Chapter

Hepatitis A: How We Are after the Introduction of Vaccines

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Abstract

Hepatitis A is a disease known for a long time. It has a universal distribution, although it has a higher prevalence in places with poor sanitary conditions due to its main form of transmission: fecal-oral. The local health conditions also influence the age of acquisition of the disease and, therefore, its clinical presentation, because the disease in young children is usually asymptomatic. It is a viral disease whose prevention is possible through improvements in the population's basic sanitation conditions and vaccination. Since the introduction of vaccines, it has been possible to see a reduction in its incidence, especially in places where universal vaccination of children has been instituted. In recent years immunoglobulin therapy is being replaced by vaccination in pre- and postexposure prophylaxis (PEP), except in specific situations. Its incidence, even in developing countries, has decreased after introduction of hepatitis A vaccine. The vaccine is recommended in two doses for children, starting at the age of 1. Argentina and, more recently, Brazil have adopted the universal vaccination of all children upon completion of 12 months of age in a single-dose regimen. Despite this breakthrough isolated outbreaks in homeless and drug users are still described in developed countries.

Keywords: hepatitis viruses, classification, diagnosis, prevention, control

Key points

- Hepatitis A is a viral disease whose prevention is possible through improvements in the population's basic sanitation conditions and vaccination.
- The incidence, even in developing countries, has been reduced since the introduction of vaccines against hepatitis A.
- The vaccine is recommended in two doses for children, starting at the age of 1.
- Argentina and, more recently, Brazil have adopted the universal vaccination of all children upon 12 months of age in a single-dose regimen.

While dealing with hepatitis A diagnosis, be aware of the signs of acute hepatic encephalopathy, because although it is a rare complication, it may require hepatic transplantation.

1. Introduction

Hepatitis A is an acute viral disease caused by the hepatitis A virus (HAV), a picornavirus that infects only primates and has a low mutation rate compared to the other viruses capable of causing acute viral hepatitis [1–3].

The hepatitis A virus is transmitted by the fecal-oral route, either through ingestion of contaminated food [1] and water [4] or person-to-person contact. It has the ability to survive on surfaces for up to 60 days, and it is relatively resistant to alcohol and ether. As a result, the hygiene of bathrooms and toys in day care facilities must be meticulous [2, 5, 6].

The disease endemic character is related to poor sanitation conditions. That explains why its prevalence is higher in developing countries, where children generally become infected during the first years of life. That justifies the predominance of the asymptomatic form of the disease in such places [2].

Although it is related to inadequate sanitation conditions, there are records of the disease even in developed countries where the major concern is the people, mainly adults, who travel to exotic locations or developing countries. Besides that, some outbreaks due to food contamination are also described. Adult's disease, unlike the one that occurs in children, is symptomatic in 80% of cases [2]. Fortunately, since the introduction of vaccines, there has been a progressive decrease in the number of the cases of hepatitis A [7].

2. The virus

Hepatitis A virus (HAV) is one of the five etiological agents of viral hepatic inflammation (HAV, HBV, HCV, HDV, and HEV), whose incidence, according to the WHO, is sporadic and occurs in the form of epidemics around the whole world, which tend to present cyclical recurrences [8]. It belongs to the genus *Hepatovirus* that belongs to the family *Picornaviridae* [9].

2.1 Structure of the virus

HAV is described as being a naked virus; however, there is evidence that it can be released from a preinfected cell, through a non-lytic path, inside a small extracellular vesicle whose membrane surrounds the entire capsid and provides protection against the mechanisms of the host immune system [10].

The HAV presents as a genetic material a single-strand RNA with positive polarity, which confers the ability to act as messenger RNA (mRNA) and to interact directly with the ribosome to initiate the synthesis of the viral proteins. Its genome is divided in three parts [11]:

1. Noncoding region 5′UTR covalently linked to viral protein VPg [11]

2. A single open reading frame (ORF) subdivided into P1, which encodes the viral capsid proteins (VP1, VP2, VP3, and VP4), and P2 and P3, which encode nonstructural proteins that act during viral multiplication [11]

3. Noncoding region 3′UTR which has a poly-A tail [11]

2.2 Biological cycle

The HAV is transmitted through fecal-oral route; the individual becomes infected from the ingestion of water and food contaminated by fecal material from another individual who had been previously infected.

