Visceral leishmaniasis and hepatitis B virus/C virus coinfection: a potential challenge for treatment

Abstract

In India, there has been no systematic study to determine the actual seroprevalence of co-infection with visceral leishmaniasis (VL), hepatitis B (HBV), hepatitis C (HCV) or both. In this study, 32 VL patients were tested, of whom 28 (8.88%) tested positive for HBV, 1 (0.317%) for HCV and 3 (0.95%) for both HBV and HCV. It is extremely difficult to treat patients who have contracted both infections. For example, one patient who had both VL and HBV co-infection required six courses of anti-leishmaniasis medication, perhaps because the co-infection was a complicating factor. This demonstrates the importance of routine HBV and HCV screening to improve treatment outcomes and support the kala-azar elimination initiative in India. Accurate identification of co-infections is crucial for effective treatment methods and reducing the burden of disease. Systematic screening of VL patients for these viruses not only helps in public health initiatives to control and eventually eradicate kala-azar, but also improves individualized treatment of patients. This strategy is particularly important in areas where viral hepatitis and viral literacy are prevalent, as these diseases represent a double burden.

Keywords: Visceral Leishmaniasis (VL), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), rK-39

Introduction

Visceral leishmaniasis (VL), mainly caused by *Leishmania donovani* in India, has a significant impact on disadvantaged populations due to variables such as malnutrition, resettlement and inadequate housing (Rodrigues et al., 2016; Topno et al., 2020a; Pradhan and Kuna, 2023). Aside from the clinical consequences, VL impairs social functioning and strains healthcare systems by putting financial pressure on families and overburdening local medical facilities (Terrazas et al., 2016; Grifferty et al., 2021). Clinicians face significant barriers in treating VL due to limited access to essential medications, inadequate training and the need to address comorbidities (Rodrigues et al., 2016; Vlassoff et al., 2023). Chronic hepatitis infections can exacerbate liver disease if VL impairs immune function and potentially causes flare-ups of existing infections. The World Health Organization estimates that 50,000 to 90,000 new cases of VL occur worldwide each year, with Brazil, East Africa and India being the most affected regions (Kone et al., 2019; Sirilert and Tongsong, 2021). *Leishmania donovani* attacks the reticuloendothelial system, particularly the bone marrow, spleen and liver, resulting in persistent fever, organ enlargement, weight loss, low platelets and high gamma globulin levels, as well as hypoalbuminemia, edema, malnutrition and diarrhea (Costa et al., 2023; Poulaki, Piperaki and Voulgarelis, 2021).

The combination of visceral leishmaniasis (VL), hepatitis B virus (HBV) and hepatitis C virus (HCV) increases the risk of serious consequences for infected persons. Studies show that co-infected people have a higher mortality rate and require longer hospital stays. Each infection exacerbates the negative consequences of the other, such as accelerating liver damage and compromising the immune system, leading to more serious health complications (Colomba et al., 2019; Ratnapriya, Sahasrabuddhe, and Dube, 2019). When VL compromises the immune system, chronic hepatitis infections exacerbate liver disease and can cause an outbreak of previous infections. Hepatitis viruses, on the other hand, can reduce immune cells and thus increase susceptibility to VL or relapse of the infection (Rana et al., 2017; Ratnapriya, Sahasrabuddhe and Dube, 2019). In India, hepatitis B and C viruses are responsible for 50–70% of acute hepatitis cases that develop into chronic liver disease. In India, around 43 to 45 million people carry the hepatitis B surface antigen (HBsAg) (Ray, 2017; Vyas et al., 2017; Bhadoria et al., 2022). Hepatitis B virus (HBsAg-positive) infects 3–4% of the population, while hepatitis C virus affects 1.8%–2.5% of the population (Vyas et al., 2017; Grewal et al., 2018; Bhadoria et al., 2022). These high prevalence rates underscore the importance of comprehensive screening,

