RESEARCH PAPER

Hepatitis A Virus-related Pediatric Liver Disease Burden and its Significance in the Indian Subcontinent

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Objectives: To study the Hepatitis A virus (HAV) infection-related pediatric liver disease burden. **Methods:** Hospital records of 431 children (age <18 y) diagnosed to be suffering from acute HAV infection during 2011 to 2018 were extracted and analyzed. Additionally, a seroprevalence study was done on 2599 participants (696 children and 1903 adults). **Results:** HAV infection accounted for about half (48.6% of acute hepatitis and 46.5% (92/198) of acute liver failure cases) of all acute onset icteric illness, with significant morbidity and mortality. As per seroprevalence data, 16.2% of children between 10-18 years of age, and 10.3% of adults aged 18-30 years remained susceptible to HAV infection. **Conclusion:** HAV infection is the major contributor the overall pediatric liver disease burden. A significant proportion of subjects remain susceptible to HAV infection even after 10 years of age. Population-based studies are required to further delineate the epidemiology of HAV infection in India for deciding introduction of HAV vaccine in the national immunization schedule.

Keywords: *Acute viral hepatitis, Hepatitis A infection, Seroprevalence rate, Vaccination.*

Hepatitis A virus infection is the commonest cause of pediatric liver disease in India, with severity varying from uncomplicated subclinical/clinical acute viral hepatitis (AVH) to acute or acute-on-chronic liver failure. In Indian subcontinent, proportion of overall AVH, acute liver failure, and acute-on-chronic liver failure cases attributed to HAV infection is around 70-85%, 40-60%, and 10-40%, respectively [1-3]. This highlights the significance of HAV infection, especially when it is one of the only few vaccine preventable hepatic diseases. Universal immunisation against HAV in children in India is still controversial with limited national epidemiological data on HAV epidemiology [4]. Thus, we thus planned this hospital-based study to assess the HAV-related pediatric liver disease burden in a high volume tertiary-care referral centre, which may serve as a template for future population-based studies on hepatitis A epidemology and vaccination policy.

METHODS

A retrospective review, from electronic case records, was done after Institutional Ethics Committee approval. We included all pediatric patients (<18 years of age at presentation) who presented with acute onset icteric illness with suspected viral hepatitis from year 2011-2018. These included patients with AVH, acute liver failure, and acute-on-chronic liver failure, defined as per standard definitions [5,6]. Previous publications from the same centre included a proportion of these subjects [2,3]. All patients who tested positive for IgM antibody for HAV using chemiluminescent microparticle immunoassay (CMIA) technology (Abbott Laboratories, IL, USA) were included in the present study (***Fig.* 1**). These patients were divided into three groups; Group I: children with AVH, Group II: Acute liver failure, and Group III: children with Acute-on-chronic liver failure.

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To assess the baseline seroprevalence for protective antibody against HAV, all subjects who were tested for total anti-HAV antibody (IgG, by CMIA technology; Abbott Laboratories, IL, USA) during the same time period were also included. This testing is the standard practice in our institute in those not previously vaccinated with HAV vaccine, or in those with doubtful vaccination history/without relevant vaccination records, before prescribing HAV vaccination. Prescription of HAV vaccine is included in our routine clinical practice as per institutional policy. Patients who tested positive for this antibody were diagnosed having either past exposure to HAV infection, or prior (but unknown) vaccination against HAV.

RESULTS

A total of 958 children and adolescents presented with acute onset icteric illness during the study period; out of these, 431 (44.9 %) were diagnosed as having acute HAV infection. Median (IQR) age of the patients was 11 (6-14) years. Male:female ratio was 2.5:1. Age-wise distribution of total subjects was: <5 years of age: *n*=67, ≥5 to <10 years of age: *n*=120, and ≥10 to <18 years of age: *n*=244. As shown in ***Fig.* 1**, majority of these subjects were in group I *i.e.* AVH group (group 1: 326 or 48.6% out of total 671 AVH cases); of these, 41.1% required hospital admission due to varied reasons including associated complications. Overall, median (IQR) length of hospital stay was 3.5 (3-5) days.

