

## Laboratory characteristics of recent hepatitis A in Korea: Ongoing epidemiological shift

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### Abstract

**AIM:** To evaluate seroprevalence of hepatitis A virus (HAV) antibody and investigate demographic, clinical, and laboratory features of recent cases in Korea.

**METHODS:** For the evaluation of hepatitis A seroprevalence, we analyzed the data from 3127 subjects including, healthcare workers and patients who visited Konkuk University Hospital, a secondary referral center, from January to October 2009. The sera with positive IgM were excluded from seroprevalence data for total HAV antibody. We retrospectively reviewed the electronic medical records of 419 patients with HAV, who were diagnosed by the presence of serum IgM antibodies against HAV. All patients presented at Konkuk University Hospital between August 2005 and September 2008.

**RESULTS:** Among 3127 sera tested, 1428 (45.7%)

were positive for anti-HAV antibody. The seroprevalence was very low in teenagers or those in their twenties, increased in those in their thirties, and was > 90% in older patients. In children younger than 10 years, seroprevalence was increased again. Most patients with HAV hepatitis were in their twenties and thirties. The  $\gamma$ -glutamyl transpeptidase increased with age and was significantly higher in patients older than 30 years. Indicators of severity, such as decreased albumin and increased bilirubin, were also more prominent in the older age group; however, the leukocyte count was higher and the frequency of leukopenia was lower in younger patients than in older adults.

**CONCLUSION:** There has been an apparent epidemiological shift in HAV seroprevalence and a change in the peak age of HAV hepatitis. This study could provide baseline data of recent hepatitis A in Asia.

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**Key words:** Hepatitis A virus; Seroprevalence; Epidemiology; Korea

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### INTRODUCTION

The hepatitis A virus (HAV) is included in the picornaviridae family of viruses, which are small, non-enveloped,

single-stranded RNA viruses<sup>[1]</sup>. They are transmitted almost exclusively by the fecal-oral route, and transmission is enhanced by poor hygiene, overcrowding, and contaminated food or drink<sup>[2]</sup>. Infection with HAV is prevalent throughout the world, but it shows diverse epidemiological patterns according to the socioeconomic conditions<sup>[3,4]</sup>. A high prevalence of this virus is associated with poor hygiene and living standards<sup>[5]</sup>. In hyperendemic areas, almost all people have protective anti-HAV antibodies as a result of subclinical exposure during childhood<sup>[2]</sup>; however, improved environmental conditions have resulted in fewer subclinical infections and a subsequent increase in the non-immune population. In Korea, there has been a rapid epidemiological shift in HAV infection as a result of rapid economic development<sup>[3,6,7]</sup>. In 1980, most adults had immunity to HAV because of childhood exposure. Currently, less than 10% of people in their teens or twenties have anti-HAV IgG<sup>[6]</sup>. Thus, adult cases of acute hepatitis A have increased rapidly during the past 10 years due to the emergence of susceptible adults in Korea<sup>[6,8]</sup>.

In this study, we evaluated seroprevalence of total HAV antibody and investigated demographic, clinical, and laboratory features of recent cases of hepatitis A in Korea, where there is an ongoing epidemiological shift. Moreover, we compared laboratory characteristics of HAV according to patient age before and after the epidemiological shift.

