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Frequency of Hepatitis A virus as a cause of anicteric hepatitis in children under 5 years: a common yet under-recognized cause

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Abstract

Background: Hepatitis A is the most common form of acute viral hepatitis in developing countries. In children < 6 years of age, most infections are asymptomatic, and if illness does occur, it is usually anicteric. This study aimed to determine the frequency of HAV in Egyptian children under 5 years presenting with gastroenteritis-like manifestations and to associate the frequency of HAV with social, demographic, and various risk factors.

Results: Among 450 children aged from 6 months to 5 years of both sexes, presenting with gastroenteritis-like manifestations and anicteric hepatitis, 200/450 children had elevated transaminases (ALT, AST) and were recruited in the study. A total number of 24 (12%) out of 200 children were found to have HAV IgM antibodies. Lower maternal and paternal education, poor sanitary and hygienic conditions, crowding, contaminated water, and lack of sanitary facilities were significantly higher in HAV-positive group (p-value < 0.05). ALT and AST were significantly higher in HAV IgM-positive group (p-value < 0.01).

Conclusion: HAV infection is common in Egyptian children with gastroenteritis-like manifestations and anicteric hepatitis. Hepatitis A is a vaccine-preventable disease.

Keywords: Anicteric, Hepatitis A, Developing countries, Anti-HAV IgM

Background

Hepatitis A virus (HAV) is one of the most frequent communicable diseases with an estimated 1.5 million cases diagnosed each year globally [7]. According to World Health Organization (WHO), HAV caused around 7134 deaths in 2016, which accounts for 0.5% of the mortality due to viral hepatitis [22].

Hepatitis A endemicity is intimately linked to hygienic and sanitary conditions, as well as other markers of socioeconomic development. HAV infection is highly endemic in developing countries with low sanitary and hygienic conditions, household crowding, and insufficient water supply [21].

Egypt is situated in an area of intermediate endemicity. More than 50% of the Egyptian population are already exposed to HAV infection by the age of 15 [9]. In Egypt, between 2001 and 2004, a sentinel surveillance revealed that the risk of HAV infection was high in Egypt's rural areas, and that children were more prone to contact the infection (median age: 4 years). HAV infection, however, was more common among young adults in urban regions (median age: 14 years) [16].

Between 2014 and 2017, HAV accounted for 93.4% of all confirmed cases of acute viral hepatitis. Children under the age of 16 were most likely to contract HAV

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(81.8%), and the majority of patients lived in urban areas (82.8%) [15].

Most infections in children under the age of 6 are asymptomatic (70%), and if infection does occur, it is usually anicteric. Therefore, the disease is underreported [11, 21].

Anicteric hepatitis is a mild form of hepatitis in which there is no jaundice. Symptoms include anorexia, GI disturbance, and slight fever. Aspartate aminotransferase and alanine aminotransferase serum levels are elevated [8].

Anicteric hepatitis A is an important entity. It is as common as viral icteric hepatitis. Diagnosis is made much less frequently, thus contributing to spread of the disease [14].

Because of obscure symptoms and the absence of icterus, the infection often goes unnoticed. This study aimed to determine the frequency of HAV in children presenting with gastroenteritis-like manifestations and anicteric hepatitis in Egypt and to identify the social, demographic, and other risk factors.

Methods

This cross-sectional study was conducted at the outpatient clinic of the Cairo University Pediatric Hospital, Egypt, during the period from June 2020 to September 2020.

All parents/guardians signed an informed consent before participating in the study. The study was reviewed and approved by the Cairo University research ethics committee (REC) (MS-169-2019) in accordance with the Declaration of Helsinki.

Inclusion criteria

Children are presented with acute onset of low-grade fever (< 38.5 °C), vomiting, diarrhea, nausea, malaise, abdominal pain, and normal-colored urine. Only children with elevated transaminases were recruited.

Exclusion criteria

These are children with jaundice, previous history of HAV infection/vaccination, chronic liver disease, or suspected bacterial or parasitic gastroenteritis (watery/bloody diarrhea, severe dehydration, high-grade fever, frequent motions > 6/day).

