Challenges in the treatment of Co-infection of Visceral leishmaniasis and Hepatitis B/C viruses

Abstract

There is a significant research gap in India due to incomplete investigation of seroprevalence of co-infection with visceral leishmaniasis (VL), hepatitis B (HBV) and hepatitis C (HCV). This study attempts to fill this gap by providing an in-depth analysis of the prevalence and consequences of these co-infections. The study of 32 VL patients revealed that 28 (8.88%) tested positive for HBV, 1 (0.317%) for HCV and 3 (0.95%) for both HBV and HCV. These results highlight how difficult it is to treat people with two diseases at the same time. An example of how co-infection makes treatment much more difficult is the fact that a patient with both VL and HBV required six courses of anti-leishmaniasis medication. The study shows how important it is for VL patients to be tested regularly for HBV and HCV to improve treatment response and support India's plan to get rid of kala-azar. Accurate identification of co-infections is necessary to reduce the overall burden of the disease and develop effective treatment regimens. Systematic testing of VL patients for HBV and HCV not only helps in controlling and perhaps even eliminating kala-azar, but also makes it easier to treat each patient as an individual, improving their health. In areas where viral hepatitis is prevalent, this strategy is particularly important as these diseases represent a double burden on public health. Implementing integrated treatment regimens and routine screening can reduce the impact of co-infection and advance the public health goal of kala-azar elimination. To improve patient outcomes and advance public health goals, the results of this study strongly support the integration of comprehensive screening programs into existing healthcare systems to improve the treatment of VL patients.

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). The study delves into the effects of VL, as well as its co-infection with HBV/HCV. Leishmania donovani, the primary cause of VL in India, primarily affects underprivileged communities, exacerbated by factors such as malnutrition, displacement, and inadequate housing. In addition to raising the likelihood of death, co-infection with HBV and HCV worsens immunosuppression and liver damage. The preliminary findings would help us to develop the Improvements in

patient outcomes and management of these co-infections require coordinated efforts from primary care physicians, hepatologists, and infectious disease experts.

Methodology

The study reveals significant issues in the management of visceral leishmaniasis (VL) and hepatitis B (HBV) and C (HCV), particularly in impoverished populations. Inadequate healthcare training, restricted access to necessary pharmaceuticals, and the requirement for specialized diagnostic equipment in areas with few resources are all examples of these gaps. These co-infections' complicated interactions and higher mortality risk are not adequately addressed due to a lack of coordinated care among healthcare professionals. Screening, vaccination, and therapy regimens that cover all bases are necessary for effective management. 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.

We further confirmed VL and performed ELISA tests to identify HBsAg and hepatitis C antibodies. The exclusion of HIV-positive individuals allowed us to focus on the specific interaction between VL and hepatitis viruses. This study provides new information on the effects of hepatitis and VL on immune function and liver health. Through the use of detailed diagnostic techniques, such as ELISA, and the methodical collection of extensive demographic and medical data, the study provides a thorough understanding of the prevalence and characteristics of these co-infections. This methodology, which emphasizes the importance of integrated treatment plans and coordinated health initiatives to improve patient outcomes, can influence public health policy in similar endemic areas. 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

This study represents a comprehensive and focused investigation of the intricate relationship between visceral leishmaniasis (VL), hepatitis B (HBV) and C (HCV) viruses in a region heavily affected by these diseases. By intentionally excluding HIV-positive individuals, the study focuses on the unique interactions between VL and hepatitis viruses and provides new insights into their combined effects on liver health and immune function.

Through the use of detailed diagnostic techniques and the systematic collection of extensive demographic and medical data, this study provides an in-depth understanding of the prevalence and characteristics of these co-infections. This rigorous approach underscores the urgent need for integrated treatment strategies and coordinated public health efforts aimed at improving patient outcomes and shaping effective public health policies in similar endemic regions. The study shows that most individuals suffering from VL and HBV/HCV have elevated AST, ALT and total bilirubin levels. Treatments such as sodium stibogluconate (SSG), which are commonly used in East African countries, pose significant hepatotoxic risks to co-infected patients. Immunosuppressed VL patients face higher relapse rates and longer treatment durations, and few suitable antileischmanic drugs are available for co-infected patients (Hofman et al., 2000; Singh, 2014; Osman et al., 2023). Treatments such as sodium stibogluconate, pentamidine or amphotericin-B can get rid of VL, but they also carry a high risk of spreading blood-borne diseases such as HIV, HBV and HCV, possibly because they use dirty needles (Miceli and Chandrasekar, 2012; Sapkota, Palaian and Shrestha, 2023). In addition, drugs such as miltefosine can damage the kidneys and liver, so people who have both HBV and HCV infection should not use them (Mahajan et al., 2015). Liposomal amphotericin B at a total dose of 40 mg/kg is now

the best drug for treating VL/HBV and HIV/VL co-infection because it has fewer side effects and is safer for the liver (Tostmann et al., 2008; Abongomera et al., 2018).

Patients co-infected with HIV and VL face significant challenges, including multiple relapses and repeated treatments. The situation becomes even more complex when VL is co-infected with HBV or HCV, particularly in tropical regions. Other viral infections such as dengue, chikungunya, Zika and Japanese encephalitis (JE) further exacerbate the cumulative liver damage from these combined infections (Kumar et al., 2019a; Kumar et al., 2023). This confluence of diseases requires a careful and comprehensive treatment strategy, especially in regions where both VL and viral hepatitis are prevalent. Individuals at high risk of VL are also more susceptible to HBV and HCV due to their weakened immune system (Kumar et al., 2019; Topno et al., 2019b; Kumar et al., 2024). Therefore, this study emphasises the importance of integrated treatment protocols that take into account the exacerbation of liver damage and 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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1.

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