Acute HAV infection contributed to 92 (46.5%) of the total 198 cases of acute liver failure (Group II). The median (IQR) age of these children was 9.5 (7-11) years. The median (IQR) length of hospitalization was 10 (7-13) days. Sixty (65.2%) had hepatic encephalopathy grade 3-4 at admission with median (IQR) jaundice to encephalo-pathy interval of 3 (2-16) days. Intensive care unit admission was required in 56 (60.9%) of these subjects with median ICU stay of 5 (IQR 2-9) days. Fifty-one of them required mechanical ventilation for raised intracranial pressure [median (IQR) duration: 5 (2-7.5) days].

Overall, 53 (58.9%) survived with their native liver, 28 (31.1%) died, and 9 (10%) underwent liver transplantation.

Of the total patients with acute-on-chronic liver failure (*n*=89), HAV infection contributed to 14.6% (*n*=13) of such subjects (Group III). The median age (range) of presentation was 6.9 (3-12) years. All had ascites and encephalopathy. Grade 3-4 hepatic encephalopathy was present in 3 (23.1%). Median length of hospital stay was 16 (range 2-60) days. ICU admission was required in 3 (23.1%) of these subjects with median ICU stay of 5 days; of these cases, 2 subjects (15.4%) required mechanical ventilation. Three (23.1%) children died and the rest survived with their native liver.

Seroprevalence results: For the seroprevalence data, a total of 696 pediatric subjects underwent testing for IgG antibody against HAV infection. These subjects were divided into three age groups *i.e.* <5 years of age (*n*=66), ≥5 to <10 years of age (*n*=247), and ≥10 to <18 years of age (*n*=383). Data revealed that 27.3%, 21.1% and 16.2% subjects were negative for the protective IgG antibody in these three age groups, respectively. Similar analysis was done in a total of 1903 adult subjects. These subjects were divided into four age groups *i.e.* ≥18 to <30 years of age (*n*=380), ≥30 to <40 years of age (*n*=437),

