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From hepatic diseases and jaundice to viral hepatitis: the configuration of a kaleidoscope

ABSTRACT

Viral hepatitis A, B, C, D and E – systemic hepatotropic viral infections – present as acute hepatitis that, depending on the etiological agent, viral load and host conditions, may evolve into chronic hepatitis, cirrhosis, liver cancer and acute fulminant disease. The ecological versatility of these viruses, their spectrum of transmission in time and space, potentialized by the sub-clinical course of a large proportion of infections, comprise an epidemiological challenge. This essay describes scenarios and tendencies in the socioepidemiologic profile, based on the history of these infections, and indicates the need to overcome patterns, models, and protocols and instead investigate each particular situation. In other words, it highlights the need to explore singularities in order to be able to develop new proposals for general actions tailored to local specificities

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INTRODUCTION

Hepatitis viruses (HV) are a group of systemic hepatotropic viral infections which can produce acute hepatitis (symptomatic or asymptomatic). Depending on the etiologic agent, the viral load and the conditions of the host, they can develop into chronic hepatitis, cirrhosis, cancer of the liver and acute fulminant forms. Their hepatotropism and similar clinical manifestations lead the etiological agents of the HV to be grouped into the same pathophysiological classification, in spite of their being caused by viruses conventionally designated by letters of the alphabet – A, B, C and E – belonging to the *Picornaviridae, Hepadnaviridae, Flaviviridae, and Hepeviridae* families respectively, and the defective hepatitis D virus to the *Deltavirus* genus. Each of them can spread in different ways and they can circulate simultaneously in the same place, with the nature and spectrum of transmission changing in time and space. This further complicates the task of designing campaigns for their prevention and control. The ecological versatility of these viruses, emphasized by the often prolonged subclinical course of infection constitutes a true epidemiological challenge.[1,14]

This article describes scenarios and trends, with the historical process of determining the HV as its central argument, based on a bibliographical revision of 162 theses from the Faculdade de Medicina da Universidade Federal do Rio de Janeiro from 1837 to 2000. The approach used aims to contribute effectively to planning public health campaigns by incorporating the wide spectrum of variables (known and assumed) which play a part in the propagation of these diseases.

THE PROCESSES OF DETERMINING THE HEPATITIS VIRUSES

New determinants and ways of spreading are added to those already well-established mechanisms of transmitting HV – fecal-oral, transfusion, sexual and vertical. Changes to the environment, to social behavior and technological risks have, over the centuries, contributed to a 'kaleidoscope' of etiologies and determining factors with peculiarities capable of producing combinations which are difficult to perceive and to understand.

Mosley[14] refers to the kaleidoscope of HV and resurrects a term coined by Winslow[21] (1908) in defending a model explaining typhoid fever. Winslow[21] named it "prosodemic typhoid?", arguing that this salmonellosis continued to circulate even after quality control of common sources of infection (mainly the water supply), because of it being spread "which spreads through or among the people by various channels, never reaching a large number at the same time, but passing from point to point by devious and various paths." Mosley[14:432] states that the concept of prosodemic infections "implies complex ecology", and that it is appropriate when discussing the behavior of hepatitis A and B, which took center stage in scientific discussions in the 1970s.

Although the term 'prosedemic' has fallen into disuse, the concept remains useful when approaching the current epidemiological complexity of HV. The 'complex ecology' added to the concept of prosedemic infection does not simply remain but amplifies.

HISTORICAL SCENARIOS

Studying health problems from a. historical perspective enables us to observe changes in epidemiological scenarios, and allows us to reinterpret the occurrence of these problems in the present. In the historical course of HV, taking the turn of the 19th/20th century as a starting point, it is possible to identify three epidemiological periods.

1º) From the dawn of the 20th century to the end of the 1950s: occurred sporadically or in the form of epidemics on diverse occasions in various regions. The majority of cases were probably caused by the hepatitis A (HAV) and hepatitis B (HBV) viruses, especially during and after the 2nd World War, and, possibly also by hepatitis C virus (HCV).[9,14,a]

2º) During the 1960s to the end of the 1970s: HA outbreaks became less frequent and incidence declined, mainly in industrialized countries, but also in the periphery countries.[14] HBV continued to circulate in areas of high endemicity where fulminant cases (isolated HBV or co-infections/super-infections with HDV) started to be identified and, among multi-transfused recipients such as hemophiliacs, became a significant cause of morbimortality in the following decades.[c] A new transmission route (sexual) for HB started to be observed with the appearance of oral contraceptives and greater sexual liberation.

