

The Changing Epidemiology of Hepatitis A in Children and the Consideration of Active Immunization in Korea

Young Mo Sohn¹, Hye Ok Rho¹, Min Soo Park¹, Ji Ho Park¹, Bo Yul Choi², Moran Ki³, and Woo-Ick Jang⁴

Abstract

Currently, Korea is a low endemicity country for HAV, especially in children. However, recent reports of hepatitis A outbreaks show that there has been a shift of disease incidence to adolescents and young adults, with 2 cases of acute liver failure in one reported outbreak. We need to study the immune status for HAV in order to provide information for the establishment of preventive measures and possible consequences of HAV in Korea. A total of 334 infants, children and adolescents less than 20 years of age living in rural areas of Kyonggi Province, Korea were evaluated for anti-HAV immune status in 1996. Five hundred and eighty-four primary school children living in the same area were separately evaluated for the natural seroconversion rate between 1993 and follow-up samples taken in 1996. Anti-HAV IgG antibody was measured by enzyme immunoassay (HAVAB EIA kit, Abbott Laboratories, Chicago, Illinois, USA). In comparison with previous reports of seroprevalence rates, our data confirmed a dramatic drop in seroprevalence rates among children and adolescents under 20 years of age living in rural areas, from over 63.8% two decades ago to 4.6% in 1996. Natural acquisition of HAV antibody in primary school children rarely occurs, registering only 0.5% during three years. Several outbreaks in young adults during 1996–1998 suggested that immunity against HAV in this population is so low that massive outbreaks are unavoidable. Teenagers and young adults, especially soldiers, who are likely to be exposed to contaminated food or water, would also have a greater risk of hepatitis A. Immunizing children with HAV vaccine as a routine schedule should also be considered in Korea in the future, particularly if the disease burden could be estimated and the cost-effectiveness of the vaccine could be proved.

Key Words: Hepatitis A, epidemiology, hepatitis A outbreak, hepatitis A vaccine, immunization

INTRODUCTION

Since hepatitis A is not a reportable disease in Korea, there have been only a few reports observing the prevalence of hepatitis A infection. However, the incidence of hepatitis A during recent decades has decreased as sanitation and living standards have improved rapidly along with dramatic economic growth, as can be seen by the increase in per capita GNP from \$594 in 1975 and \$2,242 in 1985, to \$10,037

in 1995.¹ A retrospective study indicated that the proportion of clinical hepatitis A in the 1970s was about 2–5% of all hospitalized pediatric patients.² Although there was no systematic surveillance system during the 1980s, there were very few clinical hepatitis A patients reported. However, there has been two reports of hepatitis A outbreaks in adults and children since 1996.^{3,4} There is also the possibility of outbreaks of hepatitis A infection in the future because of the naive sense of immunity against hepatitis A virus (HAV) in the population.

To evaluate the changing pattern of the immune status to hepatitis A virus in Korean children, we investigated the age-specific anti-HAV antibody seroprevalence rate in children and adolescents living in Kyonggi Province. We reviewed the seroprevalence rates reported in the literature in the past 20 years to consolidate the observed decreasing trend. We also measured the natural infection rate over a three-year follow-up period among primary

Received June 25, 1999

Accepted October 11, 1999

¹Department of Pediatrics, Yonsei University College of Medicine,

²Department of Preventive Medicine, Hanyang University College of Medicine, ³Department of Preventive Medicine, Eulji Medical College, ⁴SmithKline Beecham Korea, Seoul, Korea.

This study was supported in part by SmithKline Beecham International, Seoul, Korea.

Address reprint request to Dr. Y. M. Sohn, Department of Pediatrics, Yonsei Severance Hospital, Yonsei University College of Medicine, Yonsei P.O. Box 1217, Seoul 135-270, Korea. Tel: 82-2-3497-3354, Fax: 82-2-3461-9473, E-mail: youngmo@yumc.yonsei.ac.kr

school children to obtain basic information on the incidence of HAV infection.

