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Insights of hepatitis A virus disease burden in Indian subcontinent: why urbanized localities are vulnerable to disease outbreaks?

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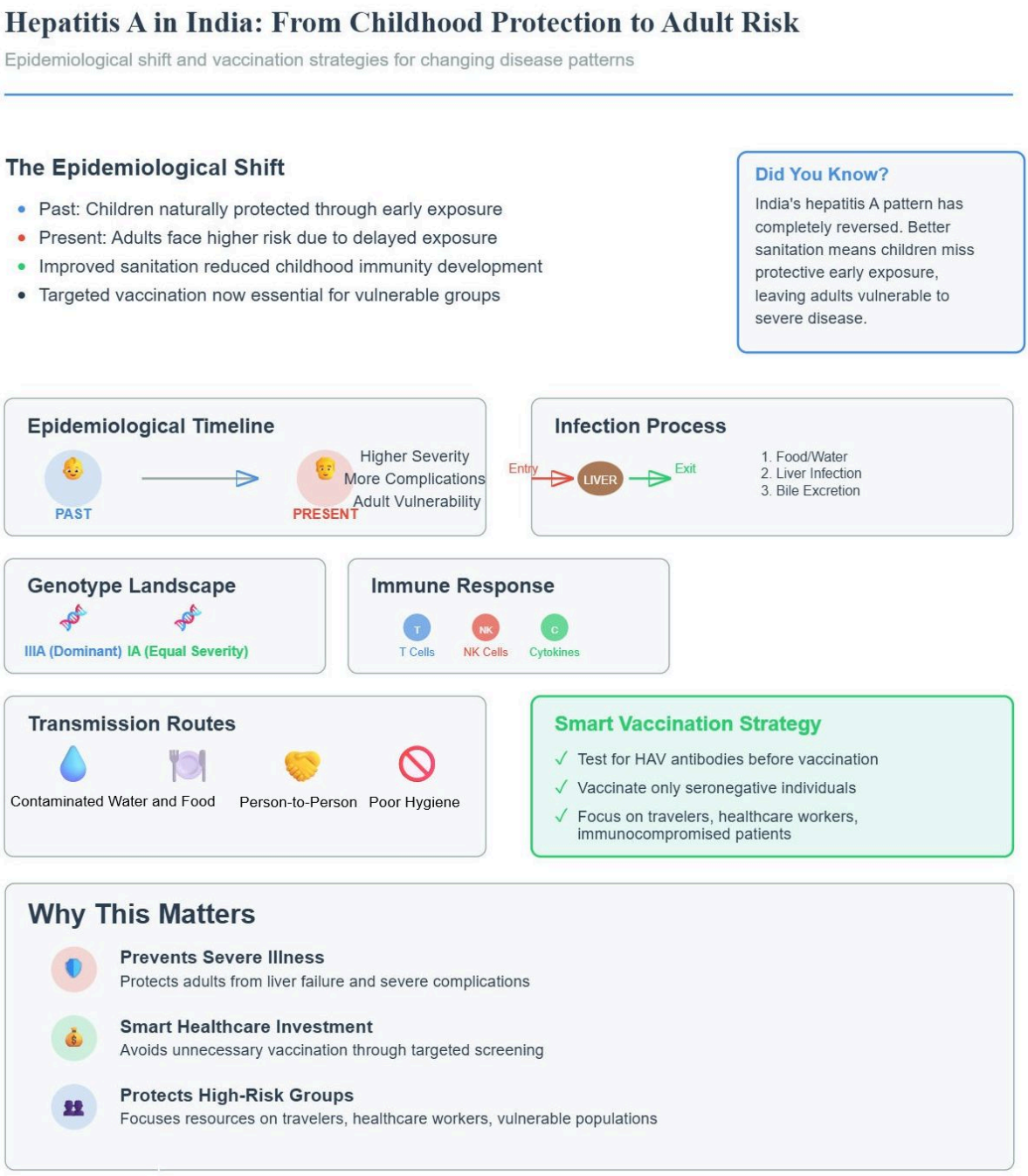
Abstract

