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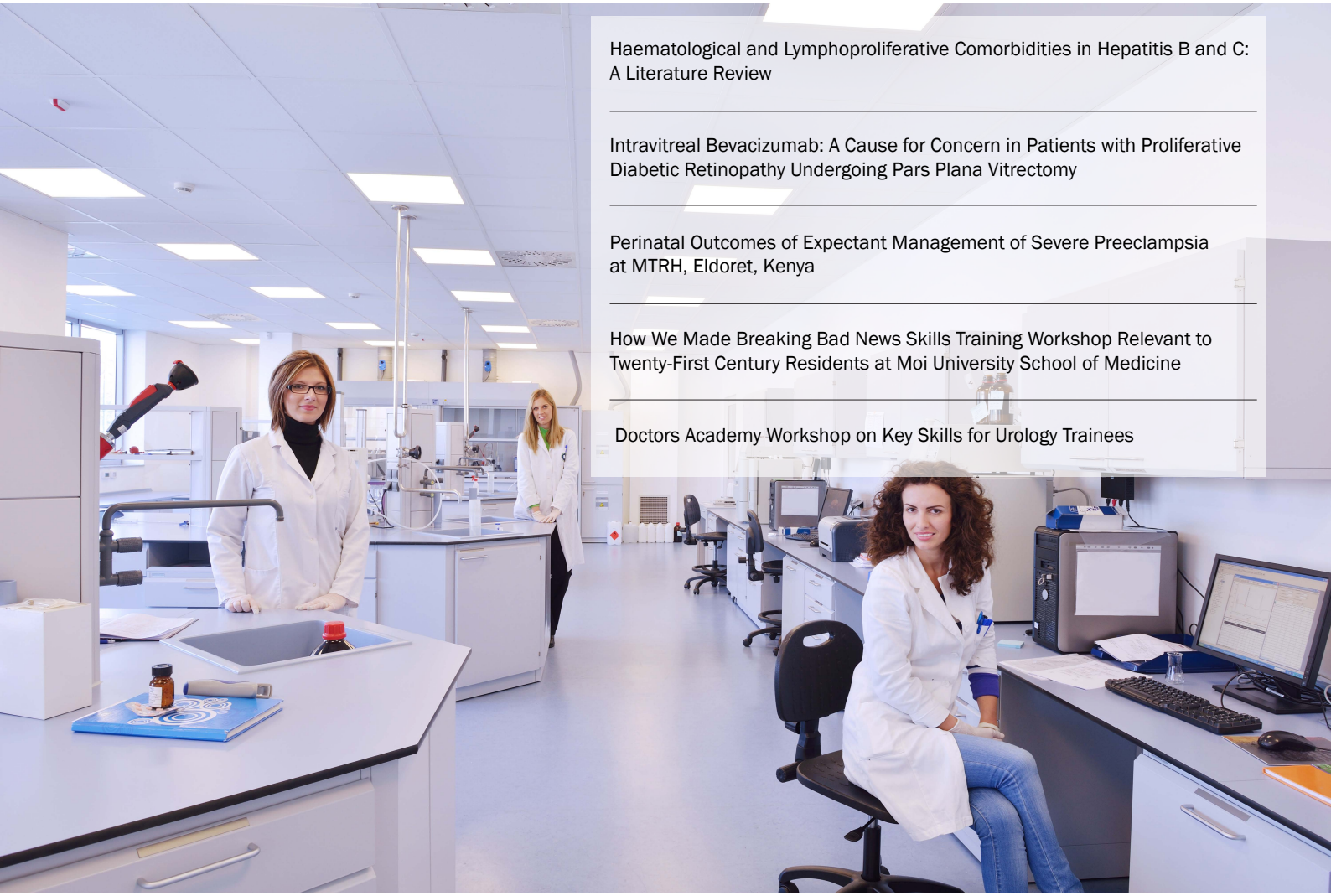

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Haematological and Lymphoproliferative Comorbidities in Hepatitis B and C: A Literature Review

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Abstract
This review describes the association of viral hepatitis C with haematological diseases and lymphoproliferative disorders in children. Emphasis is placed on discussing their mechanism of development, and a few management strategies are described. This article explains the need for proper screening in children with HCV and HBV infections to improve their treatment outcome and quality of life for a better prognosis.