3º) From the 1980s to today: HA took on an endemic-epidemic character and HB became endemic in the majority of the regions, HC and HE emerging as the tip of the epidemiological iceberg. While incidence of HC occurred between the 1960s and the mid-1980s, it began to be effectively diagnosed in the 1990s. This resulted in an increased prevalence due to identification of old (previous infections) undiagnosed cases.[10] The spread of HE (via fecal-oral transmission) is ongoing and is considered a zoonosis.[1]

[a] Fraga Filho C. Hepatite por vírus. Tese de concurso para professor catedrático da 3ª Cadeira de Clínica Médica. Rio de Janeiro: Faculdade de Medicina da Universidade do Brasil; 1952.

LIKE A KALEIDOSCOPE

In order to characterize the three historical scenarios, it is necessary to understand the natural history of the virus and the role determining factors play in the changing behavior of HV, like in a kaleidoscope.[2]

In the first period (1900-1959), HV were spread through blood, fecal-oral, sexual and vertical transmission and through occupational contact with non-human primates, although at the time this was not fully known.[14] This period, devastated by two world wars, was hailed for improvements in basic sanitation in developed countries, for the widespread use of passive and active immunization (e.g. against smallpox, yellow fever, plague, rabies) and massive blood transfusions in World War 2. Environmental improvements led to reductions in HA cases in industrialized countries,[14] but the multiple injections/infusions of potentially contaminated human biological material and the use of surgical instruments which were not sterilized sufficiently to eliminate viruses contributed to the spread of HBV and, possibly, to HCV.[10,a,b,c] Add to this increasing movement of people, the result of advances in shipping and aviation and of international commerce (e.g. food and biological products) and there is a possibility of exponential spread of different genetic lineages of viruses between continents.

In the second (1960-1979) period, identification of the Australia antigen, its use in blood donor screening and the (clinical and epidemiological) use of other serological markers of HB[d] enabled transmission via transfusion to be minimized. It also meant that the hidden depths of the 'epidemiological iceberg' could be brought to light and led to the suspicion that other viruses such as non A non B (NANB) hepatitis, transferrable through fecal-oral transmission and blood existed.[e] Significant changes in social behavior – increasing use of intravenous and inhalable drugs associated with sharing paraphernalia and sexual liberation without using condoms – facilitated the spread of HBV via parenteral and sexual transmission.[15]

Hemophiliacs glimpsed the possibility of improved survival through Factor VIII replacement therapy and HD was identified.[c] Meanwhile, medium and long-term adverse effects of medical technology from the previous period (immunization, blood transfusions) and the current (hemodialysis) period began to be seen: chronic hepatitis, cirrhosis and hepatic neoplasms.[b,c,f]

In the third period (1980 – 3rd Millennium), the development of bio-molecular technology enabled the etiology of NANB hepatitis transmitted via blood and fecal-oral transmission [HC virus and HE virus (HEV), respectively]. Better quality control of blood used in transfusions, driven in part by the AIDS pandemic,[9] meant that post-transfusion HB and HC became infrequent.[g] However, those who receive hemodialysis are the group of multi-transfused recipients at highest risk of these infections.[11,f]

Vaccination against HB and HA achieved a reduction in incidence among children in industrialized countries.[4,18] Immunization against H in children aged under one year showed a coverage of < 95% in areas where hepatitis B is highly endemic, such as the Brazilian Western Amazon in 2011.[h] This situation is reflected in the challenges for 2011/2012 listed by the Ministry of Health, such as reaching vaccine coverage of 100% among pregnant women, carrying out continuous campaigns aimed at reducing vertical HB transmission, guaranteeing vaccine coverage of 95% in the 15 to 19-year old and indigenous populations.[i] In other words, there are lower levels of cover in the regions with the highest prevalence and in social and ethnic groups at higher risk of the virus spreading. Meanwhile, in areas of low and moderate endemicity, the most common route for maintaining the horizontal chain of infection of HBV is through sexual contact,[4] an area in which progress has been moderate but steady, the magnitude of which will only be perceptible after a longer period of time.

