Scientific evidence on hepatitis Delta in Brazil: integrative literature review

Evidências científicas sobre a hepatite Delta no Brasil: revisão integrativa da literatura

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Keywords
Hepatitis D; Hepatitis B; Brazil

Descritores
Hepatite D; Hepatite B; Brasil

Abstract
Objective: Describe the level of scientific evidence on infections by the hepatitis Delta virus (HDV) in Brazil.

Methods: Integrative literature review, with research in the databases of the Medical Literature Analysis and Retrieval System Online, Latin American and Caribbean Center on Health Sciences Information, Scientific Electronic Library Online and Scopus, with analysis focusing on the leveling of the methodological rigor according to the model of Melnyk and Fineout-Overholt.

Results: The search revealed an average of two publications a year between 1987 and 2017. We selected 33 articles, the majority (91%) presented level of evidence VI. The publications were concentrated in the area of tropical medicine (46%) and virology (15%). The authors of 85% of the studies were medical professionals and the most common design was the descriptive/cross-sectional (69.6%).

Conclusion: Scientific literature on HDV infections in Brazil is focused on prevalence studies, showing incipience regarding the production of studies with stricter guidelines, such as clinical trials.

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DOI
http://dx.doi.org/10.1590/1982-0194201700091

Submitted
November 8, 2017

Accepted
December 4, 2017

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Conflict of interest: Fram DM is associate editor of the Acta Paulista of Nursing and did not participate in the evaluation process of the manuscript.
Introduction

By analyzing the serum of patients infected with the hepatitis B virus (HBV), the Italian researcher Mario Rizzetto described a new antigen-antibody system in the 1970’s, the system was named antigen/antibody Delta. (1) Subsequent studies revealed that the discovery was not of another component of HBV, but of a new virus: the hepatitis Delta virus (HDV). (2)

The HDV needs the HBV to infect humans, because it uses the surface antigen (HBsAg) on the process of pathogenesis. (2) The viral structure is composed by a single-stranded ribonucleic acid (RNA) (3), measuring between 35nm and 37nm, it produces two antigens of known clinical importance: the small Delta antigen (HDAG-S), which acts in the process of viral replication, and the large Delta antigen (HDAG-L) which, through the interaction with HBsAg, acts on the assembly of RNA. (4)

HDV infection occurs by parenteral exposure and is considered a co-infection when it occurs on the primary or acute phase of HBV infection and as a superinfection when it occurs in chronic hepatitis B. (2)

The interaction between the HDV and HBV is not fully understood yet, especially due to the fact that both viruses compete for HBsAg to assemble new viral structures. (5) Furthermore, studies indicate that the HDV is related to the early development of serious conditions of hepatic diseases, such as: Cirrhosis, hepatocellular carcinoma (HCC) and fulminant hepatitis. (6,7)

The hepatitis cases caused by HDV associated with HBV represent a serious worldwide public health problem, generating continuous demands to health services, in addition to considerable losses in the quality of life of infected patients, also showing high mortality rates. (8)

This kind of infection is distributed around the globe; HBV, the required element for HDV infection, is estimated to have already infected 2 billion individuals worldwide, of which 300 to 400 million are chronic carriers and 15 to 20 million are infected with the HDV (2,9), with an annual number of deaths estimated between 620,000 and 1 million. (10)

The HDV has worldwide distribution with variable prevalence. Two countries of Central Europe, Romania and Hungary, present, respectively, 47.6% and 13.9% of patients with positive HBsAg infected with HDV. West and central Africa, present infection ranging from 1.3% in Nigeria to 66% in Gabon. 20% of patients with positive HBsAg in Egypt are infected. In Asia, the prevalence reaches 66.7% in Taiwan and 82% in Mongolia. (4) The distribution in South America is variable, but high indicators are found across the entire Amazon basin, especially in the Western Brazilian Amazon, where the seropositivity to HDV can reach up to 85% of patients with positive HBsAg in some communities. (4,8,11)

Dating back to the mid-18th century, historical accounts record deaths of members of the French Royal Academy of Science by a disease described acute icteric fever, during an expedition through the Amazon River, in Brazil. (12) During the second half of the 20th century, studies describe a serious icteric condition, of rapid evolution and with death records of five days after the initial symptoms in the city of Lábrea, in the interior of the state of Amazonas. The condition was initially named as Labrea black fever, (13) but the cases were investigated and in 1987 it was confirmed that the Labrea black fever was, in fact, fulminant hepatitis caused by infection of the HDV in patients with HBV. (14)

Nowadays, despite the infection being recorded throughout the Brazilian territory and 77% of the cases occurring in the northern region, researchers claim that despite the high endemic indicators of HDV infection, the condition is neglected by health services. (15)

