

CHILDHOOD EPIDEMIOLOGY OF HEPATITIS A VIRUS IN RIYADH, SAUDI ARABIA

Mohamed Khalil, MBBCh, MPH, MSc, MD; Yagob Al-Mazrou, MBBCh, FRCGP, PhD;
Mohamed Al-Jeffri, MBBCh, MTM; Mansour Al-Howasi, MBBCh, FRCP

The prevalence of anti-HAV antibody in children was tested in subjects presenting at clinics in Riyadh, Saudi Arabia. A blood sample was taken to test for the presence of IgG (indicating past infection) and a questionnaire concerning personal and epidemiological data relating to hepatitis A was completed. In total, 592 children aged 6 months to 15 years were suitable for the analysis. There were 179 subjects who were positive for HAV (30.2%). The proportions of subjects positive for HAV varied significantly with age ($P=0.001$); 32%-49% in the 7-15 age range were positive compared with 13-20% aged 6 and below. There was a significant association between a positive HAV test and social level ($P=0.044$), with a higher proportion positive in the low social level. Children with jaundice, personal history of jaundice or travel abroad were significantly more likely to be HAV positive ($P=0.001$, $P=0.006$, $P=0.021$, respectively). There was also a significant association with nationality ($P=0.022$), where the lowest proportion of HAV positive children were Saudi Arabian (28%). Compared to previous studies, there is a significant decrease in the HAV exposure in Saudi children with shift from high to intermediate pattern. National strategy for prevention should be evaluated. *Ann Saudi Med* 1998;18(1):18-21.

Hepatitis A virus (HAV) is a member of Picornaviridae and one of the series of hepatitis viruses responsible for acute viral hepatitis (AVH) infections. It is transmitted via the fecal-oral route and most people become infected during childhood by the ingestion of contaminated food or water.¹ Its clinical manifestations can vary widely, but one of the most important factors affecting disease severity is age. More than 90% of HAV infections in children under the age of five can be subclinical. Thereafter, the proportion of patients with a symptomatic infection increases with age, reaching 70%-80% in adults.² Typical symptoms are anorexia, malaise, nausea and vomiting, fever and myalgia and, characteristically, patients have abnormally high levels of serum bilirubin and liver transaminases (ALT and AST) and many report abdominal pain.³ Most infected adults become symptomatically ill with jaundice² and it is usually the dark brown urine in the icteric phase which leads the patient to seek medical advice, leaving a growing pool of susceptible juveniles and adults.⁴ This study was undertaken to determine the current endemicity of hepatitis A among children in Saudi Arabia. To obtain information on possible levels of

immunity, this study measured serum levels of IgG HAV.

Patients and Methods

Recruitment to the study was conducted at three primary health care centers and the Suleimania Hospital in Riyadh, Saudi Arabia, between April 1995 and February 1996. Children below the age of 16 who presented to these centers or the hospital for clinic appointments and those admitted to the hospital for in-patient care were included in the study. In addition, healthy siblings who accompanied the presenting child were also recruited if consent was given. A sample size of 600 was calculated on the assumptions of an expected frequency of positive anti-HAV of 50%. If the true value were 50%, the 95% confidence interval for worst expected result in the true population would be 40%-60%. There was approximately equal recruitment in three age strata: up to age 5, ages 6 to 10, and ages 11 to 15. Subjects, or their parent/guardian, gave informed oral witnessed consent before participation in the study. A questionnaire was completed for each subject concerning personal and epidemiological data relating to hepatitis A. Apart from demographic data, such as age and sex, the questionnaire asked for details of the home environment (urban/rural/Bedouin, housing conditions and social level), previous contact with jaundice, nationality and travel abroad.

A sample of blood (3-5 mL) was taken from each

From the Departments of Preventive Medicine and Infectious Diseases, Ministry of Health, Saudi Arabia.

Address reprint requests and correspondence to Dr. Khalil: STAT/Advisory Medical Center for Research Development, 47 Mohamed Sayed Ahmed Street, Cairo 11421, Helwan, Egypt.

Accepted for publication 22 September 1997. Received 28 May 1997.

subject and stored at -20°C prior to serological analysis. There was a mean difference of 46 days (range: 1-212) between blood sampling and laboratory testing, although fewer than 5% of samples were tested more than 150 days after sampling. Serum samples were analyzed using an ELISA kit (modified HAVAB, Abbott Laboratories), a sample being considered positive for HAV if the IgG titre result was 10 mIU/mL or greater.

