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Review

Viral hepatitis and the immunological response: a review

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ABSTRACT

Introduction: In Brazil, viral hepatitis is infectious disease of compulsory notification and is considered a serious public health problem. Infections with A, B, C, D or E viruses trigger the activation of immune system molecules and cells at the level of innate and acquired immunity. **Objective:** The present study aimed to review the knowledge about viral hepatitis and the immune system's performance against these infections. **Methods:** This is a literature overview from academic books and scientific articles available in the Scientific Electronic Library Online, US National Library of Medicine National Institutes of Health and Google Scholar databases. Having as key words hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E and immune system. The relevant articles corresponding to the period between 1974 and 2017 were selected. **Development:** Viral hepatitis is characterized by inflammation in liver cells caused by groups of viruses that have hepatotropism in common. The diagnosis is made through serological methods and molecular biology techniques. The approach of the immune system in relation to the combat of this infection follows same particularities. **Conclusion:** This review demonstrated that the determination of the etiologic agent is essential for the conduct to be taken with the infected individual. Moreover, the immune system is directed related to the viruses elimination, presenting some particularities. In addition, this review highlights that the vaccination is the main responsible for reducing people infected by viruses A and B.

Keywords: Hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, immune system.

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1. INTRODUCTION

Endemic and epidemic communicable diseases are considered an important public health problem in all over the world including Brazil. Among them, viral hepatitis is highlighted, since in the recent years they have been changed their epidemiological behavior (FERREIRA and SILVEIRA 2004, FERREIRA and SILVEIRA 2006, LY, XING *et al.* 2012, STANAWAY, FLAXMAN *et al.* 2016)

About 90% of hepatitis cases are caused by hepatitis virus A, B, C, D and E (MACEDO, SILVA *et al.* 2013). Viral hepatitis mainly affects the liver, which is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory and neoplastic injury (BABINSKI, NUNES *et al.* 2008, KUMAR, ABASS *et al.* 2013).Therefore, in general, the viral hepatitis are characterized by an inflammation response in the hepatocytes induced by the virus, which presents hepatotropism. Moreover, these viruses can cause numerous clinical manifestations, which make their diagnosis difficult, unless the etiologic agent is known (FERREIRA and SILVEIRA 2004). During the acute infection, clinical signs and symptoms are easy to detect and present rapid progress. On the other hand, during the chronic infection, the patient presents discrete signs and symptoms, usually difficult to recover (NEVES 2006).

Nevertheless, in all hepatitis cases, cell and molecules of the immunological system are activated to produce a defense response against the invasive agent (DELVES and ROITT 2000, COELHO-CASTELO, TROMBONE *et al.* 2009). Knowing that infections caused by viruses can trigger activation of phagocytic cells and complement activation (innate immunity), as well as the T lymphocytes proliferation and the production of specific antibodies (adaptive immunity)(PEAKMAN and VERGANI 2011), the present study aimed to review the knowledge about viral hepatitis and their induced-response by the immune system.

2. METHODS

The present study was carried out through a review of the literature, using as tool material already published on the subject; academic books and scientific articles available in databases such as Scientific Eletronic Library Online (SCIELO), US National Library of Medicine National Institutes of Health (PUBMED) and Scholar Google. The following descriptors were used to search: Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E and Immune System. The criteria for inclusion of the articles were those published between 1974 and 2017.

3. DEVELOPMENT

3.1. HEPATITIS A

Hepatitis A is a disease caused by the icosahedral hepatitis A virus (HAV), a linear RNA enterovirus of the picornavirus group (Picornaviridae family) without envelope (Fig.1A).This virus has a limited time course and incubation period of approximately 3 - 6 weeks (KUMAR, ABASS *et al.* 2013). After this period, the patient presents fever, malaise and anorexia (STEVENS and LOWE 2002).

HAV transmission occurs through fecal-oral ingestion of contaminated water and food. The virus is eliminated in the feces 2 - 3 weeks before and 1 week after the onset of jaundice (STEVENS and LOWE 2002, FARES 2015). HAV can also be found in serum and saliva. However, since their blood-borne transmission occurs infrequently, donated blood is not specifically screened for HAV (KUMAR, ABASS *et al.* 2013).