Given the Brazilian context, resources available from the Brazilian Unified Health System and recognizing HDV infection as a major public health problem, the objective of this study was to, through an integrative review: describe the level of scientific evidence on HDV infection in Brazil to provide awareness on the theme to health professionals and public administrators, as well as serving as a parameter of good research and assistance practices for the development of health policies.
Methods

Integrative literature review with the theme “level of scientific evidence on HDV infection in Brazil” between the years of 1987 and 2017. The search was performed in September 2017 and went through six methodological steps, according to criteria outlined in national and international scientific literature (Figure 1). (16-19)

The first stage was to elaborate the guiding question: “what is the level of scientific evidence on HDV infection in Brazil?”. Then, we set the keywords according to the Health Sciences Descriptors (DeCS) and the Medical Subject Headings (MeSH), they are: Hepatitis D; Hepatitis B and Brazil.

On the second stage we defined the databases for searching and the eligibility criteria. For this, were considered eligible the scientific articles found through the descriptors defined on the first step, published in English, Portuguese and Spanish, the search was restricted to the Brazilian territory, the approach focused on hepatitis D or HDV and abstract available in the following databases: Medical Literature Analysis and Retrieval System Online (Medline), Latin American and Caribbean Center on Health Sciences Information (LILACS), Scientific Electronic Library Online (SciELO) and Scopus (Elsevier).

For the third stage we considered the formulation of a framework proposed by Souza, Silva and Carvalho (19) to organize the database and present the results (Chart 1), in addition to the classification of evidence models based on the model of Melnyk and Fineout-Overholt (20).

Evidence from systematic review or meta-analysis of all relevant randomized clinical trials controlled or from clinical guidelines based on systematic reviews of randomized controlled clinical trials:

I- Evidence from at least one controlled and well-designed randomized clinical trial;

II- Evidence from clinical trials well designed without randomization;

III- Evidence from well-designed cohort and case-control studies;

IV- Evidence from systematic review of descriptive and qualitative studies;

Figure 1. Methodological stages of the research
<table>
<thead>
<tr>
<th>Reference</th>
<th>Thematic considerations</th>
<th>Type of study</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botelho-Souza LF, Souza Vieira D, de Oliveira dos Santos A, Currin Pereira AV, Vilabos-Salcedo JM. Characterization of the Genotypic Profile of Hepatitis Delta Virus: Isolation of HDV Genotype-1 in the Western Amazon Region of Brazil. Interdisciplinary. 2015; 59(3):166-71.</td>
<td>Assesses the genotypic and clinical characteristics of individuals with the genotype 1 HDV in the Western Brazilian Amazon</td>
<td>Case-control study</td>
<td>IV</td>
</tr>
<tr>
<td>Crispim MAE, Fraiji NA, Campello SC, Schriefer NA, Stefani MMA, Kieschel D. Molecular epidemiology of hepatitis B and hepatitis delta viruses circulating in the Western Brazilian Amazon region, North Brazil. BMC Infect Dis. 2011; 14:94.</td>
<td>Describes the genotypes of HBV and HDV in the Western Brazilian Amazon</td>
<td>Cross-sectional study</td>
<td>VI</td>
</tr>
<tr>
<td>Nunes HM, Monteiro MRCC, Soares MGP. Prevalência dos marcadores sorológicos dos vírus das hepatites B e D na área indígena Apyterewa, do grupo Parakanã, Pará, Brasil. Cad Saúde Pública. 2007; 23(1):2756-66.</td>
<td>Studies the prevalence of HBV and HDV among the indigenous ethnicity Parakanã and assesses the impact of vaccination against hepatitis B starting in 1995 in the Apyterewa village in the state of Pará, Brazil</td>
<td>Cross-sectional study</td>
<td>( descriptive)</td>
</tr>
<tr>
<td>Oliveira MS, Silva RPM, Vallee SCN, Figueiredo EN, Fram D. Chronic hepatitis B and D: prognosis according to Child-Pugh score. Rev Bras Enferm. 2017; 70(5):1048-53.</td>
<td>Compares patients with chronic hepatitis B to patients superinfected by the D virus according to the Child-Pugh score</td>
<td>Cross-sectional study</td>
<td>( descriptive)</td>
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<td>continue</td>
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The selected studies are summarized (Chart 1), considering information such as title, author(s), journal in which it was published, thematic considerations and the classification of the level of evidence.

The studies analyzed (Chart 1) were organized to facilitate the better reading of the results. The selected studies were published between the years of 1987 and 2017; there were no studies selected for the years 1993, 1997, 1998, 2003, 2010, 2013 and 2016. We observed an average publication of two studies per year on the other years, and 2014 presented the greater volume of publications, with four studies.