After ingestion, the virus falls into the blood vessels and, through the portal circulation, reaches the hepatocytes. The first contact occurs through the basolateral membrane of the hepatocytes in the space of Disse [9]. After the processes of adsorption, penetration, denudation, and synthesis of viral genome and viral proteins, the virus is assembled and released from the host cell through a non-cytolytic process and undergoes cell exocytosis [12]. This release can occur through the apical membrane of the hepatocyte, which will cause the new virus to go to the bile canaliculi and, consequently, be sent to the intestine along with the bile. In addition, the release can also occur by the basolateral membrane, which causes the virus to return to the bloodstream [10, 12].

After being sent to the intestine, the virus will be sent to the external environment through the feces. During excretion, a large amount of virus is eliminated. This starts about 10 days before the onset of clinical manifestations [13]. The period of greatest transmissibility occurs between the previous 15 days and 7 days after the onset of symptoms [4].

3. Pathogenesis

The immune response built by the host leads to the destruction of the hepatocytes infected by the virus and causes the appearance of the symptoms and signs of the disease. The HAV's slow replication does not appear to cause cytopathic effects [13].

It is possible that several mechanisms are involved in the development of signs of the disease. In one study fibroblasts and peripheral blood lymphocytes from patients with acute hepatitis A were used to demonstrate that the IFN-γ produced by HAV-specific cytotoxic T lymphocytes might play an important role in the pathogenesis of the disease [14].

Another analysis evidenced the presence of IFN-γ, TNF, IL-2, and IL-21 produced by polyfunctional CD4 + T cells. These results place the immune response modulated by CD4 + T lymphocytes as being more crucial in the control of HAV replication [15].

In contrast to studies that propose that adaptive immunity is more important in the pathogenesis and resolution of hepatitis A, it has been proposed that cells of the innate immune system, especially natural killer and lymphokine-activated killer (LAK) cells, play a crucial role in hepatic cell damage, which is inflicted prior to that performed by cytotoxic T lymphocytes [16].

In addition, there is an antibody-mediated response. HAV-specific immunoglobulin M (IgM) antibody and IgA antibodies can be detected, from the onset of the first clinical signs, in the patient's serum or plasma during the acute phase of the disease. IgG antibodies appear 1 week after the onset of the disease and can be detected for years even after healing. IgG can also be detected in vaccinated individuals. IgM and IgG immunoglobulins can neutralize the virus by recognizing epitopes of the HAV's structural proteins, VP1, VP2, and VP3, located in the capsid [17].

4. Epidemiology

The hepatitis A virus is distributed worldwide. However, the highest incidence of hepatitis A occurs in developing countries and in the ones with poor health conditions. In developed countries the disease acquired by traveler accounts for almost half of the cases reported.

The introduction of universal vaccination of children can change this general picture. The implementation of this program may reduce the rate of seropositive children against hepatitis A virus [18].

Luxemburger and Dutta show Brazil as a country with high endemicity of hepatitis A, meaning that more than 90% of children between 5 and 14 years old were seropositive for hepatitis A [19].

After that date there have been modifications in epidemiology of this disease. Checking the Epidemiological Bulletin of the Ministry of Health of Brazil in 2018, it's possible to notice that after 2007 the incidence rate of hepatitis A has shown a progressive tendency of falling, going from 7.1 cases to 1.0 per 100,000 inhabitants in 2017.

Between 1997 and 2017, most cases of hepatitis A occurred in children under 10 years of age (53.8%). In the last 2 years, there has been not only an increase in the incidence of the disease among people from 20 to 39 years of age but also a modification in the route of contamination. There was a significant reduction in cases related to food contamination and an increase in those related to sexual transmission. The incidence reduction preceded the universal vaccine. Universal vaccination of children from 12 months onwards was introduced in Brazil's vaccination calendar only in 2014 [20].

In relation to hepatitis A mortality in Brazil, between 2000 and 2016, there were 1125 deaths associated with viral hepatitis A. There is no data yet to compare mortality after the onset of the universal vaccine of Brazilian children [20]. Considering the distribution of deaths associated with all viral hepatitis in Brazil between 2000 and 2016 (66,196 obits), the proportion of obits was 1.7% associated with viral hepatitis A; 21.4% to hepatitis B; 75.8% to hepatitis C; and 1.1% to hepatitis D. In the document there is no report of viral hepatitis E [20].