Hepatitis A represents the main cause of acute viral hepatitis in the world (FERREIRA and SILVEIRA 2004) and it is not able to advance to chronic stages of the disease (STEVENS and LOWE 2002).These cases arise singly or in outbreaks and the signs and symptoms are poorly specific. In general, the personal contact daily with an infected individual becomes responsible for most cases of this infection. Among the affected individuals, children and teenagers are the prominent group (FERREIRA and SILVEIRA 2004, KUMAR, ABASS *et al.* 2013). This fact can explain the excessive amount of reports in institutional places, such as schools and day-nurseries, and waterborne epidemics in places where people live in conditions of overpopulation and low sanitary conditions (KUMAR, ABASS *et al.* 2013).

The diagnosis of the disease is based on the search of specific antibodies in the patient's serum. The presence of anti-HAV IgM defines acute hepatitis and may disappear after 3 months of infection. The anti-HAV IgG marker is present in the convalescent phase and persists indefinitely, providing specific immunity (PEREIRA and GONÇALVES 2003, SILVA, VITRAL *et al.* 2007).

The main method used to perform these antibodies search is the enzyme-linked immunosorbent assay (ELISA), which is based on the antigen-antibody reaction (SILVA, VITRAL *et al.* 2007, STEPHENS, OLIVEIRA *et al.* 2010).

Currently, there are already two types of vaccines against HAV, composed of attenuated viruses or inactivated viruses (OGHOLIKHAN and SCHWARZ 2016). This vaccination is very important, with a high degree of safety (95% to 100% of seroconversion in healthy individuals), being able to avoid the spread of the disease in the period of outbreaks (CLEMENS, FONSECA *et al.* 2000). In Brazil, the vaccine is not yet included in the vaccination schedule of the Ministry of Health presenting high cost, but it is available free of charge to special groups at the Special Immunobiological Reference Centers (CRIES). In addition to the vaccine, long-term safe water supply in the home also reduces the spread of the disease (FERREIRA and SILVEIRA 2004).

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3.2. HEPATITIS B

Hepatitis B virus (HBV) is a DNA virus and belongs to the *Hepadnaviridae* family. The surface antigen HBsAg is embedded in the lipid envelope (Fig. 1B) (HOWARD 1986). This virus has a prolonged incubation period (4 - 26 weeks) and, unlike HAV, it is transmitted by the blood during the active phases of acute and chronic hepatitis (KUMAR, ABASS *et al.* 2013). Moreover, cases of transmission have already been reported after dental procedure (LEVIN, MADDREY *et al.* 1974, ITHARATANA 1988), transplantation (DICKSON, EVERHART *et al.* 1997), perinatal transmission (VAN ZONNEVELD, VAN NUNEN *et al.* 2003) and even endoscopy (BIRNIE, QUIGLEY *et al.* 1983). However, nowadays, transmission by blood transfusion is rare, since the serology for HBV is included during blood donor screening tests (STEVENS and LOWE 2002). In addition, the spread of the virus can be performed through vertical transmission through exudates, semen, vaginal secretion and saliva. In contrast, the viruses are not found in feces and urine (FERREIRA 2000, STEVENS and LOWE 2002, LOK and MCMAHON 2007, FRANCISCO, DONALISIOI *et al.* 2015).

Among adult patients infected with HBV, about 10% progress to the chronic stage of the disease. However, most of the newborns from infected mothers present the chronic disease due to an immature immune system (STEVENS,LOWE,2002).

The HBV is mainly diagnosed by the ELISA method. However, molecular techniques for detecting viral DNA can be performed (*e.g.* polymerase chain reaction – PCR), which can amplifies the viral nucleic acid, allowing to detect small amount of viral particles (ABE, INOUE *et al.* 1999, FERREIRA 2000, STEPHENS, OLIVEIRA *et al.* 2010).

The HBV circulates in high concentrations in blood and in minimal amounts in other fluids. It is considered approximately 100 times more infectious than the human immunodeficiency virus (HIV) and 10 times more infectious than the hepatitis C virus (HCV). According to these data, vaccination is the most effective method of prevention (90 -95% response in healthy adults). Nowadays, the HBV vaccine is composed of HBsAg virus subunit. In Brazil, it is mandatory and free of charge, with the first dose recommended after 24 h of birth (FERREIRA and SILVEIRA 2004, VRANJAC 2006).