Key Words
Hepatitis; Pediatrics; Infections; Haematology; Disorders

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Introduction

Over the last two decades, in developed countries there is a progressively decreased rate of viral HBV and HCV infections due to the heavy screening of the patients and their identification. However, this identification process was not installed in all developing and underdeveloped countries of the world. Making this an urgent concern, the risk of population more affected are children under the age of five years around the globe. With the alarms ringing, proper measures of screening, counselling and treatment are necessary to those mothers identified with a HCV or HBV infection. It is a known fact that pediatric infections are not only post-transfusional or post-delivery but could also be marked as nosocomial in developing countries. Possible precautions like disposal of needles, invasive procedures and sterile materials should be taken to prevent the fore mentioned risk. HBV and HCV infections are mentioned as silent infections, due to the fact that they are rarely found and require special tests to identify them in the pediatric populations who are highly predisposed to them[1]. From the recent statistics, it is stated that viral hepatitis C affected nearly 3.2 million people alone in the United States and 3% of general population in the world[2]. These oncohematological pathologies are often detected in children with viral hepatitis, as a result of multiple invasive manipulations and blood transfusions, and make further treatment of the underlying disease more difficult.

The aim of our study was to review the recent literature on oncohematological pathologies in children with viral hepatitis B and C.

Methods and Materials

We reviewed recent articles from pubmed central, google scholar and uptodate, using the key terms pediatrics, viral hepatitis, hematopathology, hematoncology, hepatitis B virus and hepatitis C virus.

Results

The mortality caused by viral hepatitis in 2015 was due to chronic liver disease (cirrhosis) and primary liver cancer (hepatocellular carcinoma)[3]. Most infections in children are clinically silent[4]. The risk of attaining HBV infection was greatly reduced by hygiene standards, verifying blood products and prophylactic vaccination[5]. Despite these actions, the infections of HBV are very high[6]. HBV is a partially double-stranded DNA virus which replicates with the help of reverse transcription and is characterized by its thin host range and replication in hepatocytes. HBV's DNA is covalently closed circular DNA[7]. The life cycle of the virus is not relevant, but HBV genomes are reported to integrate into the hepatocellular genome[8]. Many studies support the prognostic value of HBV-DNA levels in the estimation of HCC risk and disease prognosis[9].

The detection of HCV-encoded polymerase is not easy and with high replication rates results in a high mutation rate. Both HBV and HCV are transmitted parenterally, it can also be transmitted by intravenous drug abuse or invasive sexual practices. They can be transmitted vertically in some cases. Like HBV, HCV is not much persistent in children. HCV infection is symptomatic in 85% cases and symptoms like fatigue, vomiting and signs of liver damage are seen. Chronic form is slow progressive disease which is characterized by obstinate hepatic inflammation resulting in liver fibrosis and liver cirrhosis. HCV is a single-stranded, positive-sense RNA virus.

From the literature it is known that with addition to hepatic involvement, viral hepatitis can also lead to the extra hepatic involvement causing haematological manifestations, ranging from benign malignancies to lymphoproliferative disorders[10,11]. Several benign haematological diseases are explained like thrombocytopenia, autoimmune haemolytic anemia, aplastic anemia, red cell aplasia, neutropenia and sideroblastic anemia were identified[12,13].