Hepatitis A virus (HAV) is a spherical, non-enveloped, linear-positive single-stranded RNA virus that belongs to the Picornaviridae family. The virus attacks the liver, which leads to inflammation and the onset of jaundice. It represents a disease of the pediatric population and, in most cases, it causes an acute self-limited illness, but rarely a fulminant condition. HAV spreads from person to person through the fecal-oral route and ingestion of contaminated food or drink. It is highly endemic in large geographical areas of the world, including the Indian subcontinent, where most of the population is exposed to the virus in childhood. Most of the viral infections at this age cause asymptomatic disease that provides lifelong protection against HAV. However, our recent study showed an increased incidence of HAV infection in the adult population. This signifies a change in the pattern of age-specific seroprevalence of antibodies for hepatitis A and a huge number of non-immune susceptible individuals. Molecular epidemiological studies define various aspects of viral infection and transmission. Sequence characterization based on the VP1/P2A junction region confirmed IIIA and IA as the predominant genotypes circulating in the Indian subcontinent. The duration of the viremia is dependent on the host, and viral genotypes have no role in the severity of the disease. A mutational study confirmed the lack of genetic variations among Indian strains. Due to the high endemicity of this disease in the Indian subcontinent, vaccination is not recommended. However, individuals who are susceptible and seronegative for HAV-IgG should be targeted for vaccination. It will be a rational and cost-effective approach.

Keywords

hepatitis A virus, fulminant hepatitis, genotype, epidemiology, seroprevalence, vaccination



Graphical abstract. Changing epidemiological pattern of hepatitis A virus in the Indian subcontinent. HAV: hepatitis A virus.

Introduction

Hepatitis A virus (HAV) is a member of the Picornaviridae family and *Hepatovirus* genus [1, 2]. It attacks human hepatocytes and causes liver inflammation as well as diverse extrahepatic manifestations. Hepatitis A (HA) symbolizes a disease of the pediatric population, and in most cases, it causes an acute self-limited illness, but rarely fulminant [3, 4]. Natural infection with the virus results from ingestion of materials contaminated with feces. Virions apparently reach the liver through blood or systemic circulation and are taken up by hepatocytes [5, 6]. In the liver, HAV is recognized by the receptor on the hepatocyte membrane and enters the cell via endocytosis [6, 7]. Once inside the cell, the virus uncoats, releases viral RNA, and begins transcription [8–11]. HAV infection has three phases. The first phase involves lag phase virus replication for 1 to 2 days. The second phase results in the synthesis of both negative and positive-strand viral RNA as well as viral proteins. In this, only the production of progeny virus proceeds exponentially and

reaches the highest rates over 3 to 6 days. Persistent infection is stably established within 10 to 14 days of infection in the final phase [11–13]. After completion of viral replication in the liver, it will be excreted in bile and finally shed in stool [11, 13]. HAV is a non-enveloped (naked), linear, positive, single-stranded RNA virus [11, 12]. Similar to other picornaviral genomes, HAV is divided into three parts: (i) a 5' non-coding region (NCR) of nearly 10% of the genome, (ii) a single giant open-reading frame of 2,227 amino acids containing complete message to translate all the viral proteins (capsid proteins (P1) and non- structural proteins (P2, P3)), (iii) a short 3' NCR [12, 14] (Figure 1). Importantly, HAV genomes lack the cap assembly at the 5' end of mRNA critical for the translational initiation [10, 15, 16]. However, an alternative route is formed by the 5' NCR called internal ribosome entry site (IRES) that functions to initiate translation [17–19]. The structural or capsid protein (P1) is further divided into VP4, VP2, VP3, and VP1 regions. The non-structural P2 and P3 polyproteins are divided into 2A, 2B, 2C and 3A, 3B, 3C, 3D, respectively [18, 19]. Interestingly, the polyprotein (2,227 amino acids) is processed by the proteolytic activities of encoded viral proteins into precursor intermediates and mature proteins. Viral proteins 2A, 2B, and 2C encode 45, 251, and 335 amino acids, respectively. The translated 2A proteins are partially located on the surface of the virion (VP1) and some are assembled into the virion [19]. While 2A functions as an intermediary, both 2B and 2C proteins play an important role in the replication of viral RNA [18]**.** Non-structural P3 polyproteins encode 3A, 3B, 3C, and 3D proteins with 74, 23, 219, and 489 amino acids, respectively. 3C proteins act as the sole protease, while 3D acts as RNA-dependent RNA polymerase [20, 21] (Figure 1).