immunization and treatment programs to manage and reduce the burden of hepatitis-related liver disease. 35 countries worldwide have observed VL-HIV co-infections, with 1.5% to 9% of AIDS patients suffering from newly acquired or reactivated VL (World Health Organization, 2006; Fontoura et al., 2018). Symptoms of VL include fever, cachexia, hepatosplenomegaly, pancytopenia and hypergammaglobulinemia. VL patients may develop jaundice due to leishmanial involvement or concurrent HBV infection. In VL-positive patients, co-infection with HBV and HCV reduces survival and increases the risk of severe liver damage and hepatotoxicity (Kotsifas et al., 2011; Georgiadou et al., 2015). This scenario requires changes in leishmaniasis medications to successfully treat VL and reduce relapse rates in patients infected with both HBV and HCV. Treatment of co-infection complicates treatment and requires close monitoring of drug interactions, potential side effects and disease progression. This emphasizes the importance of collaboration between infectious disease specialists, hepatologists and primary care physicians (Bunn et al., 2018; Sirilert and Tongsong, 2021). The combined effects of hepatitis on the liver and VL on the whole body increase the risk of mortality and can lead to liver failure or other catastrophic diseases (Topno et al., 2020b). Co-infections are difficult to diagnose and monitor due to overlapping symptoms and require specialized laboratory testing, especially in locations with limited access to current diagnostic tools and knowledge (Topno et al., 2018; Topno et al., 2020c; Costa et al., 2023). To improve patient outcomes and optimize healthcare practices, professionals must work together to detect the disease early, monitor it closely, and provide effective treatment (Sirilert and Tongsong, 2021; Verma et al., 2023; Topno et al., 2023). This study highlights the prevalence of visceral leishmaniasis and emphasizes that co-infection with hepatitis B and C exacerbates liver damage and immunosuppression. This combination complicates treatment and increases the risk of mortality. Effective treatment of these diseases requires coordinated efforts by infectious disease specialists, hepatologists and primary care physicians to improve patient outcomes and manage the complexity of co-infections.

Methodology

This observational study took place at the ICMR-Rajendra Memorial Research Institute of Medical Sciences in Patna, Bihar. The research commenced after approval from the Institutional Scientific Advisory Committee and the Ethical Committee in compliance with strict ethical guidelines. The participants were first screened for visceral leishmaniasis (VL) using the rK39 rapid test. Those who tested positive underwent further testing, including invasive procedures

such as bone marrow or spleen aspiration, to confirm the VL diagnosis by identifying Leishman-Donovan (L.D.) bodies.

After VL confirmation, patients were tested for hepatitis B and C co-infections. This included serologic testing for hepatitis B surface antigen (HBsAg) and hepatitis C antibodies. The researchers collected a comprehensive medical history using a standardized questionnaire that recorded medical background, symptoms and previous treatments.

In order to focus on the interaction between VLand hepatitis viruses, HIV-positive individuals were excluded from the study to rule out possible confounding factors. This methodological approach enabled a targeted investigation of the prevalence and impact of VL and hepatitis B/C co-infection. The study utilized precise diagnostic techniques for VL confirmation and thorough hepatitis virus screening. This systematic approach should provide insights into the health challenges and infection patterns associated with VL and hepatitis viruses in the region.

Results

From 2019 to 2020, a total of 315 patients with VL were admitted to the ICMR-RMRIMS in Patna. To learn more about how common and how harmful it is for people to carry both the hepatitis B and C viruses, the researchers enrolled these patients in a study. Comprehensive demographic data was collected from all patients, including those who tested positive for both HBV and HCV or both diseases simultaneously. The purpose of this extensive data set was to shed light on the significant public health problem that these overlapping infections present by providing a complete picture of the prevalence and characteristics of these co-infections in VL patients. The study aimed to better manage and reduce the burden of these co-infections in affected groups by analyzing demographic characteristics to identify trends and correlations. These findings could inform future treatment techniques and public health measures.

In this study, a total of 32 patients were found to be positive for either HBV, HCV, or both. Specifically, 28 patients (8.88%) tested positive for HBV, 1 patient (0.317%) tested positive for HCV, and 3 patients (0.95%) were co-infected with both HBV and HCV. A significant finding was that one VL patient, who was co-infected with the hepatitis B virus, had undergone VL treatment six times between 2012 and 2020 (**Table1**). This repeated treatment could be indicative of chronic VL infection leading to the patient's co-infection with hepatitis B. The

recurring VL infections may have compromised the patient's immune system, making them more susceptible to acquiring HBV. This case underscores the complex interplay between VL and hepatitis co-infections and highlights the importance of monitoring and managing such patients closely. It also suggests that persistent VL infections could potentially increase the risk of co-infection with hepatitis viruses, emphasizing the need for integrated treatment approaches to address both diseases effectively.