MATERIALS AND METHODS

Subjects

For the evaluation of the National Immunization Program by the Ministry of Health and Welfare, a seroepidemiologic study has been carried out since 1996. At the time, a total of 334 healthy infants, children and adolescents less than 20 years of age living in Kyonggi Province, as the first group, were involved in testing for hepatitis A antibody. The sites involved were four counties including Paju, Kimpo, Yangpyong, Hwasong and four cities, Kuri, Suwon, Puchon, and Uijongbu, where a clean water supply and sanitation system had been established (Table 1). We obtained sera from 334 subjects during 1996 and measured anti-HVA IgG in 1998.

As the second group, we evaluated the HAV immune status of 584 children who were enrolled in 1993 to evaluate the immune status of the same subjects who were involved in a 1996 seroepidemiologic study of primary school children. We evaluated the natural seroconversion rate of hepatitis A among 584 paired sera from the children evaluated in 1993 and 1996.

The socioeconomic status of the families of subjects was evaluated by a questionnaire about personal hygiene, living environment and family income.

Methods of anti-HAV antibody assay

The 334 serum samples obtained from the first

group in 1996 and the 584 paired sera from the second group obtained in 1993 and 1996 were stored frozen at 70°C and labelled with name and ID number. At each blood collection in 1996, 2 ml of blood was drawn and centrifuged for separation of serum, which was then stored frozen at -70°C. Anti-HAV IgG antibody was measured by enzyme immunoassay (HAVAB EIA kit, Abbott Laboratories, Chicago, Illinois, USA). As standards, we used 3 negative and 2 positive reference reagents instead of the provided test sera. The cut-off value was calculated from the average absorbance value of the negative and positive reference reagents. We reviewed the published literature of hepatitis A in Korea and compared it with our results.

RESULTS

Anti-HAV antibody seroprevalence rate

Among 334 subjects under 20 years of age living in Kyonggi Province, 53.6% were male and 46.4% were female. There were 3.3% of subjects under the age of 1 whose seropositive rate was 27.3% reflecting maternal IgG. In total, only 15 (4.6%) subjects less than 20 years of age, apart from maternal IgG, were found to have anti-HAV IgG antibodies (Table 2). It is unlikely that a boy who had naturally acquired anti-HAV IgG antibody in 1993 serum and had lost antibody in 1996 serum by enzyme immunoassay (HAVAB EIA kit) would have lost immunity to HAV infection. Rather, we assumed that even though his antibody titer in the 1996 serum fell below the

Table 1. Age and Sex Distribution of Study Subjects Aged Less Than 20 Years of Age Living in Kyonggi Province in 1997

Age (yr)	Male	Female	Total (%)
<1	7	4	11 (3.3)
1-4	48	33	81 (24.3)
5-9	30	27	57 (17.1)
10-14	53	52	105 (31.4)
15-19	41	39	80 (24.0)
Total (%)	179 (53.6)	155 (46.4)	334 (100.0)

Table 2. Seroprevalence Rate of Anti-HAV IgG According to Sex and Age of Subjects Less Than 20 Years of Age Living in Kyonggi Province in 1997

Age (yr)	Male	Female	Total
<1	42.9% (3/7)*	0.0% (0/4)	27.3% (3/11)
1-4	0.0% (0/48)	0.0% (0/33)	0.0% (0/81)
5-9	0.0% (0/30)	0.0% (0/27)	0.0% (0/57)
10-14	3.8% (2/53)	1.9% (1/52)	2.9% (3/105)
15-19	12.2% (5/41)	17.9% (7/39)	15.0% (12/80)
Total	5.6% (10/179)	5.2% (8/155)	5.4% (18/334)

No. of positive/No. of tested.

Table 3. Natural Seroconversion Rates of HAV Infection in Elementary School Children

Sex	N	1993		1996	
		n	%	n	%
Male	299	1	0.3	2	0.7
Female	285	0	0.0	1	0.3
Total	584	1	0.2	3	0.5

N, Total number of subjects in each gender class; n, Number of seropositive subjects.

cut-off level, he would still retain immunity against HAV, which could be elicited by anamnestic response to secondary exposure.