Data was collected from the parents/guardians in the form of the following:

- Age, sex
- History of (icter, changing color of urine, previous isolation in fever hospital, previous abnormal liver function test)
- Practice of cleaning (we examined the fingernails of the child to decide whether dirty or clean).
- Maternal and paternal education which were classified as (did not complete primary, primary, secondary, or tertiary education)
- Crowding (numbers of persons living the home) categorized at two levels (> 4 or ≤ 4 persons/home)
- Household spaciousness (classified according to the number of the rooms (> 2 or ≤ 2)
- Sanitary facilities (the presence of a flush toilet, or pit toilet, or outside house) [20]

Complete physical examination was performed including the following:

- Growth parameters
- General examination for jaundice, finger nails (dirty or clean)
- Abdominal examination

Laboratory tests in the form of liver transaminase (ALT, AST) were withdrawn for all children with gastroenteritis-like manifestations. Only children with elevated transaminases were recruited. IgM antibodies against HAV virus were only done in children with transaminitis. Anti-HAV IgM was tested using ELISA (enzyme-linked immunoassay), Bioneovan Co. Ltd., Beijing, China. Children were divided into 2 groups HAV-positive and HAV-negative groups according to the results of the HAV IgM. In the HAV-positive group, further investigations were done in the form of the following:

- Complete blood picture
- Prothrombin time (PT) and international normalized ratio (INR), measured as a marker of severity

Statistical analysis

The data are summarized as mean ± SD and median (IQR) and analyzed by chi-square test and/or Fisher exact test. The comparison between two independent groups with quantitative data and parametric distribution was done by using the independent sample *t*-test, while comparisons between nonparametric data were done using the Mann-Whitney test. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following: $p < 0.05$: significant, $p < 0.01$: highly significant.

All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp., Armonk, NY, USA) release 23 for Microsoft Windows.

Results

We investigated 450 children presenting with acute onset of low-grade fever (< 38.5 °C), vomiting, diarrhea, nausea, malaise, abdominal pain, and normal-colored urine; 200/450 children had elevated transaminases (ALT, AST) and were recruited in the study. The median (range) age of the recruited children was 24 (6–60) months. Around 50% were below the age of 2 years. Males represented 52% ($n = 104$). Twenty-four children (12%) were seropositive for HAV IgM (9–60 months, median 35). Children more than 2 years old were significantly more infected with HAV ($p < 0.05$). The youngest child with HAV IgM-positive antibodies was 9 months old (Table 1). Comparing HAV-positive

Table 1 Demographic characteristics of HAV-negative and HAV-positive groups

		HAV negative $n = 176$ (88%)	HAV positive $n = 24$ (12%)	Total ($n = 200$)	*p*-value
Sex	Male	94 (53.4%)	10 (41.7%)	104 (52%)	0.280
	Female	82 (46.6%)	14 (58.3%)	96 (48%)	
Age (months)	Mean ± SD Median (IQR)	27.00 ± 17.43	35.46 ± 17.59	24 (12–43)	0.027
	Range	6–60	9–60	6–60	
Age (≤, > 2 years; *n* (%))	Age ≤ 2 years	98 (55.7%)	6 (25%)	104 (52%)	0.005
	Age > 2 years	78 (44.3%)	18 (75.0%)	96 (48%)	
Weight (kg)	Mean ± SD	11.25 ± 3.75	13.30 ± 4.24	11.49 ± 3.86	0.014
	Range	4.5–20	6.5–20	4.5–20	
Height/length (cm)	Mean ± SD	83.45 ± 14.24	88.92 ± 13.94	84.11 ± 14.28	0.079
	Range	61–110	70–108		
BMI	Mean ± SD	15.83 ± 2.25	16.59 ± 2.50	−0.67 (−1.2–0)	0.128
	Range	10.8–20.9	13.2–23.4		
BMI Z-score	Median (IQR)	−0.67 (−1.2–0)	−0.34 (−1.24–0)	104 (52.0%)	0.506
	Range	−2.5–1.2	−20.67		

Table 2 Risk factors of HAV infection among HAV-negative and HAV-positive groups

		HAV negative		HAV positive		*p*-value
		n	%	*n*	%	
Maternal education	Did not complete primary education	68	38.6%	20	83.3%	0.000
	Primary education	88	50.0%	4	16.7%	
	Secondary education or tertiary	20	11.4%	0	0.0%	
Paternal education	Did not complete primary education	62	35.2%	18	75.0%	0.001
	Primary education	90	51.1%	5	20.8%	
	Secondary education or tertiary	24	13.6%	1	4.2%	
Cleaning	Dirty	92	52.3%	18	75.0%	0.036
	Clean	84	47.7%	6	25.0%	
Household crowding (persons/home)	4 or less	82	46.6%	0	0.0%	0.000
	More than 4	94	53.4%	24	100.0%	
No. of rooms	2 or less	122	69.3%	16	66.7%	0.792
	More than 2	54	30.7%	8	33.3%	
Water source	Piped water without filter	167	94.9%	22	91.7%	0.000
	Bottled or filtered	9	5.1%	0	0.0%	
	Well	0	0.0%	2	8.3%	
Sanitary facility	Flush toilet	140	79.5%	11	45.8%	0.000
	Pit toilet	36	20.5%	11	45.8%	
	Out house	0	0.0%	2	8.3%	

to HAV-negative group, older children, higher maternal and paternal illiteracy, poor hygiene, higher number of persons per household, contaminated water, and poor sanitation were significantly present in HAV-positive group (Table 2).

