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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

KONYA İLİNDE ÇOCUK YAŞ GRUPLARINDA HEPATİT A SEROPOZİTİVİTESİ

SEROPOSITIVITY OF HEPATITIS A IN PEDIATRIC AGE GROUPS IN KONYA

Nadire Seval GÜNDEM[1], Feyza ÇETİN[1], Erkan ATAŞ[2]

[1]Dr Ali Kemal Belviranlı Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Tıbbi Mikrobiyoloji Laboratuvarı
[2]Dr Ali Kemal Belviranlı Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği

ÖZET

AMAÇ: Hepatit A virüs (HAV) enfeksiyonu özellikle gelişmekte olan ülkelerde olmak üzere tüm dünyada yaygındır. Görülme sıklığı toplumların hijyen ve sanitasyon koşullarına göre değişiklik göstermektedir. Bu çalışmada Konya ilindeki çocuk hastalarda HAV seropozitivitesinin belirlenmesi, yaş gruplarına, cinsiyete ve mevsimlere göre dağılımının araştırılması ve elde edilen verilerin önceki çalışmalarda bildirilenlerle karşılaştırılması amaçlanmıştır.

GEREÇ VE YÖNTEM: Bu çalışmada Ocak 2019-Nisan 2020 tarihleri arasında hastanemize çeşitli şikayetlerle başvuran ve anti-HAV immünoglobulin G (IgG)/immünoglobulin M (IgM) tetkikleri istenen toplam 760 çocuk hastaya ait kayıtlar retrospektif olarak incelenmiştir. Serum örneklerinde anti-HAV IgG/IgM varlığı kemilüminesan mikropartikül enzim immunassay yöntemiyle araştırılmıştır. İstatistiksel analizler ki-kare Monte Carlo exact test yöntemiyle yapılmıştır.

BULGULAR: Tüm hastalarda anti-HAV IgG seropozitifliği %52,2 oranında bulunurken, anti-HAV IgM pozitifliği %0,5 idi. Anti-HAV IgG/IgM seropozitiflik oranı ise %5,3 olarak saptanmıştır. Anti-HAV IgG/IgM seropozitiflik oranının 9-14 (%32,5) ve 15-18 (%15) yaş gruplarında 3-8 (%52,5) yaş grubuna göre anlamlı olarak azaldığı gözlenmiştir ($p<0.05$). Erkeklerde anti-HAV IgG (64,8%) seropozitiflik oranı kızlara göre anlamlı olarak yüksekti ($p<0.05$). Anti-HAV IgG/IgM seropozitiflik oranı (%42,5) kışın istatistiksel olarak anlamlı bir artış göstermiştir ($p<0.05$).

SONUÇ: HAV aşısı ülkemizde 2012 yılında rutin aşı takvimine girmiştir. Anti-HAV IgG seropozitifliğinin iki yaş altı olgularda anneden geçen antikorlarla ilişkili olabileceği, 3-8 yaş grubunda diğer yaş gruplarına göre yüksek bulunmasının ise rutin aşılama programının sonucu olduğu düşünülmüştür. Anti-HAV IgG/IgM'in birlikte pozitifliğinin kış aylarında anlamlı olması bu mevsimde artan yağışlarla birlikte kanalizasyon ve altyapı sistemlerinin yetersiz kalmasıyla açıklanabilir. HAV enfeksiyonunun sıklığı, aşı uygulamasının sıkı takibi, toplumda hijyen ve sanitasyon koşullarına dikkat edilmesiyle azaltılabilir.

ANAHTAR KELİMELER: Hepatit A, anti-HAV IgG, anti-HAV IgM, Seropozitivite

ABSTRACT

OBJECTIVE: Hepatitis A virus (HAV) infection is common especially in developing countries worldwide. Prevalence of HAV varies according to public hygiene and sanitation conditions. In this study, it was aimed to determine seropositivity of HAV in pediatric patients in Konya province, investigate its distribution according to age groups, gender and seasons and compare findings with those reported in previous studies.

MATERIAL AND METHODS: In this study, records of 760 pediatric patients admitted to our hospital with various complaints and tested for anti-HAV immunoglobulin G(IgG)/ immunoglobulin M(IgM) between January 2019-April 2020 were evaluated retrospectively. Anti-HAV IgG/IgM in serum samples were analyzed by chemiluminescent microparticle enzyme immunassay method. Statistical analysis was performed by using chi-square Monte Carlo exact test.