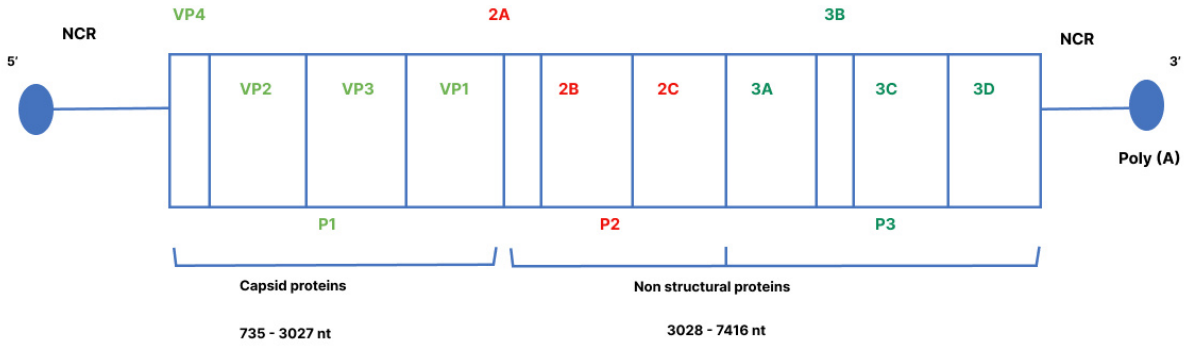


Figure 1. Genomic structure of hepatitis A virus (HAV). HAV genome is divided into a 5' NCR, a single giant open reading frame, and 3' NCR. The coding region is subdivided into regions P1, P2, and P3 (capsid proteins (P1) and non- structural proteins (P2, P3)). NCR: non-coding region. Adapted from [50]. © The Authors 2011. Licensed under a CC-BY 2.0.

Worldwide prevalence of HAV

Infection with HAV is hyperendemic in vast areas of the world, including India [22]. According to the World Health Organization, annually, approximately 1.5 million clinical cases of HA occur worldwide [23]. The worldwide distribution is uneven and is based on determinants such as socioeconomic conditions and geographic factors [24–27]. Our recent data from the northern part of India for over a 5-year period showed an increased proportion of adults with acute HAV infection in urban locations [28, 29]. This was one of the first studies related to the HAV seroprevalence in the adult population in the Indian context [29]. Later, several researchers corroborated our findings, suitably investigated the lack of prior exposure to the HAV in the socioeconomically developed urbanized pockets in the adolescent/adult population [30–32]. These unexposed susceptible individuals carry a higher risk of symptomatic infection that could lead to complications [29–32]. This shift in the epidemiological patterns of HAV has been reported from many regions of the world [33–36]. Based on these findings, the possibility of epidemics of HAV in a new group (adults) is expected. Apart from the hyperendemicity of HA, we are experiencing shifts in epidemiological patterns in urban locations. Although this menace is spreading its tentacles in India, we have limited

information or data pertinent to HAV. Therefore, this review aimed to overview clinical, epidemiological, and molecular characteristics of HAV in India.