Natural seroconversion rate of anti-HAV antibody in primary school

We tested for anti-HAV IgG antibody in 584 primary school children from 8 study sites in the rural areas of Kyonggi Province in 1993 and performed a follow-up in 1996 (Table 3). Their age ranged from 8 to 13 years; of which 51.2% were boys. The questionnaire indicated their living environment and sanitation were good, but the family income was half that of the average income in urban areas. Only one boy had anti-HAV IgG antibodies in 1993 and three children (two boys and one girl) were seroconverted in 1996. They did not have any relation to inhabitancy. The natural seroconversion rate for hepatitis A was 0.5% (3/583). However, the boy who had IgG antibody in the serum collected in 1993 lost antibody in 1996. Among the three children who were seropositive in 1996, only one subject had clinical manifestations such as vomiting and abdominal pain, though unconfirmed as hepatitis A, during the follow-up period, while the other two did not have any signs of illness.

DISCUSSION

Viral hepatitis is a worldwide problem and HAV is responsible for 75% of all hepatitis in the world. Approximately 1.4 million cases of hepatitis A are annually reported worldwide, with an estimated cost

of US \$1.5–\$3 billion.⁵ However, the actual incidence and disease burden of hepatitis A infection in developed and developing countries is thought to be higher than recognized. The actual infection rate has been estimated as 3–10 times higher than reported.⁶ In Korea, hepatitis A seemed not to be a serious disease during the last 20 years as a result of early acquisition of immunity. But during the past several years, several outbreaks of hepatitis A have occurred in young adults. These outbreaks seem to be related to national economic growth, increasing the susceptible population during early childhood in Korea. With limited seroepidemiologic data in Korea, Hong et al. in the late 1970s reported that the anti-HAV antibody seropositivity rate in children under the age of 10 was about 45%, and about 90–100% for those over 20 years, suggesting that almost everybody was exposed to HAV during childhood.^{7,8} According to the literature, the proportion of symptomatic hepatitis A in children in the 1970s was about 2–5% of all hospitalized pediatric patients.² This pattern, when GNP was \$594 in 1975 and the waterworks supply rate was 33.2% in 1970, was similar to that in highly endemic areas in other developing countries where infection occurred primarily through person-to-person contact in early childhood and outbreaks, though uncommon, occurred in schools.

Since 1980, Korea has experienced rapid economic growth and increasing family income. The living conditions and sanitation have also improved, shown by the rise in GNP from \$1,647 in 1979 to \$10,543 in 1996, while a 42% waterworks supply rate in 1974 increased to 82.9% in 1996.^{1,8} This improvement of sanitation conferred more protection on children against hepatitis A. In 1989, the anti-HAV antibody seropositivity rate reported in children under 10 years of age in rural areas of Chonbuk Province had dropped to 27%.⁹

We compared the results of previous reports on the seroprevalence rate among subjects under 20 years of age living in rural or urban areas to try to determine the evidence of the future impending risk of hepatitis A with no practical control of hepatitis A infection in adulthood.

The overall seropositive rate of HAV IgG in subjects under 20 years of age was 63.8% in 1979⁸ and 50.3% in 1989,⁹ followed by a rapid decline to 11.7% in 1995,³ 4.5% in 1996 in one study¹⁰ and 4.6% in 1996 in our data (Table 4). One study in

Table 4. Changes in Seroprevalence Rates of Hepatitis A Virus Infection in Children and Adolescents During Two Decades in Different Regions in Korea[†]

Age (yrs)	1979 Seoul and Kyonggi Province	1988 Chinju City	1989 Chonbuk Province	1995 Seoul City	1996 Daejun City	1996 Chinju City	1996 Kyonggi Province
1-19	63.8% (141/221)*	42.3% (169/400)	50.3% (85/169)	11.7% (42/359)	8.5% (22/256)	9.5% (36/398)	4.6% (15/323)
Ref.	8	11	9	3	4	11	Authors

* No. positive/No. tested.

[†] Tap water supply rate was 42% in 1974 and increased to 82.9% nationwide in 1996. However, the urban area of Seoul was 99.9%.