Recently, the person-to-person HAV outbreaks involving people who use drugs or people experiencing homelessness are ongoing in United States, and this could signal a shift in HAV infection epidemiology in the United States [21].

5. Clinical condition

The virus's incubation period is long (15–50 days), and the first symptoms are non-specific and reminiscent of common viral disease. The following may be present: fever, malaise, headache, and abdominal pain. Eventually, jaundice, hepatomegaly, splenomegaly, and bradycardia can appear. The icteric phase has a variable duration, on average from 4 to 30 days, and is associated with dark urine and acholic stools. Laboratory elevation of aminotransferases and direct hyperbilirubinemia is observed [2].

Hepatitis A can have different forms of evolution, although most patients progress to healing within 2 months. Approximately 10% of hepatitis A patients present a biphasic form, in which relapses are observed in the first 6 months of evolution. Other forms considered atypical [6] may also be observed as the prolonged form, in which the symptoms persist for up to 120 days [22], and the cholestatic form presents the following alterations: elevation of the direct fraction of bilirubin, presence of significant pruritus, malabsorption of nutrients, and weight loss. Fortunately, all these forms present evolution for healing. Only a small fraction of patients will develop acute liver failure that is associated with increased morbidity and mortality [22].

6. Diagnosis

According to CDC [23], suspected hepatitis A occurs in the presence of a suggestive clinical picture, characterized by the presence of fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, abdominal pain, or dark urine, associated with suggestive laboratory alterations of the direct bilirubin fraction or ALT > 200 IU/L, in the absence of another diagnosis that explains such alterations.

The presence of immunoglobulin M (IgM) antibody against hepatitis A virus or viral RNA detection provides laboratory evidence for the diagnosis [23].

The presence of sensorineural alterations should raise the suspicion of acute liver failure, and the diagnosis is confirmed if there is an association of sensory alterations with a high prothrombin time in more than 4–6 s (INR ≥ 1.5) [24, 25].

7. Treatment

Hepatitis A has no specific treatment, and usually only support and monitoring measures are adopted. Although the disease is self-limiting in the vast majority of cases, some patients develop severe hepatitis, which can lead to fulminant hepatic insufficiency, and need liver transplantation.

The fulminant hepatic insufficiency diagnosis should be considered in those patients with viral hepatitis who present any alteration of consciousness accompanied by some coagulation disorder [23] characterized by INR ≥ 1.5. Those findings indicate hospitalization of the patient in an intensive care unit with possibility of transfer to a liver transplant center.

It is important to be aware of the fact that the symptoms of fulminant hepatic insufficiency become noticeable late when most of the liver functions are already compromised [26]. And so, the patient need to be transferred to a transplant center as soon as possible if he or she presents metabolic acidosis with arterial pH < 7.3, arterial lactate > 3 mmol/L (27 mg/dL), INR > 6.5, creatinine > 3.4 mg/dL, and presence of grade 3 or 4 hepatic encephalopathy all within the 24-h period [25].

Special attention should also be given to the child who evolves with the cholestatic form due to the nutritional risk secondary to malabsorption of fat-soluble nutrients and vitamins. During disease, until the cholestasis is fully treated, it may be necessary to provide increased caloric intake in addition to vitamins A, D, and E. Nutritional care should be maintained until cholestasis improves [27].

8. Prevention

The Brazilian Ministry of Health advices that the prevention of the disease is best achieved by improving basic sanitation and personal hygiene conditions as follows [28]:

1. Wash the hands after going to the bathroom and before eating or preparing food [28].

2. Wash, with treated water, foods that are consumed raw [28].

3. Cook the food before eating it [28].

4. Wash dishes, glasses, cutlery, and bottles properly [28].

5. Avoid the construction of ditches near wells and river springs, so as not to compromise the water table that feeds the well [28].

6. If there is a patient with hepatitis A at home, use 2.5% sodium hypochlorite, or bleach when washing the restroom [28].

7. In nurseries, preschools, cafeterias, restaurants, and closed institutions, adopt strict hygiene measures, such as disinfection of objects, benches, and floors using 2.5% sodium hypochlorite or bleach [28].