Epidemiology and seroprevalence of HAV

As reported earlier, children experience subclinical infection with HAV at higher rates than adults. This might be due to lower standards of hygiene compared with adults [28, 29, 36]. These factors give children a prominent role in the epidemiology of HAV [34, 35, 37]. In Indian subcontinent, crowded living conditions, poor community sanitation, and inadequate water supplies promote high levels of intrafamilial, food-borne and waterborne transmission of HAV within the community [29, 38–42]. According to our recent study, a lack of childhood exposure to HAV in affluent or high socio-economic strata contributes to a large non-immune population. This shift in endemicity led to a growing proportion of unexposed individuals to HAV infection in childhood and hence an increase in susceptible adolescent and adult populations in the affluent urbanized pockets [29, 36]. Several studies concluded that the proportion of adults with HAV infection has been increasing over the years in the society of higher economic strata [28, 29, 36]. So, a clear transition from asymptomatic childhood viral infections to an increased incidence of symptomatic disease in adolescents and adults could be noticed. Earlier reports suggested that there was higher HAV seroprevalence in the lower socioeconomic group, while in the upper socioeconomic group there was lower HAV seroprevalence [28, 36]. However, we found 71% positivity for anti-HAV antibodies among the healthy subjects [29] as compared to 95% positivity in the earlier reports [28, 36]. The epidemiological shift over the last few years is due to a rapid increase in the number of non-immune individuals [29]. Another important study was reported from Sri Lanka, indicating the epidemiological shifts of HAV infection [39]. In this study, a large HA outbreak was investigated that included local residents, internally displaced, and military personnel in the main combat zone (training center) [39]. The study recruited 222 suspected cases, after thorough serological and molecular investigations, 218 patients (military personnel) were confirmed HAV positive. These findings indicated that infected persons act as a reservoir for the spread of HAV from one place to another among susceptible individuals [39]. Interestingly, the mean age of the positive patients was 22.9 years, while only 11 patients were older than 30 years [39]. The study clearly indicated a high percentage of HAV-susceptible population younger than 30 years in that geographical region, most likely indicative of an epidemiological shift. Critical factors responsible for this shift include: easy availability of safe drinking water, hygienic sanitary practices, low fertility rate among women in urbanized regions, and climate change. Importantly, climate change is now becoming an important factor that correlates with the surge in HA cases. Increase in temperature and change in rainfall pattern leads to scarcity of clean water and floods, and hence increase of the viral infection incidence. Epidemiological transformation leads to an increase in the large pool of susceptible individuals (HAV reservoir), which can have a profound impact on the magnitude and severity of the disease. Therefore, vaccination against these groups should be recommended.

Virological characteristics of HAV

HAV viremia continues after the onset of symptoms until Alanine transaminase (ALT) levels reach their peak [43–45]. The viremia of HAV terminates immediately after hepatitis development in serum samples, although feces remain infectious for longer duration. HAV RNA was detected in 62/94 (66.0%) of anti-HAV IgM positive sera (Table 1). The detection rate would have been higher if feces were used instead of serum as a source of viral RNA. Our results confirmed that the HAV RNA could be detected on average 18 days ensuing the onset of clinical symptoms [11, 44]. Genetic heterogeneity has been analyzed by sequencing different genomic regions of HAV: the VP3 carboxyl terminus, the VP1 amino terminus, and the VP1/P2A junction [44–47]. The VP3 C-terminal region is relatively conserved, the VP1 amino acid terminus presents an intermediate variability, while the VP1/P2A junction is more variable and used to distinguish one strain from another [44, 47, 48]. Worldwide prevalence of HAV strains is classified into seven genotypes (I to VII) based upon the genetic sequence of the VP1/P2A junction region [44, 47, 49, 50]. Four genotypes (I, II, III, and VII) were recovered from human HA cases, and the remaining three genotypes (IV, V, and VI) were

isolated from simian species [51–53]. The worldwide circulation of HAV genotype (s) shows that genotype I and III comprise the majority of human strains within the population studied (Figure 2) [44, 47, 49]. Nucleotide sequence strains in the respective proposed genotypes were found to vary at 15% to 20% of base positions in the 168 nucleotide P1 region, whereas within major genotypes, sub-genotypes vary at approximately 7.5% of base positions [44, 47, 49]. The phylogenetic analysis of 72 Indian isolates submitted to GeneBank from northern India showed genotype IIIA (70%) as predominant compared to IA (30%) and shared the same nucleotide homology (≥ 95.5%) to reference sequences (Figure 3). Noticeably, the most common genotypes prevalent in the Indian subcontinent were III and IA [44, 47]. The HAV mutational analysis demonstrated lack of genetic variations in VP1/P2A region among Indian strains [53]. HAV mutation rate is relatively insignificant compared to other members of the Picornaviridae family [47, 53]. The reason for the low mutation rate is due to severe structural constraints in the capsid, which prevent wide-ranging substitutions essential for the emergence of a new serotype [54]. The emergence of new serotype (new variants) is quite unlikely, though not impossible, if the virus population is forced under severe immune selective pressure, i.e., bottleneck conditions, new variants could develop within a short span of time [54, 55].