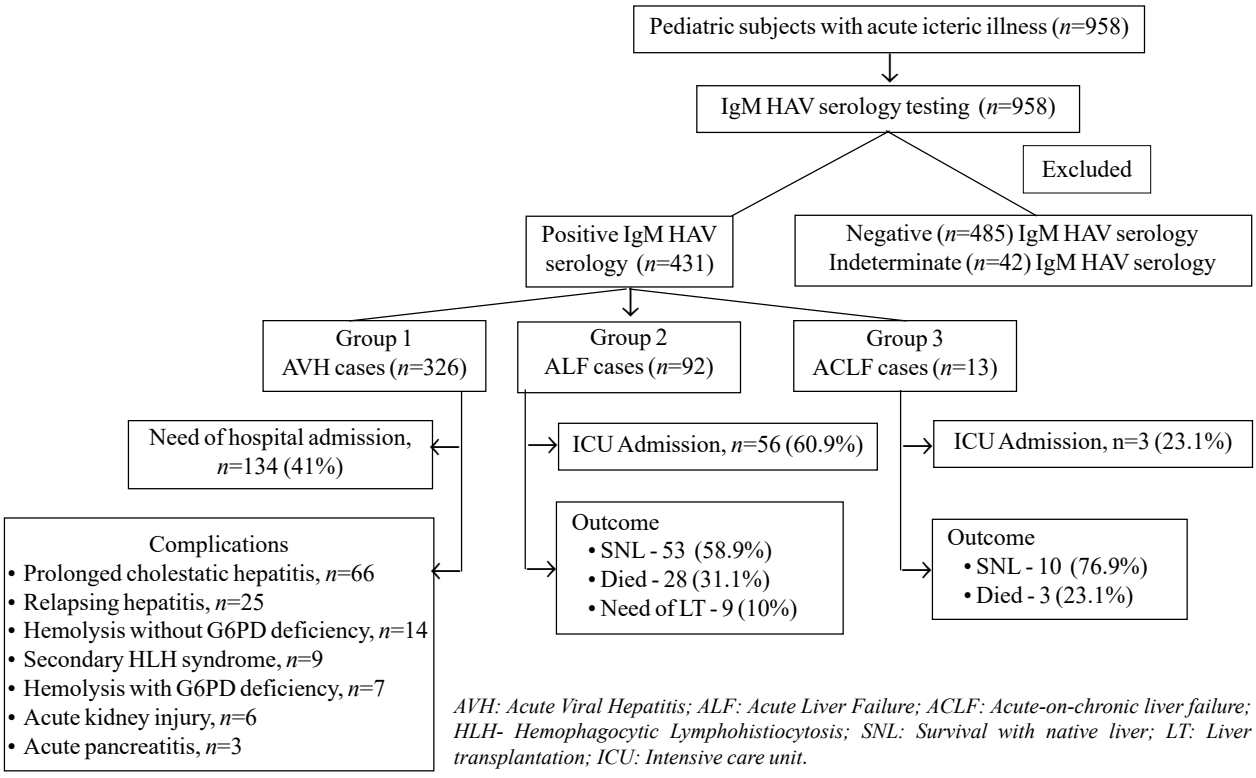

FIG. 1 *Outcomes of the pediatric subjects with hepatitis A virus (HAV) infection.*

WHAT THIS STUDY ADDS?

- Hepatitis A infection contributed to about half of cases of acute icteric illness in children reporting to our center.
- About 10-15% of population remain susceptible to HAV infection even after 10 years of age.

≥40 to <50 years of age (*n*=527), and >50 years of age (*n*=559). Of these, 10.3%, 0.7%, 0.6% and 0% subjects were still negative for the protective IgG antibody in these four age groups, respectively.

DISCUSSION

Despite being limited by its single center/tertiary care hospital-based and retrospective nature, the present study highlights the burden of HAV-related pediatric liver disease. HAV infection accounted for about half of all acute onset icteric illness and acute liver failure cases, and was associated with significant morbidity and mortality. Even after 10 years of age, almost 10-15% subjects remained susceptible to HAV infection.

Hepatitis A as the most common cause of pediatric AVH and acute liver failure has been previously also highlighted [1,2]. The currently available literature highlights the fact that HAV infection has now assumed a more significant role with increasing disease related burden, owing to tremendous success in the vaccination strategies for other diseases. As per latest available national estimates, overall 44,663 cases of HAV infection were detected between 2011-2013 [7]. This burden is reportedly much higher than the current case load (per year) for all other vaccine preventable diseases in India, except Pertussis (in year 2013) [8]. As per global estimates of mortality, HAV infection ranked sixth amongst infectious (vaccine preventable) causes of worldwide mortality (ahead of Pertussis, Tetanus, Varicella and Diphtheria) [9]. The same study also revealed that HAV infection is the only infectious disease entity with increasing mortality risks over the years, while risks have decreased for others.

Recent literature has shown that India is now witnessing an epidemiological transition from high to intermediate endemicity owing to rapid (but unequal) development and improving standards of hygiene, as highlighted by the progressively decreasing age-related seroprevalence rates, as in the present study [4,10-12]. This has created multiple heterogenous pockets in the country where there are large population groups who still remain susceptible to HAV infection. This shift or transition is a critical phase, which if compounded by inadequate preventive HAV vaccination program (as is the current scenario in India), may serve to transform the scenario from an 'endemic' to 'epidemic' pattern [4]. This could lead to repeated outbreaks of HAV related disease in such susceptible populations and also paradoxical increase in the incidence, morbidity and mortality due to HAV infection (beyond pediatric age group), as has happened in India and in other countries (***Web Fig.* 1;** concept diagram) [13-15]. The impact of introduction of universal HAV vaccine has been highlighted from several countries, including developing countries like Argentina [16-21]. Along with remarkable reduction in incidence of symptomatic infection (across all age groups; with percentage decline in HAV incidence varying from 76 to 90 % after introduction of vaccine), they could also document the fact that the monetary benefits due to reduced medical expenditure far exceeded the immunization costs [17, 21].

World Health Organization recommends that countries undergoing transition from high to intermediate HAV endemicity should consider introduction of large-scale HAV vaccination [22]. However, this decision must be based on actual national seroprevalence data (using seroepidemiologic surveys and intensive disease surveillance), along with indigenous cost-effectiveness analyses [4]. In this context, the present study highlights the significance of HAV-related pediatric disease burden in the region, and underlines the unmet need of further population-based large studies to further elucidate the epidemiology of HAV infection in India, in order to decide/prioritize the inclusion of HAV vaccination in the national immunization schedule.

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