3.3. HEPATITIS C

Hepatitis C virus (HCV) is a RNA virus encased in an envelope belonging to the *Flaviviridae* family. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope (OP DE BEECK and DUBUISSON 2003) (Fig. 1C). The VHC incubation period ranges from 2 - 26 weeks (KUMAR, ABASS *et al.* 2013), following the acute phase with fever, malaise, anorexia and jaundice (STEVENS and LOWE 2002). Some patients present asymptomatic acute phase, which contributes to the chronicity of the disease and increase the number of asymptomatic chronic individuals. This stage is characterized by immunological window, and it is the moment in which the transmission of the virus mainly occurs (STRAUSS 2001, SHEPARD, FINELLI *et al.* 2005).

Hepatitis C originates from HCV infection and is an important cause of chronic liver disease (SHEPARD, FINELLI *et al.* 2005, KUMAR, ABASS *et al.* 2013). In addition, this liver damage can progress to cirrhosis and hepatocarcinoma, and it is also considered one of the main

causes of liver transplantation (DICKSON, EVERHART *et al.* 1997, HANAFIAH, GOEGER *et al.* 2013, CHARLTON, GANE *et al.* 2015, MESSINA, HUMPHREYS *et al.* 2015).

Approximately 90% or more of post-transfusion hepatitis are caused by HCV and, since 1993, blood donors perform mandatory serological tests. However, other contaminations sources continue to spread the virus, such as medical, dental, acupuncturist, manicure, tattoo and drug users. In this way, all cutting materials can transmit the virus (STRAUSS 2001, SHEPARD, FINELLI *et al.* 2005). In non-parenteral forms of hepatitis C transmission, there is the possibility of sexual transmission, interfamilial dissemination through sharing of sharp materials or exposure of open wounds. On the other hand, maternal-fetal transmission is irrelevant in hepatitis C, with the exception of some transmissions during the childbirth (JAECKEL, CORNBERG *et al.* 2001, STRAUSS 2001, TOHME and HOLMBERG 2010).

The diagnosis is performed through serological methods and molecular biology techniques. There are two types of serological tests commonly used, the high sensitivity ELISA and the recombinant immunoblot assay (RIBA), which is of greater specificity. Both methods seek antibodies against HCV (anti-HCV), thus verifying acute or chronic infection (BRANDÃO, FUCHS *et al.* 2001, GHANY, STRADER *et al.* 2009). Molecular biology techniques are very useful for determining the infection in specific situations. PCR is most used, being a specific method that amplifies part of the genome of the virus (STRAUSS 2001).

The quantification of viral load and the identification of the HCV genotype helps to determine the duration of treatment of chronic hepatitis (BRANDÃO, FUCHS *et al.* 2001). To date there is no vaccine available against HCV, (STRAUSS 2001, FERREIRA and SILVEIRA 2004, HOUGHTON and ABRIGNANI 2005, GHANY, STRADER *et al.* 2009).

3.4. HEPATITIS D

Hepatitis D, originally known as hepatitis delta, is caused by hepatitis D, belonging to *Deltavirus* genus, without family assigned (HDV) (Fid. 1D). The HDV is composed of nucleocapsid with single-stranded circular RNA and about 200 molecules of hepatitis D antigen or delta antigen (HDAg) (POISSON, ROINGEARD *et al.* 1993). However, the manifestation of the disease is only possible in the host combined with the presence of the VHB (STEVENS and LOWE 2002, FONSECA 2010, KUMAR, ABASS *et al.* 2013).

HDV transmission occurs similar to the HBV infection, being prevalent among drug users and among patients undergoing dialysis. Rarely the chronic phase of the disease disappears and, in general, about 60% of the affected patients develop cirrhosis (FONSECA 2002, STEVENS and LOWE 2002).

