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EVALUATION OF THE RATE OF HEPATITIS A IMMUNITY IN A SMALL CITY AFTER THE VACCINATION PROGRAM: ONE CENTER EXPERIENCE

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Abstract

Hepatitis A is an infectious disease caused by hepatitis A virus (HAV). Symptomatic infection causes health care costs with loss of labor and school time. HAV outbreaks may cause economic problems by disrupting trade and tourism. The aim of this study is to determine the rate of immunity against HAV infection in a sample of pediatric population. The study group consisted of all children who underwent anti-HAV IgG evaluation for any reason between January 1, 2012, and December 31, 2020. The data about age, date of birth, sex, residence, vaccination status were retrospectively collected from the hospital record system. Anti-HAV IgG status was determined by chemiluminescent microparticle immunassay kits. The statistical analyses were presented with descriptive methods. Overall 1189 children aged 1-17 years old enrolled to the study. The rate of anti HAV IgG seropositivity was 41.2% in the whole study group. The rates of completed vaccination scheme and seropositivity were 10.7% and 92.2%. Natural immunity rate was 32.6%.The 7-17 age group was found to be susceptible to the acute infection, they were considered as the new target population of vaccination. Vaccination seemed to be the most

effective way of providing seropositivity to get rid of acute infection risk and eliminating geographic and socioeconomic differences.

Key Words: Hepatitis A, Natural immunity, Seroprevalence, Vaccination

Özet

Hepatit A, Hepatit A virüsünün (HAV) neden olduğu enfeksiyöz bir hastalıktır. Semptomatik enfeksiyon iş gücü ve okul günü kaybıyla sağlık giderleri artışına neden olur. HAV salgınları ticaret ve turizmi olumsuz etkiler, ekonomik kayıplarla sonuçlanır. Bu çalışmanın amacı bir pediatrik yaş grubu örnekleminde HAV bağışıklık durumunun saptanmasıdır. Çalışma grubu 1 Ocak 2012-31 Aralık 2020 tarihleri arasında her hangi bir nedenle anti HAV-IgG düzeyi bakılan çocuklardan oluşmuştur. Yaş, doğum tarihi, cinsiyet, yaşanılan yer, aşılanma durumu hastane kayıt sisteminden geriye dönük olarak elde edilmiştir. Anti HAV IgG düzeyleri kemiluminosen mikropartikül immün analiz kitleriyle çalışılmıştır. Veriler ve sonuçlar tanımlayıcı istatistik yöntemlerle sunulmuştur. Yaşları bir ve17 arasında değişen toplam 1189 çocuk değerlendirilmiştir. Tüm grupta anti HAV IgG seropozitifliği hızı %41,2'dir. Aşı takvimi katılımcıların %10,7'sinde tamamlanmış ve bunların %92,2'sinde bağışıklık sağlanmıştır. Doğal bağışıklık hızı ise %32,6'dır. Bağışıklama programı için ek hedef kitlenin akut enfeksiyona karşı duyarlı olduğu bulunan 7-17 yaş grubu olması gerektiği saptanmıştır. Aşılamanın akut enfeksiyona karşı bağışıklığın sağlanmasında ve hem coğrafik, hem de sosyoekonomik kısıtlılıkların dışlanmasında en etkili yöntem olduğu düşünülmektedir.

Anahtar Kelimeler: Aşılama, Doğal bağışıklık, Hepatit A, Seroprevalans

1. Introduction

Hepatitis A is an infection caused by hepatitis A virus (HAV). The virus is icosahedral in shape, 27-32 nm in dimension and non-enveloped. It has single stranded positive-sense ribonucleic acid (RNA). It is the member of Picarnoviridae family and Hepatovirus genus. The transmission way of HAV is the fecal-oral route involving the ingestion of contaminated water or food or direct contact with an infectious person. The only known reservoir of the infection is the humans (Lemon, Ott, Van Damme, & Shouval, 2018). The infection decline is strongly correlated with

socioeconomic facilities. Well sanitary and hygienic conditions provided by accessing clean and safe water consumption decrease the incidence rate of HAV infection (K. Jacobsen & Koopman, 2005). Population groups under risk of infection are well defined (WHO, 2019).

HAV infection is usually asymptomatic in children younger than six years old, but in the older populations, it causes flu-like and gastrointestinal symptoms with jaundice and lassitude. Although it is a self-limited disease, it may rarely result in fulminant hepatic failure, the incidence of this complication increases with age (Ciocca, 2000). Symptomatic infection causes heath care costs with loss of labor and school time because of hospitalization. HAV outbreaks may cause economic problems by disrupting trade and tourism (K. H. Jacobsen & Wiersma, 2010). The vaccination is offered to unimmunized travellers who visit high risk regions in the concept of travel medicine. The disease has no specific treatment; the facilities are limited with symptomatic approach. Post exposure active and passive immunization are also available (Dawid, 2008).