Age Group	**2019**						**2020**						**2019 + 2020**					
	HBV + VL		HCV + VL		HBV & HCV + VL		HBV + VL		HCV + VL		HBV & HCV + VL		HBV + VL		HCV + VL		HBV & HCV + VL	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
0-12	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
13-25	1	3	0	0	0	0	1	1	0	0	0	0	2	4	0	0	0	0
26-38	2	2	0	1	0	0	2	2	0	0	0	0	4	4	0	1	0	0
≥39	7	4	0	0	2	1	1	1	0	0	0	0	8	5	0	0	2	1
Total	**11**	**9**	**0**	**1**	**2**	**1**	**4**	**4**	**0**	**0**	**0**	**0**	**15**	**13**	**0**	**1**	**2**	**1**
Sub-total	**20**		**1**		**3**		**8**		**0**		**0**		**28**		**1**		**3**	
Grand total	**24**						**8**						**32**					

Table 1: Investigation details of VL patients either positive with HBV, HCV and HBV-HCV Co-infection

Discussion

Most people suffering from visceral leishmaniasis (VL) and hepatitis B or C (HBV/HCV) have very high AST, ALT and total bilirubin levels. Sodium stibogluconate (SSG), a common treatment for VL in East African countries, poses a risk to VL patients who are also infected with HBV or HCV due to its hepatotoxicity (Singh, 2014; Osman et al., 2023). Immunosuppressed VL patients have higher relapse rates and longer treatment times, and there are few suitable antileischmanic drugs for co-infected patients. Studies show that treatments with sodium stibogluconate, pentamidine or amphotericin-B can eliminate VL. However, they carry a high

risk of spreading blood-borne diseases such as HIV, hepatitis B and hepatitis C. This could be due to the fact that they use dirty needles for injections (Miceli and Chandrasekar, 2012; Sapkota, Palaian, and Shrestha, 2023). Some VL patients have associated another treatment option, cap miltefosine, with nephrotoxicity and hepatotoxicity, making it unsuitable for those co-infected with HBV/HCV. In contrast, liposomal amphotericin B is considered the treatment of choice for VL/HBV and HIV/VL coinfections (Mahajan et al., 2015). It has a total dose of 40 mg/kg and is associated with fewer hepatotoxic effects and side effects (Tostmann et al., 2008; Abongomera et al., 2018). The challenges for patients co-infected with HIV and visceral leishmaniasis (VL) are considerable. These patients often suffer multiple relapses and require repeated treatments. The situation becomes even more complicated when VL is co-infected with hepatitis B or C, especially in tropical regions. The combined effect of these infections leads to increased disease severity, largely due to cumulative liver damage. This liver damage is exacerbated when other viral infections such as dengue, chikungunya, zika and Japanese encephalitis (JE) are also present (Kumar et al., 2019a; Kumar et al., 2023). The combination of these diseases represents a serious health burden, underlining the need for comprehensive management strategies in the affected regions (Kumar et al., 2019; Topno et al., 2019b; Kumar et al., 2024). Individuals at high risk for VL are also more susceptible to viral infections such as hepatitis B and C due to their weakened immune system. This confluence of diseases requires careful consideration in treatment protocols to avoid exacerbation of liver damage and to effectively manage the overall health of co-infected patients.

Conclusion

The aim of this study was to determine the prevalence of HBV and/or HCV in individuals with visceral leishmaniasis (VL) despite the small sample size. It is noteworthy that one person with VL was treated for leishmaniasis six times between 2012 and 2020. This was probably because it had multiple VL infections, which may have increased the likelihood of concurrent infection with hepatitis B virus (HBV). This shows that co-infection is possible and that we need a larger sample size to get a better idea of how common and dangerous it is for VL patients to be co-infected with HBV, HCV or both. It is important to test VL patients for hepatitis B and C viruses because it would make treatments much more effective for people who are co-infected with HBV or HCV. We need this type of testing not only to help every patient, but also to achieve the goals

of the kala-azar removal program. By detecting and treating co-infections, healthcare providers can better customize treatment plans for patients who have co-infections. This improves patient outcomes and helps achieve the overall public health goal of eliminating kala-azar from the area. Regular VL treatment that includes screening for viral hepatitis would ensure timely action, reducing illness and death from these co-occurring infections. This strategy is particularly important in places where both VL and viral hepatitis are common and where co-infections can make disease treatment and elimination difficult.

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