Thrombocytopenia serves as the major problem for patients with HCV infection. Rajan et al, in a study it was described that out of 250 patients, 30% of the patients reported a chronic thrombocytopenic purupura who were HCV positive[14]. Chiao et al mentioned that, the risk of thrombocytopenia is prevalent in both patient groups who were on treatment and untreated HCV patients equally[15]. The number of HCV infection cases reported with thrombocytopenia were more than any other hepatic involvement, and no specific genotype of the virus was identified related to this manifestation[16,17]. Few studies suggest that immune mechanisms are responsible for the reduced thrombocytes count. The reduced thrombocyte count was also related advanced liver disease due to fibrosis and hepatocyte damage[18,19,20,21]. A proper treatment regime for the HCV patients associated with thrombocytopenia has to be established. Steroids and antiviral therapy with interferon alpha are mostly preferred but with their improper indications could cause reactivation of the viral rNA or increase in the viral load, becoming a threat to the patients life. McHutichinson et al in their study described the use and safety of Eltrombopag in patients with HCV associated with reduced platelet count[22] Whereas, Afdhal *et al*, in their randomised study on 292 patients, proposed Eltrombopag, reducing the need for platelet infusions for the patients undergoing invasive procedures[23]. So, dosage and the time of drug administration play a key role in further improvement keeping in mind the careful selection of the patients.

Hepatitis C is also associated with bone marrow abnormalities and coagulopathies. It is hypothesised that the bone marrow abnormalities in HCV patients could be possibly due to autoimmune destruction, hyper active spleen, antiviral treatment load and decreased thrombocytic count[24]. In patients with a sudden pancytopenia, a bone barrow biopsy for the defection of HCV RNA is suggested. In a study by Azam et al on 30 patients, 16 out of them contained traces of HCV RNA in their bone marrow samples. They visualised the inflammatory changes, hypo or hyper cellularity, high viral load, immune complexes in the marrow samples in the above mentioned 16 cases, which led them to theorise the possibility of viral replication and altered marrow micro environment, which is the cause of haematological manifestations[25]. Whereas, Lisman et al described in their study that the coagulopthies could be possibly due to thrombocytopenia, prolonged prothrombin index, reduced clotting factors and increased Von Willebrand factor and actovegin caused from endothelial dysfunction which are well understood[26].

Discussions

HCV infected patients can also be associated to extra hepatic comorbidities like lymphoproliferative disorders, with an increased prevalence in women with more than 50 years, as suggested by several epidemiological studies[27,28]. Several studies described the association of HCV with non-Hodgkins lymphoma, B cell lymphoma, myeloid malignancies, Waldenstrom's macroglobulinemia, chronic lymphocytic leukaemia and chronic myeloid leukaemia. Chronic antigenic stimulation of the immune system has been one of the proposed theories to relate HCV infections with lymphoproliferative diseases[29,30,31] Machida et al suggested the theory of HCV infection enhancing the DNA damage causing gene mutations and disrupting the natural apoptotic processes of the infected lymphocytes[32]. However, taking into consideration the data by Mazzaro et al, not all HCV infections are associated with lymphocyte abnormalities, indicating the involvement of various environmental and genetic factors influencing the B-cell disorders related to viral hepatitis[33]. As there is high evidence of association of non-Hodgkins lymphoma with HCV, every patient with lymphoproliferative diseases must be screened for viral hepatitis. With the high risk for development of hepatotoxicity, there is a necessity for close monitoring of the viral load and hepatic function.

Conclusions

Thus, broad access to therapeutic intervention before late-stage liver disease has developed as well as surveillance even after successful therapy is

required to reduce the death toll from viral hepatitis and its haematological comorbidities. In addition, a prophylactic vaccine is urgently needed to reduce new infections and to prevent reinfection after antiviral therapy[34]. Subsequent management implications are needed to treat the above mentioned viral hepatitis associated haematological disorders. Pediatric infectologists play an important role in screening and putting a confirmatory diagnosis in these fore mentioned comorbid diseases[35].

Further studies describing better pathophysiology and mechanisms of their associations and target therapies are in high demand to improve the treatment outcome and quality of life in children with viral hepatitis B and C associated with haematological and lymphoproliferative comorbidities. It should be pointed out that modern literature also indicates both the frequency of haematological disorders in HCV and HBV and the high probability of infecting these children with oncohematological pathology. Therefore, it is necessary to monitor the haematological status of children with chronic hepatitis, and monitor hepatitis markers in patients with oncohematological pathology.

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