Table 1. Time of presentation of disease/onset of clinical symptoms with respect to RNA positivity.

Duration of jaundice	AVH[a] HAV RNA/HAV-IgM (%)	FHF[b] HAV RNA/HAV-IgM (%)
0–7 Days	38/51 (74.5)	7/7 (100)
7–14 Days	18/29 (62.1)	3/3 (100)
1–2 Months	5/11 (45.5)	-
5 Months	1/ 3 (33.3)	-

a: acute viral hepatitis; b: fulminant hepatic failure; HAV-IgM: serologically positive patients; HAV RNA: serologically positive samples were confirmed by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR); AVH: acute viral hepatitis; FHF: fulminant hepatic failure. Reprinted from [50]. © The Authors 2011. Licensed under a CC-BY 2.0.

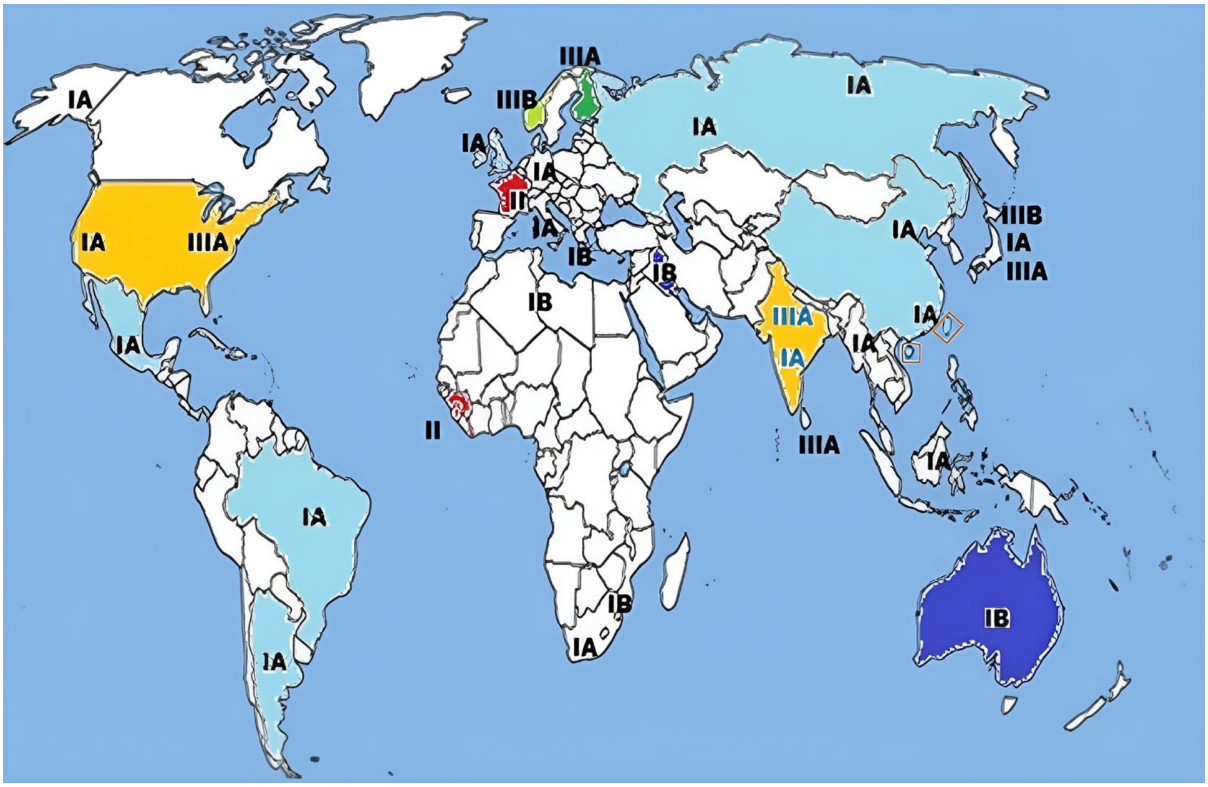


Figure 2. Worldwide distribution of hepatitis A Virus Genotype(s) according to the VP3 carboxyl terminus, the VP1 amino terminus, and the VP1/P2A junction. Reprinted from [14]. © The Authors 2013. Licensed under a CC-BY 3.0.