GNP was \$1,647 in 1979 and increased to \$10,543 in 1996.

Table 5. The Age Distribution of Reported Cases of Hepatitis A Patients Serologically Diagnosed from 85 Hospitals During 1996-1998

Age group	No. of cases (%)	Total population*	Incidence rate (/10 ⁵)
<5	12 (0.9)	3,591,874	0.3
5-14	193 (14.1)	6,699,702	2.9
15-29	875 (64.0)	12,545,037	7.0
30-49	271 (19.8)	14,466,221	1.9
>49	16 (1.2)	8,688,423	0.2
Total	1367 (100.0)	45,991,257	3.0

* The total population was based on 1997 figures.

northwestern parts of Daejeon, where an outbreak in children occurred in 1996, showed an 8.5% seroprevalence rate.⁴ Although the studies were performed in different regions, there seemed to be no definite regional discrepancy of seroprevalence in 1996. We observed that the natural positive seroconversion rate over 3 years was 0.5% in rural areas in Kyonggi Province, where the waterworks supply rate was 82.9% and family income was half that of the average income in urban areas of Seoul, where the tap waterworks rate was nearly 99.9%,⁸ suggesting that antibody acquisition is negligible in childhood. We reviewed and tabulated in aged adjustment one report studying changing patterns on the seroprevalence of HAV infection among the same population in one city, Chinju, during 10 years from 1988 to 1997.¹⁰ Tables 4 and 5 show a definite shifting of the cohort from children towards young adult groups. The sero-

positive rate of teenagers and young adults living in Chinju was 65% in 1988, decreasing to 14.6% in 1996. The results of epidemiologic study including our data indicated that Korea is in transition from high to low endemic regions.

The low natural infection rate clearly indicates that a large part of the younger population is susceptible to HAV infection with the potential for large-scale outbreaks, unless they acquire proper immunity.¹¹ This leaves a large part of the population unprotected at an adult age when disease is usually more severe, with the consequent rise in medical costs and socio-economic burden. As suggested by Pebody et al, that food-borne or water-borne outbreaks in susceptible people may become a problem in the future, this might also prove to be true in Korea.¹²

However, some observations of regional outbreaks of hepatitis A have recently been reported. Choi et al. reported a clustered HAV infection in 31 children and 50 adults hospitalized in Seogu, Daejeon in 1996.⁴ Young adults in their early 20s were particularly affected, and the source of infection was not confirmed. Lee et al. reported a nationwide survey of hepatitis A patients with HAV IgM antibody positive serologic diagnosis from 85 hospitals during two years from July 1996 to June 1998.¹³ The total reported cases were 1,367; 762 were male and 605 were female; while 64 percent of all patients were in the age between 15 and 29. The age distribution of reported cases of hepatitis A indicated that a majority of patients was in their late teens or young adulthood, especially soldiers (Table 5). Two patients died of fulminant hepatitis. The case-fatality rate was 1.5 per 10.⁵

This strong evidence of the decreasing incidence of

hepatitis A virus infection under 20 years of age during the last two decades as a result of improved personal hygiene and living conditions supported by economic growth, will increase the risk of future outbreaks occurring, such as a trip to the endemic area of Southeast Asia or imported food or even workers from these areas. In addition, with globalization and increasing international commerce and travel to and from the endemic areas of Southeast Asia, Korean people are now highly susceptible to potential massive outbreaks of HAV, especially with such a low seroprevalence rate. Moreover, under the current economic difficulties in Korea, sanitation in specific populations could deteriorate and increase the risk of infection. Hepatitis A seems to have become a major cause of acute viral hepatitis in young adults in Korea since 1996.

Inactivated hepatitis A vaccine (Havrix^R, Smith-Kline Beecham and Vaqta^R, Merk) has been available since 1997 in Korea and 150,000 doses have been injected each year. The vaccine is recommended for use in people including children who are at increased risk of infection (persons in frequent contact with hepatitis A patients, children in nurseries or schools or institutions where hepatitis A breaks out, or persons who plan to travel to hepatitis A endemic areas). Although immunization with hepatitis A vaccine is not recommended in healthy children as part of a routine immunization schedule, immunization of children over 1 year of age is recommended in some private sectors. As children constitute a reservoir for the virus where infection is often not apparent and where recent outbreaks occurred mostly in young adults with clinical symptoms, routine immunization of children might also be considered in Korea if it proves to be cost-effective. However, any immunization schedule should be evaluated as to whether children under 18 months of age would be necessary.