As a prophylactic measure for travelers, the vaccine has replaced immunoglobulin (Ig). The protection achieved by Ig when used before exposure is approximately 80–90% [20], whereas a single dose of hepatitis A vaccine provides protection of 85% of cases in the first 6 weeks and up to 95–00% after this time period [29]. Postexposure prophylaxis (PEP) with hepatitis A vaccine prevents hepatitis A virus infection when administered within 2 weeks of exposure [25, 30]. The use of Ig for PEP is indicated in the following situations: children aged <12 months; immunocompromised people; patients with chronic liver disease; and those for whom the vaccine is contraindicated. For people over 40, immunoglobulin is preferred, but the vaccine can be used on a non-distant immunoglobulin obtained [25, 28]. The recommended dose of IG was modified to 0.1 mL/kg [30].

Pre-exposure prevention for travelers aged 12 months to 40 years should be given by vaccination as soon as traveling to endemic sites is considered, and the second dose should be administered at the regular interval recommended by the vaccine manufacturer. The vaccine can be administered between 6 and 11 months for pre-exposure prophylaxis, but this dose should not be considered when the child initiates the usual vaccination schedule at 12 months of age. In the case of infants <6 months of age, Ig should be given. The dose in these cases depends on the duration of the trip: for trips with a duration of up to 1 month 0.1 mL/kg is recommended; and with longer duration, the dose will be 0.2 mL/kg repeated every 2 months until the end of the trip. Travelers aged >40 years, immunocompromised or with chronic liver disease, are recommended to be vaccinated against hepatitis A and use Ig at the dose of 0.1 mL/kg at the same time but applied at separate sites [30].

Since the introduction of vaccines, there has been a reduction in the prevalence of the disease. The vaccine is effective, even if given as a single dose, although it is usually recommended in two doses. The initial dose should be administered at 1 year of age, especially in endemic areas where contact with the virus is early. The booster dose may occur at varying intervals, usually 6–18 months after the first dose.

The effectiveness of the single-dose vaccine was initially described among people vaccinated for travel to exotic locations or with inadequate sanitary conditions [31, 32]. In 2003 a randomized, double blind study in Nicaragua showed that one dose of the vaccine had good efficacy, reaching up to 100% of children after 6 weeks (95% CI: 79.8–100%) [29].

Young children who present hepatitis A are asymptomatic and therefore able to spread the virus in the community. That is why universal vaccination of all children between 1 and 5 years of age is recommended in populations where the incidence of the disease is >20 cases/100,000 inhabitants. The monovalent vaccine (Havrix®, Vaqta®) should be administered via intramuscular injection in two doses at a 6- to 12-month interval between doses [21, 25].

In 2005, Argentina adopted a universal vaccination schedule for children aged 12 months in a single dose, and since then the incidence of hepatitis A has decreased by >80% in all age groups [33, 34].

For developing countries, this may be a cheaper and simpler strategy than two-dose schedules; however, it is necessary to deploy a surveillance system to determine in the long run whether the booster dose will be needed [34].

In Brazil, the hepatitis A vaccine was added to the national immunization program (NIP) only in 2014. Universal vaccination of children with a single dose of the inactivated vaccine was adopted at 12 months of age. In an official document, the NIP undertook to monitor the epidemiological situation of hepatitis A, aiming at the definition of whether or not to include a second dose in the child's immunization schedule [35].

The United Nations (UN) reports that viral hepatitis is a serious threat to global health, mainly related to hepatitis B and C viruses that cause chronic liver disease. The UN estimates suggest that 325 million people are infected worldwide, with 70 million on the African continent alone. Although the reports focus on hepatitis B and C because of their chronicity, the UN and WHO are committed to reducing hepatitis A-related deaths by 10 percent by the year 2030. According to the WHO, viral hepatitis A is a viral infection of the disease. It can be eliminated from Africa with vaccination and improved sanitation and access to safe drinking water. This latter measure may also reduce the incidence of viral hepatitis E [36, 37].

In order to make vaccination against HAV feasible for developing countries, it is necessary to evaluate effective and cost-effective strategies. Vizzotti et al. [38] evaluated the impact of single-dose vaccination in Argentina and found an impressive decline in hepatitis A cases accompanied by a decrease in medical and nonmedical costs in the first 5 years. The authors then suggested that this could be a simpler and less costly strategy thus becoming an economically viable alternative to other countries where hepatitis A is also endemic.