The results were expressed as the proportion of subjects in each group, or subgroup, positive for HAV with a 95% confidence interval (CI). All data were summarized using SAS (Version 6.10). Confidence intervals were not calculated for subgroups of less than 10 subjects. Evaluation of the relationship of each variable with HAV status was determined using the chi-squared test, or Fisher's exact test. Statistical significance was assumed at the conventional level of $P < 0.05$ and all quoted P -values are two-sided.

Results

A total of 604 children were included in the study. Twelve subjects were excluded from analysis on the basis of age (less than six months old). The male:female ratio was approximately 2:1 and subjects ranged in age from 6 months to 15 years. A majority of the children were of Saudi Arabian nationality (83%) and living in an urban environment (79%). Only a small proportion had a history of contact with jaundice (11%) and even fewer had a personal history of jaundice (5%).

There were 179 subjects who were positive for HAV (30.2%; 95% C.I. 27%, 34%). The HAV results for all the subgroups tested are shown in Table 1.

The proportions of subjects positive for HAV varied significantly with age, with the higher proportions among the older children ($P=0.001$); 32%-49% in the 7-15 age range were positive compared with 13%-20% aged 6 and below. With the exception of the 9-10 age group, there was no overlap in the 95% confidence intervals for children aged 7 to 15 with those for children aged six and below. There was no statistically significant difference between male and female children in the proportions who were HAV positive ($P=0.75$).

There was a statistically significant association between a positive HAV test and social level ($P=0.044$). A higher proportion of children from the low social level were HAV positive (41%) than those categorized as being in the high and medium social levels (26% and 29%, respectively), with only a marginal overlap in the 95% confidence interval for the low level and those for the high and medium levels. The effects of residential environment were less marked. Although there was a higher proportion of children living in a rural environment who were HAV positive (39%) than in urban (28%) or Bedouin (26%)

environments, the effect did not reach statistical significance ($P=0.094$). A positive test result was significantly more likely in those children who had had contact with jaundice or had a personal history of jaundice ($P=0.001$ and $P=0.006$, respectively).

The lowest proportion of HAV-positive children was seen among those of Saudi Arabian nationality (28%), with 41% of children of Middle Eastern nationality being HAV positive. Fewer than 3% of subjects were of other nationalities and the proportions who were HAV positive in these groups were generally higher. Overall, there was a statistically significant association between HAV positivity and nationality ($P=0.022$). There was also evidence of a significantly higher proportion of HAV-positive children among those who had travelled abroad ($P=0.021$). Since most of those who had travelled abroad had been to the Middle East (29% of subjects overall), with only 4% having visited the Far East or other countries, and since children had travelled to more than one destination, there was no overall evidence of an association between a specific foreign destination and a positive HAV result.

Discussion

A similar study performed 10 years ago⁴ to measure total HAV antibody (mainly IgG) found that 23% of children aged four months to four years were HAV positive. The proportion rose to 64% at ages 5 to 9 and 87% at ages 10 to 14. This contrasts quite markedly with the results of our survey, where 14% (25/183) of the children aged 4 or less were HAV positive, rising to 33% (52/158) at ages 5 to 8 and 41% at ages 9 to 15 (102/251). This would suggest a halving of the infection rate in children in a 10-year period. Similar results have been reported from a survey carried out in Riyadh two years ago.⁶ The prevalence of anti-HAV IgG in subjects aged 1 to 9 years had fallen from 53% in 1986 to 39% in 1994 and in adults aged 20 to 30 years from 91% to 78%. Both reductions were statistically significant. This trend has also been confirmed in others studies.⁷

Previously, HAV was endemic in the region; the adult incidence of anti-HAV antibodies measured in Saudi Arabia,⁴ Jordan⁸ and Egypt⁹ was over 90% in the 1980s. It would appear that the improvements in living conditions, which began only 10 years ago, have now led to a reduction in HAV prevalence. In the Mediterranean basin, a similar reduction in prevalence has been reported from Greece,¹⁰ and data from Israel¹¹ showed a statistically significant reduction in HAV prevalence in young men from 69% in 1977 to 54% in 1984 ($P > 0.0001$).

