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Discovery of Hepatitis E

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Abstract

Hepatitis E is an infectious disease with sporadic or epidemic distribution, caused by a hepatotropic RNA virus (Hepatitis E virus, HEV), discovered in the early 1980s. Two notable scientists have a significant contribution to the discovery and identification of Hepatitis E, Mohammad Sultan Khuroo and Mikhail S. Balayan. HEV is distinguished from other human hepatitis viruses by the presence of an animal reservoir. Genotypes 1 and 2 infect only humans, while genotypes 3 and 4 also circulate in animals (mainly domestic pigs and wild boars). To date, genotype 3 (HEV-3) is the most prevalent in Europe. Based on seroprevalence, it is estimated that one-third of the world's population has been infected with this virus. Outbreaks of hepatitis E have been recorded in many countries around the world. HEV infection is associated with hepatic and extrahepatic manifestations. In most cases, HEV is responsible for an acute, self-limiting hepatitis with rapid viral clearance in immunocompetent individuals. HEV remains underdiagnosed. This review article comprehensively history of HEV infection, while stressing emphasizes the importance of disease in public health.

Keywords: Hepatitis E Virus; HEV Infection; HEV Genotypes; Natural History

1. Introduction

Hepatitis E virus (HEV) is a major public health concern worldwide. The journey for the discovery of HEV started with a large outbreak of jaundice that occurred in New Delhi India (1955-1956). The first outbreaks of hepatitis E described in the literature was associated with of faecal contaminated water sources and high levels of morbidity and mortality, particularly among pregnant women. HEV genotypes 1 and 2 are the most commonly identified causative agents of hepatitis E in developing countries. They are regions to poor sanitary hygiene, where HEV infection was considered endemic. Domestic pigs and wild boars are recognized as major reservoirs for both HEV-3 and HEV-4. Studies have reported sporadic autochthonous infections and high seroprevalence rates in industrialised nations. Certain population sub-groups are at high risk for severe disease. These include pregnant women, persons with pre-existing liver disease and immunosuppressed individuals.

The earliest data on this infectious disease date back to 1858, when an epidemic outbreak of jaundice was described on the island of Martinique in the Caribbean Sea. Over eight months, the epidemic spread across the entire island, with most of the affected individuals being older adults. It is noteworthy that of 24 deaths, 20 were in pregnant women, and there were many premature or stillbirths and severe obstetric complications [1]. In 1871, a hepatitis epidemic broke out in Paris, where again a severe course with high lethality was observed among pregnant women. At that time, the first autopsies of deceased patients were performed, and the pathomorphological finding was described as "yellow atrophy" of the liver [2].

In the 1950s, two other epidemics were recorded – in Eastern Kazakhstan and Kyrgyzstan – in which high mortality among pregnant women was again reported [3]. The first thoroughly documented epidemic occurred in New Delhi (India) in 1955–1956, resulting from faecal contamination of a drinking water source, with 29,300 cases and 266 deaths.

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Autopsies of the deceased patients revealed massive hepatic necrosis [4]. This epidemic was extensively investigated by the Indian Council of Medical Research (ICMR), New Delhi, and the National Institute of Virology (NIV), Pune [5]. Later, in 1973–1974, an epidemic of hepatitis with 10,000 cases also broke out in Kathmandu (Nepal). The magnitude of the epidemic was so great that hospitals were unable to admit all those in need. Shrestha Maila described 26 women admitted in a comatose state related to rapidly developing hepatic encephalopathy [6].

From November 1978 to April 1979, a large waterborne hepatitis epidemic occurred in the Kashmir region (India), affecting about 200 settlements with an approximate population of 600,000 people and a common drinking water source. Among the 600 registered deaths, two-thirds were in pregnant women. The main characteristics of this epidemic included predominant involvement of people of young, active age, a markedly compressed epidemic curve with no observed secondary cases, and a higher rate of acute liver failure (ALF) among pregnant women compared with HEV-infected non-pregnant women (15–45 years) and men. The clinical profile showed cholestasis in about 20% of patients. Initially, it was believed to be an epidemic of hepatitis A, and the possibility that the causative agent was another unknown hepatotropic virus was not considered. Later, retrospective testing of stored patient serum samples from the epidemic in India at the National Institute of Virology (NIV) in Pune showed that the etiologic agent was unknown [7].