Hepatitis D can manifest in two contexts: coinfection and superinfection with HBV. When the coinfection with HBV is observed, the course of the acute disease is severe, but the risk of progressing to chronic disease is low. In cases of superinfection (patients with chronic hepatitis B) there is a chronic evolution and an increased risk of severe chronic liver disease (FONSECA 2002, SILVA, VITORINO *et al.* 2012).

Infection of HDV is confirmed by the detection of HBsAg (hepatitis B surface antigen), total anti-HBc (antibodies that recognize the core of HBV) and total anti-HDV (IgM and IgGantibodies against HDV) (SILVA *et al.*, 2012). In addition, the genetic material of the virus can be found in the blood and liver very early, during the first days of the acute phase (KUMAR, ABASS *et al.* 2013). A vaccine against hepatitis B is the only method to prevent HDV infection.

3.4. HEPATITIS E

The hepatitis E is caused by the infection with the virus of hepatitis E (HEV), a single-stranded non-enveloped RNA icosahedral virus Hepeviridae family (Fig. 1A). Its transmission occurs via the fecal-oral route, with water being the most responsible for contamination (PARANÁ and SCHINONI 2002, STEVENS and LOWE 2002, HOOFNAGLE, NELSON *et al.* 2012, MACEDO, SILVA *et al.* 2013). The median of the virus incubation period is approximately 6 weeks. Patients normally present mild disease characterized by jaundice (STEVENS and LOWE 2002).

The disease affects mainly young adults or middle-aged individuals, with sporadic infections in children. However, there is a high mortality rate among pregnant women, a result of acute fulminant hepatitis (HOOFNAGLE, NELSON *et al.* 2012, KUMAR, ABASS *et al.* 2013).

The diagnosis is performed by the investigation of antibodies IgM and IgG against HEV, thus determining acute and chronic infection (HOOFNAGLE, NELSON *et al.* 2012). So far, a vaccine for VHE is not available, although some studies have been conducted. However, additional studies are still necessary before the vaccine could be licensed (HAFFAR, BAZERBACHI *et al.* 2015, OGHOLIKHAN and SCHWARZ 2016).

3.5. IMMUNNE SYSTEM RESPONSE AGAINST THE VIRAL INFECTION

Humans, under homeostatic conditions, have a variety of cells and molecules responsible for the recognition of self and non-self structures. These cells and molecules constitute the immune system, which has the role to produce a response to foreign antigens (MEDZHITOV and JANEWAY 2002, PEAKMAN and VERGANI 2011, ABBAS, LICHTMAN *et al.* 2015).

Immunological responses are represented by components of innate and acquired immunity. Innate immunity is characterized as the first line of defense against microorganisms. They are most useful in protection against purulent microbes(pyogenic), fungi and multicellular parasites. The granulocytes, the complement system, the reticuloendothelial system, the natural killers (NK) cells, among others, are important cellular components of this immunity (COELHO-CASTELO, TROMBONE *et al.* 2009, CRUVINEL, MESQUITA JR *et al.* 2010, PEAKMAN and VERGANI 2011, RANSOHOFF and BROWN 2012). Acquired immunity is a specific response, developed throughout life, after direct or indirect contact with antigens capable of activate the immune system. Its components include B and T (CD4+ and CD8+) lymphocytes, which lead to the development of the humoral and cellular immune response, respectively (AKIRA, TAKEDO *et al.*