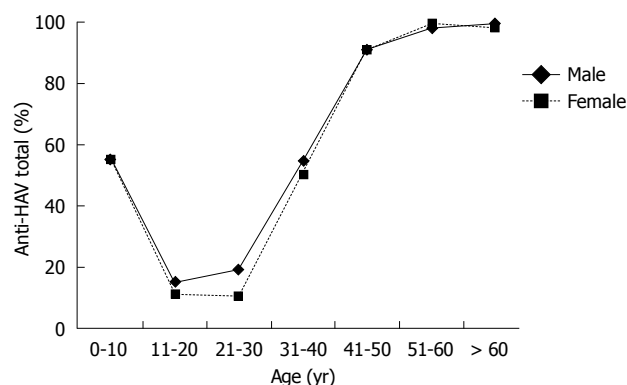
## MATERIALS AND METHODS

### Study populations

For the evaluation of hepatitis A seroprevalence, we analyzed the data from 3127 subjects, including healthcare workers and patients, who visited Konkuk University Hospital, a secondary referral center, from January to October 2009. The sera with positive IgM were excluded from the seroprevalence data for total HAV antibody. We retrospectively reviewed the electronic medical records of 419 patients with HAV, who were diagnosed by the presence of serum IgM against HAV. All patients presented at Konkuk University Hospital between August 2005 and September 2008. We investigated the clinical, laboratory, and epidemiological features of these patients and analyzed age-specific characteristics. We compared laboratory findings of patients who are younger and older than 30 years of age because these groups were considered to have been exposed to different epidemiological environments, based on the results of total HAV antibody seroprevalence in other recent studies<sup>[6,7]</sup>.

### Laboratory tests

A routine chemistry test (Neo-200FR autoanalyzer; Toshiba Medical Systems Co., Tokyo, Japan), complete blood count, and coagulation studies (Sysmex Co., Kobe, Japan) were performed. We tested serum total HAV antibody using the HAV Total immunoassay kit (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). To detect serum anti-HAV IgM, we used commercially available



**Figure 1** Age-specific seroprevalence of total anti-hepatitis A virus (HAV) antibody in Korea. The seroprevalence was very low in patients in their teens or twenties, increased in those in their thirties, and was > 90% in older patients. In children younger than 10 years, seroprevalence was increased ( $n = 3127$ ).

electrochemiluminescence immunoassay kits (Roche Diagnostics, Mannheim, Germany).

### Statistical analysis

Relationships between variables were analyzed using the Fisher exact test for categorical variables and Student's *t* test for continuous variables. Statistical analysis was performed using SPSS software, version 11.0 (SPSS Inc., Chicago, IL, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS

### Age-specific seroprevalence of total anti-HAV antibody

The median age of population tested was 31 years and 43.2% were male. Among 3127 sera tested, 1428 (45.7%) were positive for total anti-HAV antibody. The seroprevalence was different depending on age and sex (Figure 1). The seroprevalence was very low in patients in their teens or twenties, increased in the those in their thirties, and was > 90% in older patients. In children younger than 10 years, seroprevalence was increased.

### Characteristics of hepatitis A cases in Korea

The median age of 419 patients with HAV hepatitis was 29 years and 62% were male. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) showed a marked increase in almost all patients, and ALT was higher in most cases (median AST/ALT ratio 0.7). Variable elevations of alkaline phosphatase (ALP),  $\gamma$ -glutamyl transpeptidase (GGT), and total bilirubin (TB) were evident in most patients. Leukopenia, thrombocytopenia, and prolonged prothrombin times (PT) were common findings. Among 419 cases, 352 patients (84%) needed hospital admission, and the median hospitalization period was 6 d (range: 1-31 d). Frequent symptoms were nausea/vomiting (55%), fever (49%), anorexia (34%), myalgia (32%), abdominal pain (23%), and dark urine (20%).

Twenty-one patients (5%) were chronic hepatitis B carriers. There were no cases of fulminant hepatitis or death in the study period.

**Table 1** Age distribution and age-specific laboratory findings of Korean hepatitis A cases

	Age (yr)			
	≤ 20	21-30	31-40	> 40
<i>n</i> (%)	22 (5.2)	241 (57.5)	132 (31.5)	24 (5.7)
Male:female (ratio)	13:9 (1.4)	141:100 (1.4)	93:39 (2.4)	13:11 (1.2)
Laboratory finding [median (range)]				
AST (IU/L)	2130 (105-15390)	2265 (37-16330)	2128 (44-15450)	1661 (19-5980)
ALT (IU/L)	2384 (492-9020)	2601 (15-9820)	2586 (42-12420)	1988 (11-5530)
ALP (IU/L)	254 (124-711)	201 (41-936)	222 (65-883)	252 (138-527)
GGT (IU/L)	302 (128-781)	345 (8-1195)	411 (37-1705)	479 (29-705)
TB (mg/dL)	5.3 (0.3-11.0)	5.0 (0.3-21.6)	6.1 (0.4-40.2)	5.5 (0.4-17.5)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT:  $\gamma$ -glutamyl transpeptidase; TB: Total bilirubin.