Mutant HBV, which available vaccines do not prevent and, indeed, are partly responsible for, have meant a new public health approach is necessary, even considering the hypothesis of this being one of the elements which explains hidden HB. This hepatitis, only detectable by looking for HBV-DNA, can be transmitted by blood transfusion, hemodialysis and transplants, as donor screening and periodic monitoring of chronic patients is done by serologic tests.[7] This, still hidden, part of the iceberg is incorporated into the kaleidoscope of HVs

[b] Morgado A. Hepatite transmitida por gamaglobulina [dissertação de mestrado]. Rio de Janeiro: Faculdade de Medicina da UFRJ; 1975.
[c] Mello CEB. A prevalência da infecção pelo vírus da hepatite Delta (VHD) em hemofílicos HBsAg positivo: contribuição a seu estudo [dissertação de mestrado]. Rio de Janeiro: Faculdade de Medicina da UFRJ; 1988.
[d] Coelho HSM. Hepatites crônicas - diagnóstico e tratamento: estudo de 40 casos [dissertação de mestrado]. Rio de Janeiro: Faculdade de Medicina da UFRJ; 1981.
[e] Toledo JA. Hepatites não-A não-B: contribuição a seu estudo. Tese de concurso para Professor Titular do Departamento de Clínica Médica/ Gastroenterologia. Rio de Janeiro: Faculdade de Medicina da UFRJ;1984.
[f] Equi CMA. Estudo da incidência e dos fatores de risco nas hepatites por vírus B e C nos pacientes em tratamento de hemodiálise no HUCFF/ UFRJ [dissertação de mestrado]. Rio de Janeiro: Faculdade de Medicina da UFRJ; 1995.
[g] Coelho HSM. Detecção de anticorpos contra o vírus da hepatite C na prevenção da infecção pós-transfusional pelo vírus da hepatite C [tese de doutorado]. Rio de Janeiro: Faculdade de Medicina da UFRJ; 1998.
[h] Ministério da Saúde. Imunizações: cobertura. Brasília; 2012 [cited 2012 May 31]. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?pni/cnv/cpniuf.def
[i] Ministério da Saúde. Hepatites virais: desafios para o período de 2011 a 2012. Brasília (DF); 2010.

and its future socio-epidemiological impact is part of the history being constructed.

Controlling the viral load of HC and HB viruses by using antivirals is current, but technological advances and risks can sometimes go hand-in-hand. These drugs may provide an adaptive advantage so that mutations resistant to currently used antivirals appear.[5]

Dependent upon HBV, HDV's apparent restriction in circulation to regions or groups of intravenous drug use,[15] involves exploring possible explanations. In addition to unsafe practices regarding drug use, the mobility, origin and socio-demographic characteristics of the endemic regions and the groups of drug users in cities may be factors. The persistent presence of areas with higher HBV endemicity may guarantee the circulation of HDV, if not adding new links to the chain of infection without geographic or demographic limits.

With the issue of basic sanitation overcome, or at least minimized, and with the adult population tending to become progressively more susceptible, person to person contact is now considered the principal risk factor in HAV infection in developed areas. HA outbreaks are observed among hemophiliacs via transfusion; among intravenous drug users via blood; and among homosexual men via person to person contact through fecal-oral transmission, and these groups are vaccinated.[4]

A different, multi-faceted design is produced in countries such as Brazil, which is a socio-environmental mosaic when it comes to basic sanitation. The official HA vaccination strategy aims to protect individuals who are carriers of other diseases,[9] besides that recommended by pediatricians in the private health network.[19] Randomly vaccinated people, living alongside those with natural immunity and those who are susceptible in the Brazilian population, and the heterogeneity of the sanitation infrastructure, contribute to those who are susceptible delaying contact (into adulthood) with HAV. This means that person to person transmission remains dependent on multiple and uncertain factors.