No differences were observed between male and female children, supporting previous observations.^{4,7} A higher prevalence of anti-HAV was detected in children from the lower social level and rural environment, although the

TABLE 1. Proportion of subjects positive for HAV in each subgroup.

Variable	Total in group	Positive for HAV	Proportion of subgroup positive for HAV*
All subjects	592	179	30.2% (27%, 34%)
Sex			
Male	388 (65.5%)	119	30.7% (26%, 35%)
Female	204 (34.5%)	60	29.4% (23%, 36%)
Age (yrs)			
0.5-2	88 (14.9%)	11	12.5% (6%, 19%)
3-4	95 (16.0%)	14	14.7% (8%, 22%)
5-6	59 (10.0%)	12	20.3% (10%, 31%)
7-8	99 (16.7%)	40	40.4% (31%, 50%)
9-10	100 (16.9%)	32	32.0% (23%, 41%)
11-12	79 (13.3%)	35	44.3% (33%, 55%)
13-15	72 (12.2%)	35	48.6% (37%, 60%)
Environment			
Urban	465 (78.5%)	132	28.4% (24%, 32%)
Rural	108 (18.2%)	42	38.9% (30%, 48%)
Bedouin	19 (3.2%)	5	26.3% (6%, 47%)
Social level			
High	108 (18.2%)	28	25.9% (18%, 34%)
Medium	391 (66.0%)	113	28.9% (24%, 33%)
Low	93 (15.7%)	38	40.9% (31%, 51%)
Contact with jaundice			
Yes	66 (11.1%)	35	53.0% (41%, 65%)
No	526 (88.9%)	144	27.4% (24%, 31%)
History of jaundice			
Yes	28 (4.7%)	15	53.6% (35%, 72%)
No	564 (95.3%)	164	29.1% (25%, 33%)
Nationality			
Saudi Arabian	490 (82.8%)	136	27.8% (24%, 32%)
Middle Eastern	86 (14.5%)	35	40.7% (30%, 51%)
African	7 (1.2%)	3	42.9%
Indian	4 (0.7%)	2	50.0%
Southeast Asian	4 (0.7%)	3	75.0%
Other	1 (0.2%)	0	0
Travel abroad			
Yes	198 (33.4%)	72	36.4% (30%, 43%)
No	394 (66.6%)	107	27.2% (23%, 32%)
Destination			
Middle East	171 (28.9%)	63	36.8% (30%, 44%)
Far East	23 (3.9%)	9	39.1% (19%, 60%)
India	6 (1.0%)	4	66.7%
Africa	3 (0.5%)	1	33.3%
Other	25 (4.2%)	8	32.0% (13%, 51%)

*There was a 95% CI, and confidence interval was not calculated for subgroups of fewer than 10 subjects.

latter did not reach statistical significance. Clearly, this is due to a slower improvement in living conditions and hygiene in the lower social level and possibly also in rural communities. As would be expected, children with a history of jaundice or exposure to jaundice were significantly more likely to be anti-HAV positive.

The nationality differences we observed suggest that HAV endemicity is decreasing more rapidly in Saudi Arabia, with its high per capita income, than in other Middle Eastern countries. Saudi children who travel abroad are presumably more likely to be exposed to the

virus than those who remain at home, particularly since most were travelling to countries in the Middle and Far East rather than areas of low endemicity such as Western Europe and the USA.