**Table 2** Comparison of laboratory characteristics according to age (mean  $\pm$  SD)

	Age (yr)		<i>P</i> value
	≤ 30 ( <i>n</i> = 263)	> 30 ( <i>n</i> = 156)	
Male:female	154:109	106:50	0.061
Laboratory finding			
AST (IU/L)	2254 $\pm$ 2598	2056 $\pm$ 2542	0.450
ALT (IU/L)	2583 $\pm$ 1999	2494 $\pm$ 2140	0.669
AST/ALT ratio	0.9 $\pm$ 1.3	0.8 $\pm$ 0.7	0.326
ALP (IU/L)	205.8 $\pm$ 109.5	227.1 $\pm$ 117.2	0.062
GGT (IU/L)	342 $\pm$ 197.9	421 $\pm$ 299.6	0.006
TB (mg/dL)	5.0 $\pm$ 4.0	6.0 $\pm$ 6.0	0.051
Albumin (g/dL)	4.0 $\pm$ 0.3	3.8 $\pm$ 0.3	0.000
Globulin (g/dL)	2.9 $\pm$ 0.4	3.1 $\pm$ 0.4	0.012
Leukocyte count ( $\times 10^9/L$ )	5.0 $\pm$ 1.9	5.6 $\pm$ 2.5	0.002
Leukopenia (%)	33.3	20.5	0.003
Platelet count ( $\times 10^9/L$ )	169 $\pm$ 74	181 $\pm$ 75	0.111
Thrombocytopenia (%)	45.6	39.0	0.218
PT (s)	15.1 $\pm$ 2.5	15.1 $\pm$ 3.3	0.978
Prolonged PT (%)	43.5	38.7	0.356
aPTT (s)	41.7 $\pm$ 5.3	41.1 $\pm$ 5.6	0.302
Prolonged aPTT (%)	24.0	17.6	0.173
Hospital stay (d)	6.5 $\pm$ 4.6	6.7 $\pm$ 7.4	0.771

PT: Prothrombin times; aPTT: Activated partial thromboplastin time.

### Age distribution of recent hepatitis A in Korea and age-specific laboratory findings

Patients with HAV were mostly in their twenties (57.5%) and thirties (31.5%) (Table 1). The number of patients in the other age groups ( $\leq 20$  or  $> 40$  years) were relatively few (5.2% and 5.7%). There was only one patient younger than 10 years old. Men were more prevalent in all age groups, and this tendency was more pronounced for men in their thirties (M/F ratio 2.4). GGT increased with age ( $P = 0.011$ ), but other laboratory findings were not significantly different between age groups.

We compared laboratory findings of the patients who are younger and older than 30 years old (Table 2). Levels of the enzymes AST, ALT, and ALP were not significantly different between the two groups; however, the older age group showed a significant increase in GGT, decrease in albumin, and increase in globulin (decreased A/G ratio) ( $P = 0.006$ ,  $P = 0.000$ , and  $P = 0.012$ , respectively). TB was also increased in the older group,

although this was not statistically significant ( $P = 0.051$ ). In contrast, abnormalities in hematological parameters were more severe in the younger group, especially with regard to decreased leukocyte count. The results of coagulation studies and duration of hospital stay were not significantly different.