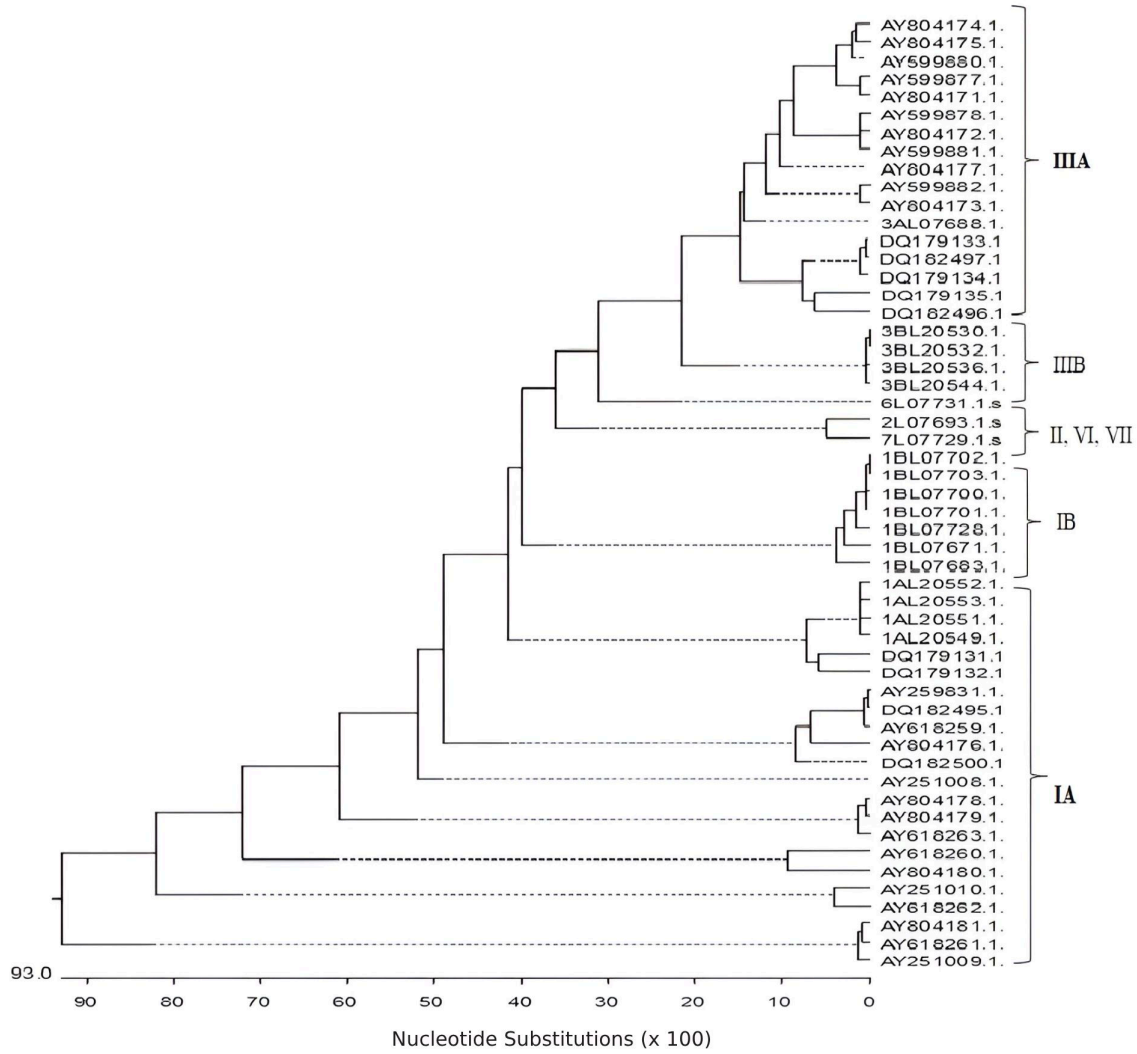


Figure 3. A neighbor-joining phylogenetic tree for isolates of hepatitis A virus based on the sequencing of the VP1/P2A region. The phylogenetic tree shows the reference sequences related to genotypes (I, II, III, VI & VII) prevalent throughout the world, as well as Indian isolates representing genotype **IA** and **IIIA** of acute and fulminant cases.

