Cost–effectiveness of prescreening versus empirical vaccination for hepatitis A in Egyptian children with chronic liver disease

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مردودية تحري أضداد فيروس التهاب الكبد A قبل التلقيح ومقارنته بالتلقيح بدون التحري لدى الأطفال المصريين المصابين بمرض كبدي مزمن

هناء القراقصي، رقية السيد، منى الرازقي، نهال الكوفي، سماح منصور

الخلاصة: هدف الباحثون في هذه الدراسة إلى التعرف على معدل انتشار أضداد فيروس التهاب الكبد A في 172 طفلاً مصاباً بمرض كبدي مزمن، وإلى حساب مردودية التحري قبل التلقيح لالتهاب الكبد A. واتضح أن أضداد فيروس التهاب الكبد A إيجابية لدى 85.1٪ من الأطفال؛ ولو أن نسبة الانتشار المصلي لتلك الأضداد بلغت 62.1٪ لدى الأطفال الذين تقل أعمارهم عن 5 سنوات، و94.4٪ لدى الأطفال الذين تزيد أعمارهم على 5 سنوات. وخلص الباحثون إلى ارتفاع مردودية تحري الأضداد قبل تلقيح الأطفال المصابين بمرض كبدي مزمن ممن تزيد أعمارهم على 5 سنوات، في حين أن التحري قبل التلقيح قد لا يكون مرتفع المردودية لدى الأطفال الذين تقل أعمارهم عن 5 سنوات.

ABSTRACT The aim of the study was to determine the prevalence of anti-hepatitis A virus (anti-HAV) antibodies among 172 children with chronic liver disease, and to calculate the cost–effectiveness of prescreening prior to hepatitis A vaccination. Anti-HAV antibodies were positive in 85.1%. However, seroprevalence of anti-HAV antibodies was 62.1% in children < 5 years and 94.4% in children 5+ years. We conclude that while it is cost-effective to do prescreening before hepatitis A vaccination for children with chronic liver disease aged 5+ years, prescreening might not be cost-effective in those aged < 5 years.

Rapport coût-efficacité du prédépistage comparé à la méthode empirique de vaccination contre l'hépatite A chez des enfants égyptiens souffrant d'une affection hépatique chronique

RÉSUMÉ Les objectifs de cette étude étaient de déterminer la prévalence des anticorps anti-VHA (virus de l'hépatite A) parmi 172 enfants souffrant d'une affection hépatique chronique et de calculer le rapport coût-efficacité du dépistage préalable à la vaccination contre l'hépatite A. Les anticorps anti-VHA étaient positifs chez 85,1 % de ces enfants. Toutefois, la séroprévalence de ces anticorps était de 62,1 % chez les enfants de moins de 5 ans et de 94,4 % chez les enfants de 5 ans et plus. Nous en concluons que si un dépistage préalable à la vaccination contre l'hépatite A chez les enfants atteints d'une affection hépatique chronique qui sont âgés de 5 ans et plus est d'un bon rapport coût-efficacité, il ne l'est peut-être pas chez les enfants de moins de 5 ans.

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Introduction

During recent years many reports have discussed the outcome of acute hepatitis A in patients with chronic liver disease (CLD) [*1–4*]. Acute hepatitis A virus (HAV) superinfection causes more severe disease, acute hepatic failure and higher fatality rates in patients with underlying CLD, specifically chronic hepatitis B (HBV) and chronic hepatitis C virus (HCV) infections [*5–9*].

Two biological products, HAV vaccine and hepatitis A immunoglobulin, have been used successfully to prevent HAV [*10*]. In the mid-1990s 2 formalin-inactivated HAV vaccines were licensed by the United States Food and Drug Administration for use in preventing disease in persons 2 years and older [*11–13*].

It has been proposed that hepatitis A vaccine should be part of the routine management of patients with CLD, preferably as early as possible in the natural course of their disease [*14–16*]. Serologic testing for hepatitis A before vaccination is likely to be cost-effective only among persons who have a high likelihood of previous infection [*10*].

The aim of the present work was to determine the prevalence of previous exposure to hepatitis A in children with CLD in comparison to a group of age- and sex-matched controls; and to estimate the cost–effectiveness of prescreening versus empirical vaccination for hepatitis A in this age group.