The first attempts to identify the causative agent were made by D. Wong and M. Khuroo in 1980. Dr. M. Khuroo proposed the existence of a fifth human hepatitis virus, enterically transmitted and similar to hepatitis A virus (HAV). In the same year, an article was published in The American Journal of Medicine with a title introducing the disease under the term ET-NANBH (enterically transmitted non-A, non-B viral hepatitis) [8]. The disease was generally self-limiting, except in pregnant women, in whom fulminant liver failure was more frequently observed and a large number of deaths were recorded.

The discovery of the hepatitis E virus (HEV) is associated with the name of the Russian virologist Mikhail S. Balayan. In August 1981, Dr. Balayan, together with Alexander Andjaparidze and Svetlana Savinskaya, was investigating an outbreak of hepatitis among Soviet soldiers in a military camp in Afghanistan. In an effort to provide a detailed clinical description of the disease, Balayan volunteered to infect himself by ingesting a concentrated inoculum prepared from faecal samples of nine patients, collected 1 to 4 days after the onset of jaundice. Upon his return to Moscow, on the 36th day after ingestion of the faecal suspension, he developed a severe form of hepatitis. In 1983 in Tashkent (Uzbekistan), he and his colleagues succeeded, using electron microscopy, in identifying spherical virus-like particles (VLPs) with a diameter of 27-30 nm in the faeces. The researchers also demonstrated transmission of the infection to primates and excretion of VLPs in their faeces [9].

The first confirmed outbreak in Africa occurred among Angolan refugees in Namibia. In 1983, in Namibia's Kavango region, an outbreak of jaundice unfolded, affecting hundreds of people living in settlements without drinking water and waste disposal facilities. Many of them were Angolan refugees; 72% of the affected individuals were men aged 15–39 years. Fifteen years later, in the analysis of samples from this epidemic, HEV was detected by reverse transcription–polymerase chain reaction (RT-PCR) in the faeces of 9 of 16 tested patients [10]. This first report of hepatitis E confirmed by virus detection from southern Africa extended the known range of HEV and highlighted its risk for refugees. Reyes et al. succeeded in isolating fragments of the viral genome from bile obtained from an experimentally infected animal [11]. In 1991, the entire viral genome was cloned and sequenced [12]. Genomic sequences of viral isolates from Asia and Mexico showed significant differences, indicating the presence of genomic heterogeneity. Around this time, the newly discovered agent was named hepatitis E virus (HEV), using the next letter in the "hepatitis alphabet" after the first four already known hepatitis viruses. In addition, the symbolism of the letter "E" reflects the enteric mode of transmission, the endemic distribution, and the tendency to cause epidemics.

Hepatitis E is endemic in China, where nine outbreaks were recorded between 1982 and 1991. Between 1986 and 1988, the largest epidemic affected 120,000 people, with 707 deaths, 414 of which were among pregnant women. Genotype 1 (HEV-1), identified in 1983, is found in Asia, Africa and South America. Initially, the virus was thought to have a limited geographic distribution and to circulate only in regions with high population density, poor sanitary conditions and restricted access to drinking water – factors that facilitate the faecal-oral route of transmission. In Mexico, HEV-2 was detected during an epidemic between 1986 and 1987, with most cases reported from Africa [13]. These two genotypes cause infections only in humans and are transmitted through contaminated water. HEV-3 and HEV-4 were identified in 1995 and 2003, respectively. HEV-3 is distributed worldwide and mainly in industrialized countries. HEV-4 is found in East Asia, including Japan, China and South Korea. HEV-4 has also been isolated from a patient after consumption of contaminated venison [14]. Overall, human infection is mainly transmitted by HEV-1 to 4, and a recently reported HEV-7. In areas with high HEV endemicity, the disease is caused mainly by genotypes 1 or 2, while in developed countries, HEV-3 or HEV-4 are responsible for sporadic cases of locally acquired infection. HEV-3, HEV-4 and HEV-7 are zoonoses

whose main reservoir is domestic and wild pigs, and for HEV-7, camels. HEV-7 was discovered in 2014 and is prevalent in the Middle East.

The first report of vertical transmission of HEV was in eight women with acute hepatitis E, seven of whom delivered at term and one preterm. HEV RNA was detected by PCR in the umbilical cord. Several cases providing direct evidence for HEV transmission via blood products have been reported thus far. Since the first described case in 2006, several transfusion-transmitted (TT) hepatitis E cases have been reported to the French hemovigilance network [15]. TT hepatitis E can evolve to chronic HEV infection in immunocompromised patients.

The first observations indicated that hepatitis E is endemic in developing countries and that almost all reported cases in developed countries were associated with travel to an endemic region. Serological studies have demonstrated that HEV may also be endemic in the USA and Europe. In the period 1989-1992, acute HEV infection was documented in six people in the USA who had returned from international travel [16]. In Bulgaria, the first case of hepatitis E was confirmed in 1995 [17].