The most interesting technological advance of the 21st century, as regards HV may be the identification of a mode of transmission. Applying molecular analysis enables the genotypes of the HE virus to be mapped and to observe their distribution according to diverse risk factors and epidemiological forms. Genotypes 1 and 2 are most frequently associated with epidemic forms and 3 and 4 with sporadic cases. Genotypes 1 and 2 are spread between humans through water, mainly in areas where basic sanitation is inadequate. Zoonotic propagation of genotypes 3 and 4, predominantly in areas with better sanitation conditions, is suggested by the occurrence of cases and outbreaks related to eating pork,[14] by the elevated prevalence of HEV antibodies in diverse animal species and by the isolation of homologous genome sequences among humans and animals.[1] Transmission by transfusion and vertical transmission are included in HEV transmission.[1] Although person to person transmission is not common, due to its versatility and it being widespread in industrialized countries, it is possible that it will continue to spread in this way.

Even with the diminishing potential for sexual and vertical HCV transmission, there have been reports of acute cases in which unsafe sexual practices are indicated.[4,12] Despite the facility with which this virus can be spread by parenteral transmission,[13] it is possible that it will maintain itself spreading from person to person randomly by various methods, rarely reaching a large number at the same time.

ECOLOGY OF VIRAL AGENTS

The 'creativity' in HVs' historical course shows that the viruses are more flexible in maintaining the species than the scientific certainties are. They have been the targets of diverse preventative campaigns, but as some risk factors and determining processes are controlled, others emerge. Its multiple, versatile mechanisms of transmission may lead to it spreading in unforeseen ways. HAV and HEV virus can keep themselves in natural reservoirs (biological filters), like molluscs, and be conveyed mechanically by insects. HBV and HCV can remain infectious on inert objects/surfaces for up to a week,[18] contributing to a new mode of transmission: that of invasive cosmetic procedures, such as removing the cuticle, piercings and tattoos.[10]

This 'creativity' seems to defy scientific and technological advances and instigate the constant evolution of the viruses. Blood transfusions avoided (and avoid) the deaths of millions of people, as in the 2nd World War and contributed to the spread of HB and HC and the emergence of AIDS. Scientific research and public policy resulting from these infections resulted in controlling spread by blood. The expansion in organ transplants also played an 'ecological role' in maintaining these viruses in circulation. Methods of prevention and control have been developed, and others need to be perfected or created. Fischer et al[6] indicate future advances such as the routine use of rapid biomolecular diagnostic tests in screening pre-transplant infections in donors and transplantees and in the early diagnosis and treatment of post-transplant infections.

HE epidemiology in infected animals contributes new knowledge on its determination processes. Pigs (at 2-3 months) show transient viremia of up to two weeks and the virus is eliminated in feces for between three and seven weeks, when they are "intensively handled, placed in different pens and are intensely exposed to agents coming from animals in other pens".[20] Thus, rather than consumers, it is perhaps those who work with the animals who are most exposed to HEV. Recognizing that HE may

be zoonotic makes the question increasingly complicated. As well as provoking massive epidemics and having high mortality rates (19%) in pregnancy, particularly in the 2nd and 3rd trimesters,[1] it can be spread unnoticed through its reservoirs' production and food chains. It is possible that an additional risk of HEV spreading will come into being through the increased chance of contamination from the ground (and, by extension, from vegetables) and from the water supply due to the increase in pig farming in Brazil's expanding agribusiness.[17] Even if this process is confined to large farms which are sensitive to market demands, it is necessary that sanitary conditions are observed when disposing of the waste of these animals.[17] HE markers are not currently used in clinical practice and in monitoring, i.e., in spite of scientific evidence, their epidemiological relevance is slowly revealed.

TRENDS AND MODELS OF APPROACH

The dynamic relationships between host, reservoir and etiological agent are well-known. The difference, in the case of HVs is that this dynamic is reproduced in infections which can: evolve unnoticed, have similar clinical manifestations and occur simultaneously in individual or collective ways.