Methods

The study was carried out over a period of 1 year from January 2004 to December 2004 at the Paediatric Hepatology Unit, Cairo University Children's Hospital, Egypt. We enrolled all children with CLD whose parents gave written consent to participate in the study. The study included 172 children: 101 with CLD and 71 healthy age- and sex-matched brothers, sisters and contacts of the patients as a control group.

Inclusion criteria for children with CLD were: willingness to participate; any CLD regardless of etiology; no previous history of vaccination against hepatitis A; and children of both sexes. Exclusion criteria were: children with uncontrolled coagulopathy; children with decompensated liver disease; children with known immunological deficiency; and infants < 2 years of age.

All children were tested for anti-HAV antibodies; 5 mL of blood were drawn aseptically by venepuncture and serum was prepared using standard techniques. Total anti-HAV antibody was detected using a competitive enzyme immunoassay (ELISA) using commercially available kits (DiaPro Diagnostic Bioprobes Srl., Milan, Italy).

The seroprevalence of hepatitis A antibodies was compared between children with CLD and their matched controls. Also children with CLD were divided according to age into 2 groups, 5+ years and < 5 years, and the seroprevalence of hepatitis A antibodies was compared between the 2 groups.

Liver function tests were done for all patients for total and direct serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase (GGT), serum albumin and prothrombin time and concentration. Results of liver function tests were compared between the group previously exposed to hepatitis A and those negative for anti-HAV antibodies.

The costs of empirical vaccination versus prescreening were calculated according to the local costs in Egypt. The cost of a single test of anti-HAV antibodies is

approximately US$ 7 and the cost of 2 vaccine doses is approximately US$ 35.

Statistical analysis

Statistical analysis was done using the statistical package *SPSS*, version 10. Descriptive statistics were presented as means, standard deviations (SD) and number and percentage (frequency distributions). The chi-squared test was used to assess the association between groups. $P < 0.05$ was considered significant.

Results

The study included 172 children, 100 males (58.1%) and 72 females (41.9%). Their ages ranged from 2 to 18 years, with a mean of 7.8 (SD 4.0) years.

The etiological diagnoses of the 101 patients with CLD included autoimmune hepatitis (14 patients, 13.9%), cholestatic diseases of infancy (16 patients, 15.8%), viral hepatitis, 4 HBV infection and 9 HCV infection (12.9%). The remaining 58 patients (57.4%) had miscellaneous causes for their CLD.

Of the 101 patients, 86 (85.1%) with CLD were positive for anti-HAV antibodies, compared with 55 (77.5%) controls, but the difference was not statistically significant ($P = 0.197$) (Table 1). Among the anti-HAV positive group 58.2% were males compared with 41.8% females but the difference was also not statistically significant ($P = 0.993$).

The mean age of patients with CLD at the time of screening for hepatitis A was 8.6 (SD 4.4) years and the male:female ratio was 1.7:1. Comparison of the mean age at screening for hepatitis A of both seropositive and seronegative cases revealed a statistically significant difference: 9.2 (SD 4.0) years versus 5.4 (SD 4.9) years respectively ($P < 0.001$).

Among the 86 children with CLD who were positive for anti-HAV antibodies, 68 (79.1%) were 5+ years old and 18 (20.9%) were < 5 years old.

No statistically significant difference was found between CLD patients with positive or negative HAV antibodies when the results of all liver tests were compared (total and direct serum bilirubin, AST, ALT, alkaline phosphatase, GGT, serum albumin and prothrombin time and concentration).

According to age, among the 101 children with CLD, 29 were < 5 years of age: 18 were anti-HAV positive (62.1%) and 11 (37.9%) were negative. In the 72 patients who were 5+ years, 68 (94.4%) were anti-HAV positive and 4 (5.6%) were negative. This difference was statistically significant ($P < 0.01$) (Table 2).