Observing the academic training of the main author of the study, 85% of the studies were from medical professionals, 6% from biomedical professionals, 3% from nurses, 3% from pharmacists/biochemists and 3% from biologists.

The research were published in eight categories of journals, 46% of the area of tropical medicine, 15% of the area of virology, 12% of the area of infectious diseases, 9% of the area of medical sciences, 9% of the area of public health, 3% of the area of hepatology, 3% of the area of nursing and 3% of the area of biomedicine.

Regarding research design, 69.6% were cross-sectional studies, 15.2% were literature re-
views, 6.1% were case-control studies, 6.1% were case reports and 3% were clinical trials.

By classifying the level of evidence according to the method adopted, we observed that: 91% of the studies were of type VI, i.e., evidence derived from a single descriptive or qualitative study; 6% were of type IV, evidences from well designed cohort and case-control studies; and 3% of type III, i.e., evidences from well designed clinical trials without randomization.

**Discussion**

The result of this integrative review depicts the scientific production on HDV infection in Brazil over the past three decades, and, despite being a major cause of severe complications of hepatic disease in patients with hepatitis B and variable distribution, with areas of high prevalence on the country, the results demonstrate a discrete scientific production.

Of the studies identified in this review, 91% correspond to the level of evidence VI, i.e., studies with descriptive cross-sectional design, most of them focused on the analysis of prevalence, resulting on a low level of evidence.

The main areas of production are concentrated in tropical medicine journals. Brazil is a tropical country and still bears a high burden of communicable diseases. Although advances on the control of vaccine-preventable diseases and HIV infection are seen on the last two decades, infectious diseases still constitute a serious public health problem in the country.

Most studies, 85%, have a medical professional as the primary author, although it is a theme inherent to the practice of medicine, due to the need for scientific research to produce good clinical practices; other areas of the multidisciplinary field of health hold equal importance on the need for scientific production as a guiding mechanism for the improvement of care, especially when preventable harms, such as hepatitis D, are considered, an argument that contrasts with researchers who claim, for example, that the scientific production of nursing is still incipient in Brazil.

However, initiatives such as the national program for the prevention and control of viral hepatitis, which seeks the systematization of the programmatic actions in health, providing the nursing professional with protagonism and autonomy to manage care on the three levels of health care. Due to the professional assignment, there is interest in constructing health strategies from new knowledge, both in care and adequacy of public policies.

The World Health Organization recognizes the HBV infection, a necessary condition for the HDV infection, as a public health problem that requires urgent response, reiterating the importance of prevention, particularly through vaccine strategies, this highlights the importance of the nurse as a transforming agent in this health-disease-curing process.

However, to evaluate the quality of scientific production in health it is necessary to consider the structural and promotion conditions existing in Brazil for higher ranked classifications. This goes beyond the theme of this integrative review. Stimulating undergraduate research was only implemented in Brazil in 1988 and despite the advances in recent decades, the Brazilian scientific production faces obstacles regarding the quality of the studies produced, something directly related to the scarcity of resources.

Additionally, when the object of analysis is a theme like HDV infection, aspects related to the quality of care and to the rational use of resources, both in the public and private sectors, end up exerting pressure on health professionals who lack contextualized scientific evidence for better performance practices.

The production of scientific evidence, such as meta-analytic reviews or randomized clinical trials, does not exclude the importance of descriptive studies and the value of personal experiences, but evidences to care for patients subject to the evolution to severe conditions, such as those infected with HDV, are of fundamental importance to make the best clinical decisions. However, we note that all of the epidemiological studies and the data on
information systems must be used to understand hepatitis B and D in the country, and to support the development of individual and collective interventions that minimize the influence of the disease on the population.

Despite the importance of study reviews to synthesize research results or even the production of relevant research, actions must go beyond simply stimulating scientific production, but fundamentally, using the results of these studies as transforming elements in clinical practice.⁶⁰

Conclusion

We conclude that the scientific literature on HDV infection in Brazil is centered on research with descriptive/cross-sectional design, being incipient on studies with higher levels of evidence. This information points to the need for further research focused on the definition of risk factors, drug and therapeutic analysis and the effectiveness of prevention and control programs, to sustain the adoption of innovations in public policies and healthcare.

Collaborations

Oliveira MS, Valle SCN, Souza RM, Silva RPM, Figueiredo EM, Taminato M e Fram D contributed to the design of the manuscript, in writing the study, with critical and relevant review of the intellectual content and with the approval of the final version to be published.

References