In the past in Korea, hepatitis A did not cause major problems in adults since most people acquired anti-HAV antibodies through natural infection during childhood, when the disease is mainly asymptomatic. Our recent data showed a dramatic drop in seroprevalence rates in children and adolescents under 20 year of age from over 60% two decades ago to about 4.5% currently. Natural acquisition of hepatitis A antibody in primary school children rarely occurs. Korea seems to be a country in transition from a high to low endemic region and faces the paradox of

increasing disease burden with decreasing disease incidence. Since 1996, several outbreaks of hepatitis A in young adults and school children have indicated that there is a need for active immunization of adolescents and young adults at increased risk. Korea requires an evaluation of the cost-effectiveness of implementing a routine schedule of HAV immunization in children.

ACKNOWLEDGEMENTS

We acknowledge the technical assistance of Jeong Bae Ahn and Seok-Hyun Kim in the National Institute of Health Korea.

REFERENCES

1. National Statistical Office. Korea statistical year book 1998. National statistical office. Republic of Korea 1998; 45:505-7.
2. Lee EJ, Pai SK, Kim JT, Kim WC, Yoon DJ. Clinical observation of communicable hepatitis. *J Korean Pediatr Soc* 1976;18:561-6.
3. Chung KM, Lim HJ, Kwon OS, Park HT, Kim JH, Yon JE, et al. An outbreak of apparent hepatitis A infection in Kyonggi-Seoul area. *J Korean Soc Intern Med* 1996; 51:S35.
4. Choi JW, Lee KI, Lee DJ, Han JH, Hwang SS, Lee KS. An outbreak of acute hepatitis A infection in North-western part of Daejeon in 1996. *J Korean Pediatr Infect* 1997;4:90-6.
5. Halder SC. Global impact of hepatitis A virus infection: changing patterns. In: Hollinger FB, Limon SM, Margolis HS, editors. *Viral Hepatitis and Liver Disease: Proceedings of the 1990 International Symposium on Viral hepatitis and Liver Disease: contemporary issues and future prospects*. Baltimore: Williams & Wilkins; 1991. p.14-20.
6. Kane MA. Perspectives on the control of hepatitis A by vaccination. *Vaccine* 1992;10:S93-6.
7. Hong WS, Kim JY. Seroepidemiology of Hepatitis A and B infections in Seoul. *J Korean Soc Intern Med* 1982; 25:19-26.
8. Lim DS, Cho KH, Kim HC. Epidemiologic study of Hepatitis A viral hepatitis in Northwestern area of Chonbuk Province in 1989. *J Korean Soc Intern Med* 1992;43: 57-63.
9. Ministry of Environment. 97 statistics of sewerage. Ministry of Environment Republic of Korea; 1997. p.55-70.
10. Kim EA, Cho YK, Lim JY, Jung YS, Lee SE, Kim YS, et al. Seroepidemiologic study of anti-hepatitis A virus IgG during 1988-1997 in Chinju, Korea. *Korean J Gastroenterol* 1998;32 Suppl 1:107.

11. Rooney PJ, Coyle PV. The role of herd immunity in an epidemic cycle of hepatitis A. *J Infect* 1992;24:327-31.
 12. Pebody RG, Leino T, Ruutu P, Kinnunen L, Davidkin I, Nohynek H. Food-borne outbreaks of hepatitis A in a low endemic country: an emerging problem. *Epidemiol Infect* 1998;120:55-9.
 13. Lee CH, Chung KW, Moon YM, Yoo JY, Suh DJ, Lee SG, et al. An outbreak of hepatitis A in Korean young adults in 1998. *Korean J Gastroenterol* 1998;32 Suppl 1:105.
-