## DISCUSSION

In highly endemic areas with poor socioeconomic conditions, HAV infection occurs in young children, possibly due to a lack of transmission control and the ubiquitous presence of HAV in the environment<sup>[5,9]</sup>. In contrast, HAV exposure is relatively rare in developed countries such as the United States, Canada, and countries in Western Europe because possible transmission factors are controlled<sup>[2,4,10,11]</sup>. The majority of symptomatic cases occur in adolescents, adults, and people with risk factors<sup>[4]</sup>. HAV infection in non-immune adults can cause severe hepatitis<sup>[12-14]</sup>. Complications include coagulopathy, encephalopathy, renal failure, prolonged disease, and disease relapses<sup>[9]</sup>. In the past in South Korea (1980s), HAV was endemic, and most adults acquired natural immunity through asymptomatic infection<sup>[7,15]</sup>. Due to the rapid improvement of socioeconomic conditions, the childhood incidence of HAV infection and the immune population have decreased, thus, the incidence of adult infection has increased steadily due to a lack of natural immunity<sup>[7,8,16,17]</sup>. After 2000, symptomatic cases of HAV infection increased markedly and the age of affected patients was significantly higher before 2000 than after 2000<sup>[7]</sup>. This transitional pattern also has occurred in other Asian populations that have similar environmental conditions<sup>[2,3]</sup>. In our study, seroprevalence increased with age and showed an abrupt rise in patients older than 30 years of age compared to those younger than 30 years of age. These results are consistent with other recent studies in Korea<sup>[6,7]</sup>. This is thought to be due to different epidemiological and socioeconomic environments during the economic development of Korea. Of note, with the recent increase of HAV vaccination in childhood, seroprevalence has increased in children younger than 10 years (Figure 1).

We evaluated the features of recent hepatitis A cases at a single center where we have observed a rapid

increase in the number of cases in recent years. These cases were analyzed for age-specific laboratory characteristics. In our study, most patients with HAV were in their twenties and thirties and most were male. The male predominance was especially true of patients in their thirties, which may be due to more exposure to the virus in men of that age. Besides markedly increased levels of enzymes related to acute hepatitis, most patients also showed increased TB levels and PT. Hematological abnormalities such as leukopenia and thrombocytopenia were noted in about one third of patients with hepatitis A (Table 2). These findings reflect more severe manifestations of acute hepatitis. Eighty-four percent of patients required hospitalization, which is much more than previously reported in the United States<sup>[4,9]</sup>, but similar to other recent reports in Korea<sup>[6,7]</sup>.

Although other enzymes were not significantly different between age groups, GGT increased with age and was significantly higher in patients older than 30 years ( $P = 0.006$ ). Indicators of severity, including decreased albumin and increased TB<sup>[1,18]</sup>, were also more predominant in the older group ( $P = 0.000$  and  $0.051$ , respectively) (Table 2). However, the leukocyte count was higher and the frequency of leukopenia was lower in younger patients than older adults ( $P = 0.002$  and  $0.003$ , respectively).

In conclusion, we investigated age-specific seroprevalence and laboratory characteristics of Korean patients recently infected with HAV. There has been an apparent epidemiological shift and change in the peak age of infection. This study could provide valuable baseline data of recent hepatitis A in an Asian area with an epidemiological shift.

## COMMENTS

### Background

In Korea, there has been a rapid epidemiological shift in hepatitis A virus (HAV) infection over the past decade as a result of rapid economic development. Adult cases of acute HAV have increased rapidly during the past 10 years due to the emergence of susceptible adults in Korea.

### Research frontiers

The transitional pattern of HAV epidemiology has occurred in Korea and other Asian populations that have similar environmental conditions. The large scale data from various populations regarding this issue would be valuable for establishing recent epidemiological features of HAV infection.

### Innovations and breakthroughs

In 1980, most adults had had immunity to HAV because of childhood exposure. Currently, less than 10% of people in their teens or twenties have anti-HAV IgG. In this study, the authors evaluated seroprevalence of total HAV antibody, with large-scale data, and investigated demographic, clinical, and laboratory features of recent cases of HAV in Korea, where there is an ongoing epidemiological shift.

### Applications

There has been an apparent epidemiological shift in HAV seroprevalence and a change in the peak age of HAV hepatitis. Overall, these cases have revealed a severe pattern of acute hepatitis. This study could provide valuable baseline data of recent hepatitis A in an Asian area with an epidemiological shift.

### Peer review

This manuscript is of interest.

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