Table 1 **Seroprevalence of anti-hepatitis A virus (anti-HAV) antibodies among patients with chronic liver disease (CLD) and controls**

Variable	Patients with CLD (*n* = 101)		Controls (*n* = 71)		Total (*n* = 172)		*P*-value
	No.	%	No.	%	No.	%	
Anti-HAV negative (*n* = 31)	15	14.9	16	22.5	31	18.0	0.197
Anti-HAV positive (*n* = 141)	86	85.1	55	77.5	141	82.0	
Total (*n* = 172)	101	100.0	71	100.0	172	100.0	

Table 2 **Seroprevalence of anti-hepatitis A virus (anti-HAV) antibodies in patients with chronic liver disease below and above 5 years of age**

Age (years)	Anti-HAV negative (*n* = 15)		Anti-HAV positive (*n* = 86)		Total (*n* = 101)		*P*-value
	No.	%	No.	%	No.	%	
< 5 (*n* = 29)	11	37.9	18	62.1	29	100.0	< 0.01
5+ (*n* = 72)	4	5.6	68	94.4	72	100.0	

Discussion

Fulminant infection may develop in patients with CLD if they are exposed to HAV [*10*]. There has been some debate about the cost–effectiveness of hepatitis A vaccination in this population [*8,17–19*]. Hepatitis A should be given to persons who have evidence of chronic liver disease and those who are awaiting or have received a liver transplant; these groups are at high risk for complications from superimposed insult to the liver [*10*]. We carried out the present study to determine the susceptibility of children with CLD to HAV infection, and evaluate the cost–effectiveness of prescreening for HAV antibodies prior to vaccination versus empirical vaccination.

Different anti-HAV antibody prevalence patterns have been described that match variations in economic development, levels of sanitation and awareness that affect food-borne infections. In areas with high endemicity, 90% of children are infected by around 10 years of age. The infections are asymptomatic, and viral hepatitis A is not a clinical problem. In areas of medium endemicity, the 90% seroprevalence level is not reached before early adulthood [*20*].

The highest seroprevalence of HAV is observed in adults in urban Africa, Asia and South America, where evidence of past infection is nearly universal [*21*]. In Egypt, a seroprevalence of HAV IgG in residents of the Nile delta of > 95% in children aged 1–3 years was reported [*22*].

In the present study the seroprevalence of anti-HAV antibodies was comparable among patients with liver disease and their contacts (85.1% versus 77.5%). The high prevalence of HAV antibodies among our patients and controls highlights the role children play in Egypt as reservoirs of infection. The virus spreads easily from asymptomatic young children to other young children and adult contacts [*10*].

Ferreira et al. in Brazil reported a 24% prevalence of anti-HAV among patients with liver disease up to 16 years of age; this difference could be attributed to the differences in socioeconomic background [*20*].

The age-stratified frequency of anti-HAV antibodies showed that the prevalence of protective antibodies increased with increasing age. This was in accordance with Acharya et al. who showed that the prevalence of anti-HAV antibodies among Indian children was 80% by 5 years of age but was 100% by the age of 16 years [*23*]. Kocak et al. from Turkey reported a seropositive rate of anti-HAV of 44% among people with liver disease between 1.5 and 20 years old, and the prevalence of antibodies increased with age [*24*].

Prescreening versus empirical immunization for hepatitis A in patients with CLD remains a controversial issue and little comparative data are available on prescreening cost–effectiveness strategy [*14*]. Serological testing for hepatitis A

before vaccination is likely to be cost-effective only among persons who have a high likelihood of previous infection.

In Egypt, the cost of testing for anti-HAV is around US$ 7 per test, and the cost of the 2 doses of hepatitis A vaccine is around US$ 35. Based on our results, in the group of children with CLD 5+ years of age, the total cost of prescreening 100 children and vaccinating 5% is approximately US$ 900, while empirical vaccination will cost US$ 3500. Expenses are reduced to 25% if prescreening is carried out in this age group. However, in children < 5 years of age, the total cost of prescreening 100 children and vaccinating 40% is approximately US$ 2100 versus US$ 3500 for empirical vaccination. Taking account also of the costs of the increased number of visits for prescreening, the possibility of drop-outs after blood testing in a group with higher susceptibility to hepatitis A and the increased number of needle-pricks per child, we can conclude that the reduction in expenses in the age group < 5 years is small compared with the age group 5+ years.

In conclusion, we recommend that all children with CLD > 2 years old be given the hepatitis A vaccine to prevent serious complications from superimposed liver insult on their diseased livers. Prescreening is cost-effective in children 5+ years of age while prescreening in children < 5 years of age may not be cost-effective.

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