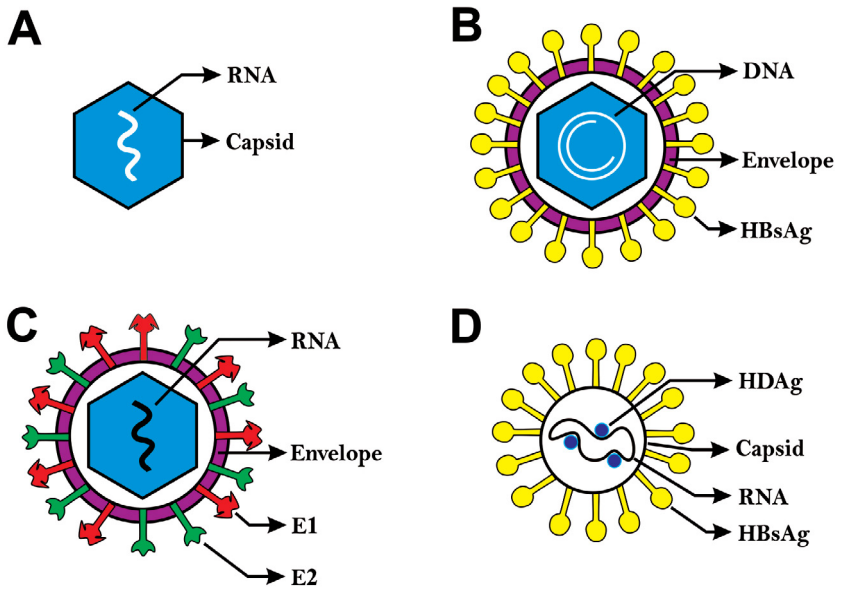

Figure 1. General structure of hepatitis viruses. (A) Hepatitis A and E viruses - HAV and HEV**. (B)** Hepatitis B virus - HBV. **(C)** Hepatitis C virus - HCV. **(D)** Hepatitis D virus - HDV.

2001, AKIRA, UEMATSU *et al.* 2006, MESQUITA JR, ARAÚJO *et al.* 2010, ABBAS, LICHTMAN *et al.* 2015).

The viruses are obligate intracellular microorganisms that replicate within cells, infecting diverse cell populations, using normal cell surface molecules as receptors to infect the cell (DELVES, MARTIN *et al.* 2013, ABBAS, LICHTMAN *et al.* 2015). The viral genome can be composed of DNA molecules, RNA or both. Among the viruses that cause hepatitis A, B, C, D and E, only HBV has DNA genetic material (STEPHENS, OLIVEIRA *et al.* 2010).

DNA viruses perform viral synthesis in the nucleus of the host cells and RNA viruses in the cytoplasm. The viral replication process interferes with the production and function of normal cellular proteins (NAGY and POGANY 2012). This mechanism is due to the cytopathic effect of the virus, which the infected cell is lysed. Non-cytopathic viruses leave the viral genetic material in the host cells and may cause latent infections, producing proteins that may or may not modify cellular functions (ABBAS, LICHTMAN *et al.* 2015).

When the organism is confronted with this infectious process, the components of innate and acquired immunity are activated to defend the host (DELVES, MARTIN *et al.* 2013). Initially, viruses encounter the barriers of the innate immune system, which acts "nonspecifically" against the invading agent. In this phase the role of type I interferons and NK cells are very important. Interferons are produced by infected cells and present the ability to protect uninfected cells besides to contribute to the development of the acquired immune response (MACHADO, ARAÚJO *et al.* 2004). At the same time, interferons induce the major histocompatibility complex class I (MHC-I) proteins to recognize the viral antigens by the immune system, activating the T CD8+ response and NK cells, aiming at the destruction of infected cells and consequently preventing viral replication. Moreover, along with other cytokines (*e.g.* IL-12), interferons can activate Th1 response (ABBAS 2012)

Therefore, after the activation of the acquired immunity, the immune response is also mediated through antibodies and T CD8+ lymphocytes (cytotoxic) (MESQUITA JR, ARAÚJO *et al.* 2010, PEAKMAN and VERGANI 2011). The B lymphocytes differentiate into plasma cells, which secrete antibodies, and these molecules are effective in destroying the virus during the extracellular stage. The antiviral antibodies act as neutralizing antibodies, by binding to the viral envelope or capsid antigens, thereby preventing entry of the virus into the host cell. In addition, the antibodies have the ability to opsonize viral particles and contribute to their elimination through phagocytosis (ABBAS, LICHTMAN *et al.* 2015).

The CD4+ (helper) T lymphocytes also play an important role in virus elimination. Viral antigens can also be expressed on the surface of APCs by MHC class II molecules through a mechanism named cross-presentation (HEATH and CARBONE 2001). From this moment on, the helper lymphocytes (most Th1 differentiated by interferon) act on the secretion of cytokines, which stimulate the production of antibodies by B lymphocytes, as well as the production of the cell-mediated immune response (ABBAS, LICHTMAN *et al.* 2015).

