found that only four blood donors are infected with low levels of HBV-DNA without detectable HBsAg [47]. Based on the high population of countries in the Americans, especially southern countries, more studies among blood donors would elucidate the status of OBI among blood donors in these countries.

CONCLUSION

According to the reports mentioned above, it seems that the prevalence of OBI is frequent in blood donors worldwide, especially in Iran. One plausible reason for the high prevalence of OBI among blood donors may be related to the use of ELISA techniques to detect HBsAg. Moreover, the rate of HBV infectivity is variable between countries, hence, the differences between countries, even in the same region. Subsequently the prevalence of OBI among blood donors may be related to the rate of HBV infection prevalence. Previous stud-

ies also reported that the HBV genotype can affect the outcome of infection, thus, another reason for the differences may be contributed to the prevalent HBV genotype varying among the countries. On the other hand, other variables may include the differences in PCR test sensitivity and the pool sizes of samples. It should be noted that many countries have not been included in this review. In some cases this reflects the lack of research into OBI in those countries. Alternatively, the medical systems do not consider DNA analysis in the detection of HBV. For example, in many Australian pathology laboratories, antigen detection is regularly used but DNA testing is an option selected by the patient's doctor and is frequently ignored. It would appear that using quantitative PCR to screen for HBV-DNA is crucial if we want to initiate a strategy that prevents further transmission of the disease. In addition, based on the high prevalence of OBI in blood donors we suggest that investigators design a follow up study to evaluate the recipients of the OBI infected blood and its components using HBV markers. Finally, the authors propose that the clinical services managers in countries with a high prevalence of OBI have a serious obligation to use complementary tests such as anti-HBc screening of blood donors in addition to using sensitive tests including quantitative and qualitative PCR to detect HBV-DNA.

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Declaration of Interest:

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