Clinical and biochemical features of HAV

The pediatric cases are very often evolving without specific symptoms, albeit marked by a rise in serum transaminase levels. The first clinical sign of HA noticed in most of the patients was the appearance of dark urine [34, 35, 37, 44]. Patient's prodromal period lasts for 1–2 weeks, and they mostly suffer from loss of appetite, fatigue, abdominal pain, malaise, anorexia, fever, nausea, vomiting, and flu-like complaints [34, 35, 37, 44]. In 85% of the HAV cases icteric phase begins within 1–2 weeks of initial symptoms, and jaundice becomes apparent when the serum bilirubin level starts exceeding 5–10 mg/dL. Children are often asymptomatic, while adolescents and adults are usually symptomatic [34, 35, 37, 44]. Symptomatic illness leads to jaundice in approximately 70% of patients. Levels of aminotransferases (highly sensitive markers of liver damage) of HAV-IgM positive patients were raised to significantly high levels that range from 1,000–1,500 IU/L [29, 36]. Viral symptoms usually last for less than 2 months, although 10–15% of symptomatic persons may have prolonged or relapsing illness lasting up to 6 months [29, 44] (Table 1).

Mode of transmission

HAV is most commonly transmitted through close person-to-person contact in households and extended family settings [25]. Young children have the highest infection rates, and in most communities with sustained transmission, asymptomatic children are the primary source of infection [29, 44]. However,

transmission can also be sustained in communities of adults with risk factors for infection, such as men who have sex with men or illicit drug users [56–59]. In our recent study, the majority of the patients having IgM anti-HAV positivity were from unhygienic and overcrowded places as well, and some had intrafamilial contacts [44]. The food and water contaminated with feces are important agents that cause HAV transmission in India [29, 44]. India still lacks adequate sanitation, where the sewage system is outdated and very often contaminated water seeps into the drinking water supply route. The unhygienic street foods, which are very common in India, are also a major transmission factor.

Characterization of fulminant HA

Fulminant HA is a rare complication, with a reported incidence of 0.015 to 0.9% of overall cases worldwide, including India [44, 50, 60]. Despite advances in medical management, fulminant hepatic failure in its most severe form carries a high mortality rate. The encephalopathy developed within 1–2 weeks of the onset of symptoms [44]. The mortality in grade III and IV encephalopathy was highest in our study [50]. Our study showed that HAV-related fulminant hepatitis resolves more spontaneously than fulminant HA associated with other etiologies [50] (Table 2). Fujiwara et al. [60] reported that viral strains isolated from fulminant hepatitis patients showed relatively few nucleotide substitutions in the 5' NCR when compared with a substantial sequence variation in virus strains from non-fulminant hepatitis. The nucleotide variations in the central portion of the 5' NCR of HAV may affect the severity of HA infection [60]. This is in sharp contrast to recent findings that the 5' NCR sequence differences are not associated with severe or mild disease [61–63]. This corroborates our recent finding that confirms no evidence of viral genome variations and the severity of the HAV infection [64]. Phylogenetic characterization confirmed genotype IIIA as the predominant form compared to IA in the fulminant cases of HA (Figure 3). We also confirmed that the duration of viremia relies on the host, as viral genotypes had no role in fulminant cases. Significantly, the clearance of viral infection and the disease manifestations are associated with the host cellular immune response [61, 62, 64]. Immunological data from Hussain et al. [50] suggest that the $CD8^+$ lymphocyte counts of fulminant HA were quite high and significant compared to acute HA. We found a significant decrease in the $CD4^+/CD8^+$ T lymphocyte ratio of FHF compared to acute viral hepatitis ($p < 0.05$). Apart from decreased helper/suppressor ratio and high viral load with elevated ALT levels was significantly associated with fulminant hepatitis ($p < 0.05$), indicative of the fact that HAV-related liver failure is triggered by diminished cellular immunity and high viral load [50]. The natural killer (NK) cells, NKT cells, and even $CD8^+$ T cells that are not HAV specific, play a critical role in causing liver damage during HAV infection [65]. Moreover, infection of liver cells with HAV causes natural death to the cells, and it has been identified as another important factor contributing to liver damage in a mouse model of HA [65]. Indeed, larger and prolonged studies are needed to confirm disease manifestation associated with viral titer, mutation, and immunological factors [63, 65–68].