3.6. PARTICULARITY OF THE IMMUNE SYSTEM DURING HEPATITIS

The Th1 and Th2 response levels during hepatitis extremely related to disease progression/control. Th1 cells produce the cytokine IFN-γ and are regulated by the production of IL-12 via the Tbet transcription factor, being important for the immune response against intracellular pathogens. Th2 cells produce IL-4, IL-5 and IL-13 cytokines and are regulated by the transcription factor GATA3, being important for response to parasites, allergens and Th1 response control (ZHU, YAMANE *et al.* 2010, ABBAS, LICHTMAN *et al.* 2015). In hepatitis C, the imbalance of Th1-Th2 has demonstrated to be responsible for liver cirrhosis and, consequently, hepatocellular carcinoma. The authors shown that the patients that present a Th2

response developed cirrhosis and a chronic progression (SAKAGUCHI, KAYANO *et al.* 2001).

The regulatory T cells or Tregs (CD4+CD25+Foxp3+) are also involved during viral hepatitis. Tregs are specialized T cell population that suppresses the effector functions of many cells of the immune system such as T, B, NK and dendritic cells (SHEVACH, DIPAOLO *et al.* 2006). In general, patients that presents chronic and chronic severe hepatitis present high population of Treg cells, which decrease the elimination of the virus (XU, FU *et al.* 2006, EBINUMA, NAKAMOTO *et al.* 2008). Using VHB infection, the role of Tregs cells were elucidated. Its is known that the most important cytokine that differentiates Tregs cells is TGF-β (FANTINI, BECKER *et al.* 2004). In the liver, the main source of this cytokine is the hepatic stellate cells (HSCs) (ICHIKAWA, MUCIDA *et al.* 2011). The chronic infection with HBV can induces HSCs cells to produce high amounts of TGF-β and, consequently, increases the conversion of Treg cells (JUNG and SHIN 2016). The immunosuppression induced by Tregs triggers the inhibition of Th1 and T CD8+ response which can led to hepatocellular carcinoma (WANG, XI *et al.* 2017).

The cytokines that demonstrated to be important during viral hepatitis are interferon alpha and tumor necrosis factor alpha.

Cells produce interferon alpha (IFN-α) when they detect viral infection. It triggers the production of proteins that block viral replication as well as breaks the production of proteins that viruses need to replicate (ABBAS, LICHTMAN *et al.* 2015). Therefore, for more than 20 years, interferon-alpha (IFN-α) is used in patients with B, C and D chronic hepatitis (HOOFNAGLE 1994, ZEIN 1998). It is the only licensed immunomodulatory drug with also inhibition of virus replication (CASTET, FOURNIER *et al.* 2002). Moreover, it does not induce drug resistance and presents a higher likelihood for HBsAg clearance (PERRILLO 2009).

The tumor necrosis fator apha (TNF-α) is involved in inflammation and immune regulation, along with cellular differentiation and proliferation. It recruits neutrophils and monocytes at sites of infection, is a pyrogenic molecule (indices fever) and induces the production of acute phase proteins. At low concentration, it is important for eradication of the virus with minimal damage (antiviral activity). Nevertheless, when there is an overproduction, the outcomes can be harmful and be responsible for the infection persistence, especially during VHB infection (BIERMER, PURO *et al.* 2003, ABBAS, LICHTMAN *et al.* 2015, VALAYDON, PELLEGRINI *et al.* 2016, XIA, STADLER *et al.* 2016). The therapy using immunosuppressant anti-TNF-α inhibitors has been used for patients with hepatitis B which present genetic variants and do not respond to IFN-α therapies (TANAKA 2016).

4. CONCLUSION

Viral hepatitis is considered a public health problem worldwide. The disease is characterized by liver cells inflammation, caused by viruses presenting hepatotropism. The immune system is directed related to the viruses elimination, presenting some particularities. The determination of the etiological agent is essential for the treatment of the infected individual, especially for the cases that can develop hepatocellular carcinoma. Moreover, in case of HAV and HBV, vaccination is the best way for preventing infection.

CONFLIT OF INTEREST

The authors declares that there is no conflict of interest regarding the publication of this paper.

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