In 1998, a major scientific advance in the study of HEV infection was achieved when genomic sequences confirmed that human HEV is similar to HEV in pigs, suggesting a zoonotic route of transmission. It has been established that many different animal species worldwide have antibodies against HEV [18].

The availability of sensitive serological tests for specific anti-HEV antibodies made it possible to perform a detailed assessment of the prevalence of HEV. Infection with HEV is associated in most patients with the appearance of anti-HEV IgM antibodies at the onset of the disease, and at approximately the same time or shortly thereafter, anti-HEV IgG antibodies are also detected [19]. Anti-HEV IgM antibodies are a marker of recent infection, while IgG indicates past exposure to the virus. Anti-HEV IgG remains detectable for a long period of time, although the exact duration of its persistence is unclear. Newly developed molecular and serological assays for the diagnosis of HEV have led to several studies in different geographical regions that have helped determine the frequency of HEV infection among patients with epidemic and sporadic hepatitis, as well as the seroprevalence in different population groups.

Initially, HEV was classified in the family Caliciviridae, but was later assigned to its own genus and a separate family [20]. Hepatitis E virus is a nonenveloped virus with a positive-sense, single-stranded RNA genome (ssRNA) and belongs to genus Hepevirus of the Hepeviridae family.

The course and clinical presentation of hepatitis E is highly variable. Observations show that hepatitis E usually presents as a self-limiting disease with mild or asymptomatic course in immunocompetent individuals. The clinical manifestation of acute icteric hepatitis associated with HEV-1 or HEV-2 infection is similar to that of other hepatitis viruses, with three phases (prodromal, icteric, convalescent). After an incubation period of 2 to 6 weeks, the symptoms of hepatitis appear. In some patients, prodromes may be absent. Jaundice occurs in about 40% of symptomatic cases in developing countries and in up to 75% of symptomatic cases in developed countries. The infection by HEV in children typically asymptomatic or manifested as a very mild disease without jaundice, and usually, it often goes undiagnosed. Subpopulations have been defined in whom the disease may have a more severe course, including with fatal outcome, and these are pregnant women, patients with chronic liver disease and elderly individuals. Chronic HEV infection can occur in immunocompromised individuals. In 2008, two parallel articles from Southern France were published in the New England Journal of Medicine describing chronic infection in recipients of transplanted organs [21]. Persistent HEV infection is possible in individuals receiving immunosuppressive therapy, as well as in those with hematological diseases or HIV infection. The immune response to HEV in people living with HIV (PLWHIV) diverges from the typical seroconversion pattern observed in the general population. Instead of a swift transition from IgM to sustained IgG antibodies conferring immunity, PLWHIV may exhibit prolonged HEV RNA presence without seroconversion, or only transient detection of IgG antibodies [22].

Viremia appears several days before the onset of symptoms and persists for about 2-3 weeks [23]. Faecal excretion of HEV is longer. HEV RNA has been detected in the cerebrospinal fluid (CSF) of some patients with HEV-3 infection and neurological manifestations [24]. Many studies have indicated that symptomatic HEV infection is not limited to the liver. In rare cases, HEV infection may lead to various extrahepatic manifestations (neurological, haematological, renal, pancreatitis). The first case of neurological disease related to HEV infection was reported in 2000. Sood et al. reported a 50-year-old man in India with Guillain-Barré syndrome (GBS) after acute HEV infection [25]. The first documented case of HEV-associated acute pancreatitis in non-fulminant cases described by Mishra et al. in 1999 [26].

With no specific treatment, prevention remains the most effective control strategy. Many HEV vaccine candidates have been under investigation. HEV vaccine with trade name as Hecolin® (is a recombinant VLPs -based vaccine is the only

licensed HEV vaccine in China. It was approved by the Chinese Food and Drug Administration in 2011 was launched in October 2012. It is recommended for people aged 16 years and above who are at high risk of HEV infection.

In Bulgaria studies on the prevalence in the HEV infection among general population, patients with acute hepatitis, rick groups and animals growing [27].

2. Conclusion

Hepatitis E was first recognised during a water-borne epidemic of hepatitis in Kashmir Valley in the early 1980s. Since then, knowledge regarding the disease has expanded. Currently it is known that acute HEV infection is primarily seen in immunocompetent individuals and has a favorable prognosis. Chronic HEV infection is exceedingly rare in immunocompromised patients. Hepatitis E is a common cause infectious disease, especially in endemic countries.

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