Historically, hepatitis A virus was only rarely the cause of acute viral hepatitis (AVH) infections in Saudi Arabia, thanks to immunity acquired during childhood exposure. This is still the case in other Middle Eastern countries.¹² During the last four years, two studies have been carried out to determine the causative agent in cases of AVH in Saudi Arabian cities. HAV has been found to be responsible for 5% of adult cases of AVH³ and the major etiological agent in 11% of AVH patients over the age of 12 and 59% of patients aged 1 to 12 years.⁶ Recently, hepatitis outbreaks have been reported in rural towns following a large temporary influx of residents during the Gulf crisis. Cases of hepatitis A infection were significantly more likely to occur in households with poor sanitation or overcrowding.¹³ The problem of two groups with differing immunities living in close proximity has been recognized in other countries where immigrants from both European and Asian backgrounds come together.¹⁴ In time, HAV endemicity in Saudi Arabia may fall to low European levels, but the intermediate position, where there is a susceptible adolescent and young adult population in conjunction with a high level of circulating HAV, can result in large outbreaks in the age groups in which infection is symptomatic. Moreover, the presence of expatriate workers from regions where endemicity remains high may also be a cause of acute viral hepatitis infection in the local population. Also, the high proportion of children entering the schools without immunity may lead to explosive outbreaks. The need for close national surveillance and more effective general preventive measures is obvious during this period of transition. Vaccines against hepatitis A have recently been developed and have been shown to afford long-term protection against disease.¹⁵⁻¹⁶ The availability of vaccines and their widespread use will provide an opportunity to lower the overall incidence of hepatitis A disease. According to our study, the use of the vaccine should be encouraged in Saudi children. Further studies can be carried out to make solid recommendation of the vaccine in other groups at risk.

Acknowledgements

This study was supported in part by a grant from SmithKline Beecham. The authors would also like to thank Dr. T. Yasin of SB Middle East for his support of this project.

References

1. Zeldis JB, Shabib SM, Tufenkeji H. Diagnosis of viral hepatitis. Ann

- Saud Med 1995;15:1-5.
2. Ghabrah TM, Strickland GT, Tsarev S, et al. Acute viral hepatitis in Saudi Arabia: seroepidemiological analysis, risk factors, clinical manifestations, and evidence for a sixth hepatitis agent. *Clin Infect Dis* 1995;21:621-7.
 3. Centers for Disease Control. Protection against viral hepatitis. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1990;39:1-26.
 4. Shobokshi O, Serebour F, Abdul-Rahim SM. The prevalence and pattern of hepatitis A viral infection in the western region of Saudi Arabia. *Saudi Med J* 1986;7:402-8.
 5. Ramia S. Antibody against hepatitis A in Saudi Arabians and expatriates from various parts of the world working in Saudi Arabia. *J Infect* 1986;12:153-5.
 6. Arif M, Al-Faleh FZ, Al-Frayh AR, Ramia S. Reduction in the prevalence of antibody to hepatitis A virus among young Saudi adults: implications for hepatitis A vaccine. *Saudi J Gastroenterol* 1995;1:93-6.
 7. El-Hazmi MA. Hepatitis A antibodies: prevalence in Saudi Arabia. *J Trop Med Hyg* 1989;92:427-30.
 8. Toucan AU, Sharaiha ZK, Abu-El-Rob OA, et al. The seroepidemiology of hepatitis A virus infection in Jordan. *Trop Gastroenterol* 1988;9:76-9.
 9. El-Raziky EH, Zakaria S, Kamel M, Goldsmith R. Frequency of hepatitis A, B and other types of acute hepatitis in hospitalized adult patients in Egypt. *J Egypt Med Assoc* 1985;68:463-77.
 10. Kremastinou J, Dalapothaki V, Trichopoulos D. The changing epidemiologic pattern of hepatitis A infection in urban Greece. *Am J Epidemiol* 1984;120:703-6.
 11. Kark JD, Camhy NA, Bar Shany S. Reduction in hepatitis A antibody prevalence among young adults in Israel. *Public Health Rev* 1992/93;20:31-40.
 12. Bassily S, Hyams KC, El Ghorab NM, Ansari AA, Fanous AS. Acute sporadic hepatitis in adults living in Cairo, Egypt. *Am J Trop Med Hyg* 1986;35:1040-44.
 13. Bubshait S, Al-Qatani MS, Miller G, Fontaine RE. Hepatitis A epidemic in two Saudi towns. Symposium on Advances in Diagnosis and Management of Infectious Disease, Jeddah, 17-18 Jan. 1993.
 14. Karetnyi YV, Mendelson E, Shlyakhov E, et al. Prevalence of antibodies against hepatitis A virus among new immigrants in Israel. *J Med Virol* 1995;46:61-65.
 15. Werzberger A, Mensch B, Kuter B, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med* 1992;327:453-7.
 16. McMahon BJ, Beller M, Williams J, Schloss M, Tanttala H, Bulkow L. A program to control an outbreak of hepatitis A in Alaska by using an inactivated hepatitis A vaccine. *Arch Pediatr Adolesc Med* 1996;150:733-9.