RESULTS: Anti-HAV IgG seropositivity was found to be 52.2% while anti-HAV IgM positivity was 0.5% for all patients. Seropositivity rate of anti-HAV IgG/IgM was detected as 5.3%. It was observed that anti-HAV IgG/IgM seropositivity rate significantly decreased in age groups of 9-14 (32.5%) and 15-18 (15%) compared to 3-8 (52.5%) age group ($p<0.05$). Males had significantly higher seropositivity rates of anti-HAV IgG (64.8%) compared with females ($p<0.05$). Seropositivity rate of anti-HAV IgG/IgM (42.5%) demonstrated a statistically significant increase in winter ($p<0.05$).

CONCLUSIONS: HAV vaccine has been included into routine vaccination program in our country, in 2012. It was thought that anti-HAV IgG seropositivity might be related to maternal antibodies in patients under two years of age and its higher rate in 3-8 age group compared to other age groups has been the result of routine vaccination. Seropositivity rate of anti-HAV IgG/IgM together significantly increased in winter. This can be explained by insufficiency of sewerage and infrastructure systems with increasing rainfall in this season. Frequency of HAV infection can be reduced by strict follow-up of vaccine administration and attention to hygiene and sanitation conditions.

KEYWORDS: Hepatitis A, anti-HAV IgG, anti-HAV IgM, Seropositivity

Geliş Tarihi / Received: 30.06.2021
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Yazışma Adresi / Correspondence: Uzm. Dr. Nadire Seval GÜNDEM
Dr Ali Kemal Belviranlı Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Tıbbi Mikrobiyoloji Laboratuvarı
E-mail: sevalgndem@yahoo.com
Orcid No (Sırasıyla): 0000-0003-3157-6849, 0000-0001-5714-3617, 0000-0001-6582-9950
Etik Kurul / Ethical Committee: Konya Necmettin Erbakan University Meram Medical Faculty Ethics Committee (02.10.2020/2840).

INTRODUCTION

Hepatitis A virus (HAV) is a non-enveloped, single-stranded positive-sense RNA virus belonging to genus Hepatovirus within Picornaviridae family and causes hepatitis, a mild, self-limited non-chronic disease (1 - 4). HAV has six genotypes and only one serotype. Genotypes I–III are detected in human infections (5). Transmission of HAV mainly occurs through consumption of contaminated food or water and direct contact via fecal-oral route. Occasionally, it is transmitted by transfusion of contaminated blood or blood products (6 - 8). Healthcare workers, intravenous drug users, homosexuals, travelers to intermediate or high endemic regions, and people requiring life-long treatment with blood products are specific groups in danger of HAV infection (9).

HAV infections in childhood are mostly asymptomatic. Symptoms like fever, fatigue, malaise and jaundice develop with increasing age (7, 9, 10). Complications of HAV like fulminant hepatitis can develop in adolescents, adults, patients with underlying liver diseases and immunocompromised patients. Fortunately, it occurs in less than 1 percent of patients. While mortality rates in young adults are approximately 0.1%, it is going to increase to 2.1% for adults aged over 40 years (2, 4, 6).

HAV infection is diagnosed by serological methods with detection of HAV specific antibodies in serum samples (6). Anti-HAV immunoglobulin M (IgM) and immunoglobulin G (IgG) usually arise within several weeks after the first clinical symptoms of infection. While anti-HAV IgM decreases within (3 – 6) months, IgG provides life-long immunity. Seropositivities of total antibodies or anti-HAV IgG occur because of infection or vaccination so detection of those antibodies indicates immunity to HAV (5, 9, 11).

Determination of the age specific seropositivity of HAV in a country enables identification of infection-susceptible population for vaccination. Also, it is essential in consequence of serious complications of HAV in older people (6). The aim of this study was to determine seropositivity of HAV in pediatric age groups in Konya, Turkey, investigate its distribution according to age groups, gender and seasons and compare the findings with those reported in previous studies.

MATERIAL AND METHOD

A total of 760 serum samples of patients aged 0-18 years who admitted to pediatric outpatient clinics of our hospital and tested for anti-HAV IgG and IgM for screening and diagnostic purposes between January 2019-April 2020 were included in this retrospective study. Test results were examined retrospectively from the laboratory information system. Patients were divided into age groups such as (0-2), (3-8), (9-14) and (15 - 18). Exclusion criterias are lipemic and hemolyzed serum samples and repeated results of same patients for anti-HAV IgG and IgM.