9. Future perspectives

Since both the world population and the life expectancy are increasing, it's imperative that new techniques, fast, accessible, and sensitive ones, are developed in order to guarantee accurate diagnosis and proper treatment to anyone who is suffering from a disease. With new technologies being released in a daily basis and several researches being done in fields like molecular diagnostics, immunodiagnostics, and gene therapy, it's possible that this goal may be achieved within the following decades.

So as to improve the diagnosis of hepatitis and several other diseases, either through the detection of pathogens or elements present due to the host's immune response, it's essential that new, highly sensitive tests become available in healthcare facilities, especially in endemic regions.

One possibility is to use new techniques that are being developed and allow the detection of antibodies. One example is the capacitive immunosensor developed to detect anti-Zika virus and anti-chikungunya virus antibodies in low concentrations using microwire electrodes [39].

Another possibility is to use the CRISPR-Cas technology to detect the pathogen's genetic material. This technique was developed based on the analysis of a specific defense mechanism of bacteria and archaea, organisms in which clusters of regularly interspaced short palindromic repeats (CRISPR), a specific region of the DNA, are transcribed into CRISPR RNA (crRNA) when they are infected by viruses [40, 41]. When the crRNA and the trans-activating crRNA (tracrRNA) associate with Cas9, an enzyme, the crRNA-Cas9 complex will then target a foreign DNA and cut it [40, 41].

Studies have shown that, through modification, the CRISPR-Cas complex is capable of targeting RNA [42] and adapting to different intracellular environments,

such as the eukaryotic one [43]. Other experiments with CRISPR-Cas demonstrate that it can detect both Zika virus and dengue virus, RNA viruses [44]. Besides, this last analysis has also shown that a test based on this technique would be fast and sensitive and the costs would be low [44].

Regarding the treatment, some studies have shown that genome editing using the CRISPR-Cas system might also allow the development of effective antiviral therapies. Experiments done in vitro using human cells demonstrate that this system can target herpesvirus and provide either clearance of some strains of this virus or cause decay in other strains' replication [45]. Another work, by demonstrating that the CRISPR-Cas system was able to inhibit the accumulation of hepatitis B virus (HBV) DNA in human cells, has shown that this system has the capacity to be developed into an effective therapy for viral diseases [46].

Nevertheless, to ensure a decrease in the number of people infected with hepatitis, it's also important to develop strategies to prevent the spread of the virus. Since hepatitis A is transmitted through a fecal-oral pathway, to achieve this goal, it's essential that the water used by the population receives proper treatment in order to guarantee that all the pathogenic organisms are eliminated. In this context, water and sanitation projects developed by humanitarian organizations can contribute to the decrease in the number of people infected with fecal-oral transmitted diseases.

Some examples are the water safety plans (WSPs), created by the World Health Organization, and the Sustainable Development Goal 6, created by the United Nations. The former focusses on assembling a team that will develop a WSP considering all the hazardous events that can affect the safety of a water supply so as to determine and validate control measures that will be used to develop and implement improvements, which ensure that the drinking water supply is safe and accepted by the population [47]. The latter sets the goals for the following decades and analyzes indicators in order to monitor and promote the implementation of plans of action made to ensure universal and equitable access to safe and affordable drinking water for all, access to adequate and equitable sanitation, hygiene for all, end open defecation [48], and several other measures that can help control fecal-oral transmitted diseases.

10. Conclusion

Hepatitis A is a viral disease whose prevention is possible through improvements in basic sanitation and vaccination of the population. The vaccine provides good protection and is recommended in two doses for children, starting at the age of 1 year. The efficacy of the single-dose vaccine has been reported between people traveling to exotic locations and then by developing countries that have adopted this single-dose schedule. In those places where the single-dose schedule has been adopted, a surveillance system should be in place to determine whether the booster dose will be necessary over the long term. Patients with hepatitis A present evolution to the healing in the majority of the cases, but it is necessary to be aware that, in rare occasions, they can develop acute hepatic insufficiency, which is associated to greater morbimortality.

Conflict of interest

The authors declare no conflict of interest.

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