Fever was present in all children. Vomiting was significantly present in HAV-negative group, while hepatomegaly and tender liver were significantly more in HAV-positive group (Table 3). Liver enzymes were significantly more elevated in HAV-positive group ($p = 0.000$) (Table 4).

We found a highly statistically significant positive correlation between the age of the children and liver enzymes ($r = 0.343$, 0.228, and p-value < 0.001).

Coagulopathy in the form of prolonged PT, median (IQR) 47 (34–94) s, was seen in 9 children in the HAV IgM-positive group. The median (IQR) INR of 6 of them was 4.4 (2.8–7.5) which was not corrected after vitamin K (10 mg/day) for 3-successive-day intake indicating acute liver failure.

Thrombocytopenia was found in 4 (16.7%) of HAV-positive group.

Discussion

To the best of our knowledge, this is the first study in Egypt to report the frequency of HAV as a cause of anicteric hepatitis in children under the age of 5 years.

Table 3 Clinical manifestations of HAV negative and positive groups

	HAV negative	HAV positive	*p*-value
n	176	24	
Abd. pain	37 (21.0%)	3 (12.5%)	0.327
	139 (79.0%)	21 (87.5%)	
Nausea	141 (80.1%)	24 (100.0%)	0.016
Vomiting	175 (99.4%)	19 (79.2%)	0.000
Arthralgia	66 (37.5%)	13 (54.2%)	0.117
Diarrhea	157 (89.2%)	19 (79.2%)	0.156
Right hypochondrial tenderness	50 (28.4%)	19 (79.2%)	0.000
Hepatomegaly	6 (3.4%)	5 (20.8%)	0.000

The present study showed that 12% of recruited children were infected with HAV. Children were presenting with clinical features suggestive of anicteric viral hepatitis. This is a strikingly high frequency. Undiscovered sufferers from anicteric hepatitis due to HAV infection are the primary source of HAV spread, because they are not recognized.

In a previous study from Egypt, acute HAV infection was diagnosed in 97% of children and was considered as a chief etiology in children presenting with symptomatic acute hepatitis [6].

Benzamin et al. [2] study included 161 children from Bangladesh, aged 5 months to 16 years, admitted with acute hepatitis. The most common etiology of anicteric hepatitis was *Salmonella* hepatitis (66.7%), followed by HAV (16.7%). Three (23%) patients died in the acute liver failure group; all were due to HAV. HAV was the most common etiology of fulminant hepatic failure in Talat et al. [17] study.

Among the different demographic factors we investigated, the age significantly affected the prevalence of anti-HAV IgM ($p = 0.02$; 0.01). Seropositivity increases in increments as age increases. Children above the age of 2 years were significantly more infected. Older children are less dependent with more outdoor play exposing them to the risk of infection. Young children infected with HAV do not have many symptoms and can even be asymptomatic. It is possible for them to have HAV infection without realizing and facilitate the silent spread of infection.

It has been observed in other age-specific seroprevalence studies that prevalence increases with age, probably due to close interaction within a school setting [4, 18].

We were unable to identify a significant sex-related difference in our study which is consistent with previous studies [4].

Our study revealed that crowded households, lower maternal and paternal educational level, poor personal and domestic hygiene, use of piped unfiltered drinking water, and living in areas with poor infrastructure pose the greatest risks of HAV infection. Our fear is that because of vague symptoms and the absence of jaundice,

Table 4 Liver enzymes of HAV-negative and HAV-positive groups

		HAV negative	HAV positive	Total	*p*-value
n		176	24	200	
AST (IU/L)	Median (IQR)	145 (113.5–204)	953 (623.5–1036.5)	161 (116.5–225.5)	0.000
	Range	74–337	401–1345	74–1345	
ALT (IU/L)	Median (IQR)	121.5 (87–169)	823 (660.5–974)	137.5 (89–200.5)	0.000
	Range	67–607	400–1089	67–1089	

the infection often passes unnoticed leading to the spread of infection.

A study from India showed that infection-induced antibodies were seen in the lower-middle socioeconomic status group [1].

All children (100%) in our study is presented with fever. Vomiting was present in 97% of all children and was significantly more in HAV-negative group. Kumar et al. [10] conducted a study in children diagnosed with acute viral hepatitis A. Jaundice was present in all the patients as this was the inclusion criteria. Fever was present in 82.1% and hepatomegaly in 98.7%. In our study, hepatomegaly was present in 5 (20.8%) of HAV-positive children.