Using aseptic technique, 2-5 mL blood samples were taken by venopuncture of antecubital region, centrifuged at 4.000 rpm for 10 minutes to separate the sera and analyzed on the same day. Serum samples were analysed for anti-HAV IgG and IgM using chemiluminescent microparticle immunoassay method in test kits and autoanalyzer (Architect i2000; Abbott Diagnostics, Abbott Park, Illinois, USA) consistent with manufacturer's instructions. Anti-HAV IgM values equal to or higher than 1,2 S/CO were classified as positive while those lower than 1.2 S/CO were accepted as negative. Anti-HAV IgG values equal to or greater than 1 S/CO indicated positive and lower than 1 S/CO demonstrated negative.

Ethical Committee

The study was approved by Review Board and Ethics Committee of Konya Necmettin Erbakan University Meram Faculty of Medicine on the date of 02.10.2020 (Ref No: 2020/2840). Informed consent was conducted in accordance with the Ethics Committee and approval procedures.

Statistical Analysis

Data analyses were performed by Statistical Package for the Social Sciences (SPSS version 20.0) (IBM Inc., Chica go, IL, USA). The relationship between test results and variables was evaluated by Chi-Square Monte Carlo exact test. Also, this analysis method was used to determine whether independent variables like age and gender were associated with HAV seropositivity. The results were considered significant at probability value of <0.05 ($p<0.05$).

RESULTS

A total of 760 patients were included in this retrospective study. The mean age of patients was 10.5±5,1 years (age interval: min:0, max:18 years). Of 760 patients, 307 (40.4%) of them were female and 453 of (59.6%) of them were male. There were 42 (5,6%) patients younger than 2 years old. While 248 (32.6%) patients were in the age group of 3-8, the age groups of 9-14 and 15-18 comprised of 237 (31.1%) and 233 (30.7%) of patients, respectively.

Of 760 patients, 397(52.2%) were anti-HAV IgG positive and 4 (0.5%) were anti-HAV IgM positive. The seropositivity rate of anti-HAV IgG/IgM was detected as 5.3% (n=40). The highest seropositivity rates of anti-HAV IgG (43.8%) and IgM/IgG (52.5%) were found in the age group of 3-8 and this finding demonstrated a statistically significant difference between other age groups (p<0.05). The seropositivity rate of anti-HAV IgG/IgM decreased in age groups of 9-14 (32.5%) and 15-18 (15%) compared to 3-8 (52.5%) age group (p<0.05)**(Table 1)**.

Table 1: Distribution of anti-HAV IgG and IgM seropositivities according to age groups

Age groups	Anti-HAV IgG positivity		Anti-HAV IgM positivity		Anti-HAV IgG/IgM positivity		Anti-HAV IgG/IgM negativity		Total			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	X^2	*P**
0-2 age	23	5.8	0	0	0	0	19	6	42	5.6	84.78	p<0.05
3-8[a] age	174[b]	43.8	2	50	21[b]	52.5	51	16	248	32.6		
9-14 age	87	21.9	1	25	13	32.5	136	42.6	237	31.1		
15-18 age	113	28.5	1	25	6	15	113	35.4	233	30.7		
Total	**397**	**100**	**4**	**100**	**40**	**100**	**319**	**100**	**760**	**100**		

* Chi-square Monte Carlo Exact Test, [a,b]: Different superscript letters denote the significant difference between proportions

Males composing of majority of patients (59.6%) had significantly higher seropositivity rates of anti-HAV IgG (64.8%) compared with females (p=0.017) **(Table 2)**.

Table 2: Distribution of anti-HAV IgG and IgM seropositivities according to gender

Gender	Anti-HAV IgG positivity		Anti-HAV IgM positivity		Anti-HAV IgG/IgM positivity		Anti-HAV IgG/IgM negativity		Total			
	n	%	n	%	n	%	n	%	n	%	X^2	*p**
Female	140	35.2	2	50	17	42.5	148	46.4	307	40.4	9.51	p<0.05
Male[a]	257[b]	64.8	2	50	23	57.5	171[b]	53.6	453	59.6		
Total	**397**	**100**	**4**	**100**	**40**	**100**	**319**	**100**	**760**	**100**		

* Chi-square Monte Carlo Exact Test, [a,b]: Different superscript letters denote the significant difference between proportions

Seropositivity rate of anti-HAV IgG/IgM (42.5%) demonstrated a statistically significant increase in winter (p=0.001) **(Table 3)**.