An individual who is infected by HBV during hemodialysis may also have been infected by HCV and could pass them on to household contacts by sharing shaving gear or cuticle nippers. Cumulatively, HBV could then be transmitted to sexual partners. The way in which the viruses spread is more important in designing prevention programs than in identifying etiological agents. It is not enough to know how many cases of each etiology occur, but also the contribution of each and its potential for transmission.[14]

Data on passive notification of clinically manifested cases, i.e. the visible tip of the iceberg, are often not representative of the total, not just in volume of cases, but in their etiological specifics. Monitoring and control programs based on these visible cases may not reach the necessary effectiveness, as the unseen 'hidden depths' remain unknown. As the historical course shows, the invisible part of the iceberg may reproduce itself through other processes of determination, guaranteeing the circulation of viral agents and 'mocking' the prevention methods.

Monitoring the hidden depths – such as through vigilance centered in sentinel laboratories[8] – is one method of bringing these unknown infections to light. However, preventative measures based on actual data will continue to be limited to opportunities of the public health campaigns when faced with the epidemiological versatility of these diseases. Recognizing the importance of this epidemiological characteristic of HVs, another of the challenges proposed by the Ministry of Health for 2011/2012 is to establish sentinel monitoring in Public Health Laboratories, as has taken place in other disease control programs such as that for AIDS.[i]

The current challenge is to prevent these viruses from spreading through other means and, at the same time, maintain control campaigns aimed at the epidemiological of past infections. Measures for controlling the quality of water, blood/blood products, food and medico-dental and esthetic procedures and vaccination strategies for specific groups need to be constantly re-evaluated.

The Epidemiological tendency, based on historical scenarios, is for these viruses to continue to appropriate new ways of spreading. Modes so multiple that they make specific campaigns inappropriate. Health monitoring based on monitoring and projecting scenarios, in addition to the data on identified cases and risk factors, incorporating presumable determination processes and the residents' empirical knowledge of the place they live and its territorial singularities may make control of HVs more effective.

Developing preventative campaigns directed at production chains adds greater impact. Actions in the blood production chain (screening donors, blood product/derivatives production processes and even controlling recommendations for blood transfusions) has enabled control of the spread of diverse transfusion transmissible infections. Identifying possible vulnerabilities in the pork production process (from rearing to sale and distribution) may contribute to avoiding/reducing the possibility of swine-man HEV transmission (through animal feces to animal handlers), interrupting the man-to man fecal-oral transmission spread.

Technological and scientific advances in diagnosis, treatment and prevention are taking place. Public health strategies must not only incorporate these, but also consider the complexity and versatility of the HVs etiological agents when recognizing the existence of non A-E HV. Preventing these health problems demand different approaches which identify and act on the weak links of the chain of infection, aiming to interrupt them and promoting dialogue between the technical areas of control. Immediate actions are necessary, but effective control requires interventions in the process of social determination of health-disease targeted at the entire population and based on the principle of precaution.[3]

We speak of complexity, but act as if the spatial-temporal evolution of the disease were linear. On the other hand, epidemiological models which use only mathematical scientific knowledge or that of social sciences will remain of limited use. The more our knowledge of the epidemiology of HV advances, the more uncertainties are identified. It is necessary to overcome uncritical confidence in models, standards, protocols which seem to be definitively established

and return to the epidemiological investigation of each situation in order to identify new issues.

INFINITE AND INCONCLUSIVE COMBINATIONS

The kaleidoscope of HV follows its historical course, the social fabric of its mirrors reflecting an infinite combination of etiologies and modes of transmission which express the dynamics of these health problems and challenge the construction of new scientific knowledge. According to Aggarwal & Naik:[1]

"Nearly 10 years ago, we believed we had a good understanding regarding the distribution and epidemiology of hepatitis E, and that it was a disease predominantly restricted to developing world. However, since then, increasing numbers of autochthonous cases, zoonotic spread and chronic infection with possible progression to cirrhosis have been demonstrated in non-endemic areas. This has led to major shifts in our understanding of this filed and has generated intense new interest in this illness. It should therefore not be surprising if the additional data that accrue over the next few years lead to new and better understanding of this enigmatic form of viral hepatitis."

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