Table 2. General characteristics of hepatitis A related fulminant hepatic failure.

Patient's code[c]	Sensorium	HE[d] grade	Other viral etiologies	Viral load copies/mL	Remarks
Ind-127	Drowsy, confused	Grade IV	**HCV + HEV**	388619	Died
Ind-223	Restless	Grade I	**-**	342870	Recovered
Ind-305	Restless	Grade I	**-**	116806	Recovered
Ind-322	Coma, cannot be aroused	Grade IV	**HCV + HEV**	9156522	Died
Ind-448	Restless	Grade I	**-**	301043	Recovered
Ind-464	Coma, cannot be aroused	Grade IV	**HBV + HEV**	7276522	Died
Ind-472	Restless	Grade I		1734	Recovered
Ind-201	Restless, Confused	Grade II	**HEV**	316806	Recovered
Ind-480	Restless	Grade I	**-**	1072	Recovered
Ind-63	Coma, cannot be aroused	Grade III	**HCV**	4009476	Died

c: Ind, corresponds to Indian isolates, the sequence submitted in GenBank; d: hepatic encephalopathy, the occurrence of confusion, altered level of consciousness, and coma; HBV: hepatitis B virus; HCV: hepatitis C virus; HE: hepatic encephalopathy; HEV: hepatitis E virus.

Prevention and management

Vaccination can prevent HA infections and spread; developed countries have effectively implemented universal mass vaccination for children [69]. In high-endemicity countries like India, vaccination is not recommended because nearly every young child will acquire immunity very early in life following asymptomatic infection [25]. We have to apply a two-pronged approach to contain this epidemic, as HA may become a major health problem in India in the years to come [29]. First, there is an urgent need to improve public health measures to prevent epidemics of HA, since most HA cases reported in children are from poor sanitation and hygienic surroundings [29, 50]. Second, we have reported a diminishing seroprevalence of HAV infection among the adults (including chronic liver patients) in Indian metropolitan cities [28, 29]. Similarly, individuals in high-risk groups in wealthier countries still lack adequate protection [69]. Changed epidemiological patterns would intensify the disease burden and may cause large community outbreaks that would lead to increased healthcare costs. The creation of HAV antiviral medications could be crucial for managing HAV outbreaks that do not advise a universal vaccination programme [69]. Therefore, seronegative individuals for IgG anti-HAV should be vaccinated to reduce the risk of acquiring this infection. This would be a rational and cost-effective approach in the context of the Indian subcontinent.

Conclusions

HAV involves multiple hepatitis outbreaks and is a major public health problem in the Indian subcontinent. It was mostly reported from poor sanitary and unhygienic surroundings, which highlights the need for evolving the public health measures to avert epidemics of viral HA. Diminished cellular immunity underscores the severity of fulminant cases linked to HA. Phylogenetic analysis of acute and fulminant HAV genetic sequences confirmed genotype IIIA as predominant compared to IA, with no preference for disease severity. The mutational analysis confirmed the lack of genetic variations in the VP1/P2A region among Indian strains. Metropolitan cities in the Indian subcontinent experienced altered epidemiology due to an increased incidence of symptomatic infection in the adolescent and adult population. Therefore, individuals who are susceptible and seronegative for HAV-IgG should be targeted for vaccination. It will be a rational and cost-effective approach.

Abbreviations

ALT: Alanine transaminase

HA: hepatitis A

HAV: hepatitis A virus

NCR: non-coding region

Declarations

Author contributions

ZH: Conceptualization, Investigation, Supervision, Writing—original draft, Writing—review & editing. IS: Writing—review & editing, Investigation. SK: Writing—review & editing. RS: Writing—review & editing. KP: Writing—review & editing. VP: Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

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Not applicable.

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