Morad et al. [12] conducted an Egyptian study on 80 children with HAV infection: 50 with acute hepatitis, 12/50 presented with anicteric hepatitis, and 30 children presented with fulminant hepatic failure, and 2/30 were anicteric. They found statistically significant association between acute hepatitis A virus, fulminant hepatic failure, and low socioeconomic level and poor hygiene ($P < 0.008$; $p = 0.04$). They also reported that prolonged PT more than 25.87 s showed an increasing risk for developing fulminant hepatic failure in children with acute HAV.

In Kumar et al. [10] study, coagulopathy was observed in 15.4% of HAV-positive patients. In our study, 9 (37.5%) children of HAV-positive group fulfilled the criteria for fulminant hepatic failure diagnosis. This biochemical evidence of acute liver injury (< 8-week duration), no evidence of chronic liver illness, and hepatic-based coagulopathy are defined as a $PT > 20$ s or $INR > 2$ regardless of the presence of clinical hepatic encephalopathy. Due to the nature of this cross-sectional study, no follow-up data is available.

Our study recommends compulsory HAV vaccination due to the possible occurrence of fulminant hepatic failure in anicteric children. The absence of jaundice may delay the diagnosis of HAV infection in young children.

In the present study, thrombocytopenia was found in 16.7% of children with positive HAV IgM. Cheema et al. [5] found thrombocytopenia in 10% of the patients; 22.1% were less than 5 years of age. Thrombocytopenia improved in all patients spontaneously. The authors could not find any evidence of disseminated intravascular coagulation or bone marrow suppression. It is reported that immune thrombocytopenic purpura may be the only symptom of acute hepatitis A, with no accompanying symptoms such as jaundice, vomiting, or stomach pain [19]. Shenoy et al. [13] also reported a case of child with severe thrombocytopenia as an initial manifestation of acute HAV infection.

At 12 months, the recommended age for HAV vaccination, Arankalle et al. [1] found in their study that infants had the lowest IgG antibody prevalence. The infants who belong to lower- middle socioeconomic status had a reduced HAV exposure as a result of improved hygiene and targeted immunization policies. The authors emphasized the need of HAV vaccination regardless of socioeconomic background.

The youngest age of infection with HAV in the current study was 9 months. We recommend receiving the vaccine at the age of 9 months in areas with high prevalence, driven by the need to provide protection before the infant is likely to be exposed to infection, to reduce the potential for the development of severe complications, and to limit the spread of disease in which the diagnosis may be missed. Infants will still need routine vaccination after the first birthday due to passively acquired maternal antibody. In certain countries (USA), infants aged 6–11 months traveling to countries with high or intermediate endemic HAV receive a vaccine dose and are revaccinated with 2 doses, separated by at least 6 months, between age 12–23 months [3].

Our study highlights the fact that the real extent of hepatitis A among anicteric children is not well known and shows unexpected prevalence among children presenting with vague gastrointestinal symptoms.

Limitations of the study

This study is cross sectional with no long-term follow-up of the HAV-positive group. We could not evaluate the etiology of anicteric hepatitis in the HAV-negative group to give a better estimate of the various causes of this condition in Egypt. Another limitation is that the viral load of HAV was not quantified by PCR to correlate its level with the disease severity.

Conclusions

In Egypt, anicteric hepatitis due to HAV infection is not uncommon. The frequency of HAV infection in children less than 5 years presenting with anicteric hepatitis was 12%. Risk factors associated with HAV infection were older age, crowded environment, lower maternal and paternal educational level, poor sanitary and hygienic conditions, use of contaminated drinking water, and living in areas with poor infrastructure. Our study highlights the need for increased public awareness of the disease, improved sanitation, water supply, hygiene, and adding HAV vaccination to mandatory vaccines in Egypt. We recommend starting HAV vaccination early at 9–12 months in areas with high endemicity, such as Egypt, to provide protection before exposure, to limit the disease spread caused by missed diagnosis, and to reduce incidence of potentially fatal complications.

Abbreviations
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HAV: Hepatitis A virus; SD: Standard deviation.

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Authors' contributions
YNA, manuscript preparation and drafting the article. ESZ, concept and design of study and final approval of the version to be published. ASF, analysis and interpretation of data. ENS and AMA, laboratory tests, analysis, and interpretation of data. EN, concept and design of study and review and editing of manuscript. All authors had full access to the data (including statistical results and tables), approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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Availability of data and materials
Data will be made available by the corresponding author to the editor after a request email from the editor. The reason for sharing the data should be justified, and it will be shared after all the authors approve the same.

Declarations

Ethics approval and consent to participate
The study was reviewed and approved by the Cairo University research ethics committee (REC) (MS-169-2019). Informed written consent has been taken. Ethical statement was mentioned in method section.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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