Table 3: Distribution of anti-HAV IgG and IgM seropositivities according to seasons

Seasons	Anti-HAV IgG positivity		Anti-HAV IgM positivity		Anti-HAV IgG/IgM positivity		Anti-HAV IgG/IgM negativity		Total			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	X^2	*P**
Winter[a]	91	22.9	2	50	17[b]	42.5	76	23.8	186	24.5	24.65	p<0.05
Spring[a]	107[b]	27	0	0	9	22.5	59	18.5	175	23		
Summer	103	25.9	2	50	4	10	75	23.5	184	24.2		
Autumn[a]	96	24.2	0	0	10	25	109[b]	34.2	215	28.3		
Total	**397**	**100**	**4**	**100**	**40**	**100**	**319**	**100**	**760**	**100**		

* Chi-square Monte Carlo Exact test , [a,b]: Different superscript letters denote the significant difference between proportions

DISCUSSION

HAV infection is especially common in developing countries worldwide (12). According to recent reports, it is estimated that approximately 1.4 million new cases occur throughout the world every year (13, 14). Seroprevalence of HAV differs from one region to another in a country or between countries in terms of geographical, environmental, socioeconomic and sanitary conditions (7, 9).

Turkey in which the seropositivity of HAV ranges between geographical regions, has an intermediate endemicity in line with epidemiological informations (12, 15). Our study conducted in Konya province where is found in Central Anatolia region of Turkey indicated the seropositivity rate of anti-HAV IgG in pediatric population as 52.2%. Similar to this finding, a study from Van province located in Eastern Anatolia of Turkey revealed seropositivity rate of anti-HAV IgG as 54.9% among 1-15 year old children (13). Additionally, a study conducted between 2011-2013 years in İstanbul supported these findings with anti-HAV IgG rate of 55% among children aged 0-16 years (15). On the other hand, a lower seropositivity rate (37%) of anti-HAV IgG in chidhood was reported from Yozgat, a province in Central region of Turkey (4). The differences between HAV seropositivity rates obtained in Turkey can be associated with changing of hygienic and sanitation conditions of regions, socioeconomic and nutritional habits of populations from one region to another.

Some studies conducted in Turkey reported that seropositivity rates of anti-HAV IgG or total antibodies increased significantly with age (3, 4, 7, 16, 17). A study from Germany indicated significantly increasing seropositivity rates of anti-HAV IgG with age and reported that this mi-

ght be related with vaccination or infection (18). Besides this, anti-HAV IgG seropositivity rates in adolescence were reported as ranging between 2% to 20% from countries in North America, Austria and Norway (19). A study investigating HAV frequency in Brazil, in 2006, reported a significantly higher rate of HAV seropositivity in 15-19 (65%) age group compared to 10-14 (46%) age group and revealed that some individuals may already be infected with HAV during adolescence (20). In a study from Sri Lanka, anti-HAV IgG seropositivity rates were obtained as 70.4% and 66.8% among the age groups of 1–10 and 11–20, respectively, and reached to 93.2% from the age of 31 to 40 years (6). These studies demonstrated that vaccination programs in childhood will reduce the incidence of HAV infection and periodic serological testing has been recommended to identify variation in endemicity across age groups. In our study, seropositivity rates of HAV IgG/IgM antibodies decreased gradually with age among the age group of 3-8 (52.5%) compared to 9-14 (%32.5) and 15-18 (15%) age groups. This difference can be related with improving environmental and living conditions and taking strict precautions for elevating hygien level. It may also coincide with the start of the national vaccination program.

Studies from endemic regions suggested that serological tests should be done for detection of not only IgG or total antibodies but also IgM antibodies and even further testing was needed to research serotype of HAV (5, 11). In a study carried out by Tewari et al. from India, the rate of anti-HAV IgM seropositivity was reported as 33.7% in symptomatic children aged 5-15 years who presented with fever, jaundice, nausea and vomiting (5). A study conducted to determine HAV serological markers at a public child care center in Brazil indicated the rate of anti-HAV IgM seropositivity as 10.5% among tested individuals: 6 staff members and 38 children 79% of whom were asymptomatic (8). Anti-HAV IgM seropositivity rates were found to be lower in studies investigating HAV serological markers in patients who applied to various departments of hospitals for screening and diagnosis. In a retrospective study examining the relationship between age groups and HAV antibodies in Turkey, anti-HAV IgM seropositivity rates were reported as 13.2% and 13.7% for 0-10 and 11-20 age groups, respectively (12). In another study from Turkey, the seropositivity rate of anti-HAV IgM was 4.9% in 0-10 age group, while it was 6.8% in 11-20 age group (3). In our study, anti-HAV IgM seropositivity rate was 0.5% in all children who underwent anti-HAV IgG and IgM tests for screening and diagnostic purposes. Although the anti-HAV IgM seropositivity rate obtained in our study was low, it is clear that children can easily transmit the virus to each other and to individuals of all age groups. It is considered that it would be beneficial to vaccinate children to prevent HAV infection from shifting to advanced ages.

In China, HAV vaccine has been included within the national immunization program since 2008 and a study performed to compare changes in seroepidemiology of HAV between 2006 - 2014 years indicated the positive effect of vaccination with increased anti-HAV IgG levels among children (10). A study from USA documented high seropositivity rates among the participants aged 2-19 years due to vaccination instead of naturel infection (21). In a study performed by Kurugöl et al from İzmir, Turkey, in 2008, the potential risk of HAV epidemics has been emphasized due to the detection of increased number of susceptible adolescents and HAV vaccine has been suggested to be added into the national vaccination program of Turkey (17).

In 2012, HAV vaccine has been included into the routine childhood vaccination program in Turkey (4). In our study, significantly higher seropositivity rates of anti-HAV IgG were determined (43.8%) in the age group of 3-8 compared to other age groups. Anti-HAV IgG levels can not explain whether this is natural or vaccine-related immunization but it is predicted that this favourable outcome may be associated with the effect of routine HAV vaccination program. Anti HAV IgG seropositivity rates detected in the age group of 9-14 (21.9%) and 15-18 (28.5%) indicated that patients among these age groups were susceptible to HAV. In a study conducted in Konya province, in 2019, HAV vaccination rates in patients over the age of 18 were reported as 13.4% and it was determined that HAV vaccina-

tion rates, including risk groups, are not at the desired levels (22). Studies conducted in Turkey and other countries indicated no significant association between gender and HAV seropositivity. This finding may possibly be due to the fact that males and females forming a population are often exposed to the same environmental, sanitary and socioeconomic conditions (1 - 4, 13, 15, 17, 19, 21). On the other hand, Tseng et al from Taiwan detected significantly higher anti-HAV IgG levels in females than in males and attributed this to variation of immune response between genders to vaccine administration (23). In a study from Germany, males had significantly higher anti-HAV antibody levels than females and it was thought to be associated with hygienic behaviors and eating habits (9).

This finding is consistent with the data obtained in our study, as anti-HAV IgG seropositivity rates (64.8%) were significantly higher in men (59.6%), who constitute the majority of the patients.

A study from India have identified seasonal variation for HAV epidemiology and reported a rise within the number of cases, especially during the monsoons in August (5).On the other hand, in our study, a statistically significant increase was detected in the seropositivity rate of anti-HAV IgG/IgM during the winter months. This finding can also be explained by insufficiency of sewage and infrastructure systems together with increasing rainfall in winter. A study from Black Sea region of Turkey partially supported this data as they indicated higher seropositivity rates of anti HAV IgM in both autumn and winter (14).

Our study has some limitations. First of all, limited sample size of our study may not reflect total pediatric population in Konya. Additionally, vaccination status, living and socioeconomic conditions of patients could not be questioned. Even though these, our study contributed recent data to literature on seropositivity of HAV in pediatric age groups.

In conclusion, serological screening of population is important to determine susceptible individuals and changes in HAV epidemiology. The proportion of seronegative patients obtained in our study pointed out that this population was at risk of HAV infection and a catch up vaccination program should be implemented for these individuals to prevent a HAV outbreak among unvaccinated children and teenagers.

Also, knowledge of age specific seropositivity of HAV in different cities of a country will guide routine vaccination programs. Frequency of HAV infection can be reduced by applying strict follow-up programs for vaccine administration, paying attention to educate population about hygiene and healthy life style and improving sanitation conditions.

This study was presented as an e-poster at the "TMC ONLINE SYMPOSIUM of MICROBIOLOGY, 25-27 December 2020.

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