Active immunization has been available since 1990's, but the decision of universal immunization for pediatric population is based on the endemicity of the infection. In high endemicity areas, universal immunization is not recommended because most of the population is infected by the age of six, thus adult population is protected by natural immunity. In low endemicity countries, vaccination is offered to high-risk populations rather than universal immunization. Universal childhood vaccination is recommended to intermediate endemicity countries, for the sake of adolescents and adults if public health care facilities are available (WHO, 2000). The rates of anti-HAVIgG seropositivity may vary according to geographical, sanitary, hygienic and socioeconomic conditions between different age groups, populations or different regions of the same country. The western and central regions of Turkey have intermediate endemicity whereas eastern and southern regions have high endemicity. Migration between regions is a common and major problem in Turkey[8, 9]. (Demiray et al., 2016; WHO, 2012). Therefore, Turkish Ministry of Health added HAV vaccine to the national immunization schedule of childhood in October 2012 and recommended to all children born after March 1, 2011 since then (Turkish Ministry of Health, 2022).

The aim of this study is to provide current data about the age-specific anti-HAV seroprevalence in our province which is located in the middle northern Turkey, one of the intersection point of important highways between eastern and western Anatolia. In addition, contribution to adopt appropriate vaccination policies for other target age groups was intended. Most of the studies

reflect the data of the period before the vaccination program in our country whereas the present report declares the previous and later data.

2. Materials and Methods

2.1. Study design, setting and participants

This is a cross-sectional study based on retrospective records. It was conducted at the pediatric clinics of a secondary health care center in the middle northern Anatolia. All children aged between 1 and 17, who underwent anti-HAV IgG evaluation for screening or diagnosis between January 1, 2012 and December 31, 2021 enrolled. The data about age, sex, residence, date of birth, vaccination status and anti-HAV IgG were retrospectively collected from the hospital record system. The participants born after March 1, 2011 were estimated to be vaccinated.

2.2. Laboratory studies

Seroprevalence studies are based on the detection of antibodies against HAV in the serum or plasma (anti-HAV IgG) and age specific rates of seropositivity provide the evaluation of HAV infection status of the population living in the study area (Carrillo-Santisteve et al., 2017; WHO, 2012) Anti-HAV IgG status was determined by chemiluminescentmicroparticleimmunassay (CMIA) kits (ARCHITECT HAVAb-IgG®, Abbott GmbH Co, Wiesbaden, Germany) providing qualitative detection in the venous blood in this study. The results were evaluated according to the cut-off relative light unit (RLU) values determined by the manufacturer. When the ratio between the serum sample RLU and the cut-off RLU was <1.00 it is defined as “non-reactive” and interpreted as “negative.” When this ratio was ≥1.00, it was defined as “reactive” and interpreted as “positive.”

2.3. Ethical statements

The study was approved by the Ethical Committee of Non- Invasive Clinical Researches of Amasya University (Registration number: 06/01/2020– E.487).

2.4. Statistical analyses

The analyses were performed using SPSS® version 16 (SPSS, Inc., Chicago, IL, USA). The data were presented as percentages, frequencies, medians and minimum–maximum, ranges or mean

± SD by descriptive statistics, when indicated. Cross- tables with chi-square test ($\chi 2$) were used to identify statistically significant differences between groups at 95% confidence interval. Probability factor (p) <0.05 was regarded to be statistically significant.

3. Results and Discussion

Overall, 1189 children aged between 1 to 17 years old (mean: 8.75±4.99) enrolled to the study. A total of 574 (48.3%) of the participants were females and 615 (51.7%) were males. 18.3% (n=218) of the participants were from rural areas. The rate of anti HAV IgGseropositivity in whole group was 41.2% (n=490) ignoring age, residence, and vaccination status. Seronegativity was detected in 699 (58.8%) of the participants. The rate of seronegativity was higher in children older than six years old and urban area residents which were statistically significant (p<0.0001 and p=0.0004 respectively).

Since vaccination is applied at the 18th and 24th months, some individuals were vaccinated incompletely. Fifty-two (4.4%) of the participants were under 18 months old and they were too young to get the first dose. However, 40.4% (n= 21) of them had anti HAV IgG positivity which was estimated to be the result of maternal immunity or natural infection and 31 (59.6%) were seronegative. The median age of seronegative infants was 14 months. The rate of seropositivity in 19-24 months old infants was 61% (n=25). Twenty participants in this group were vaccinated with the first dose of HAV, the rate of seropositivity was 60% (n=12). Sex and residence had no statistically significance on seropositivity rate of this group (p=0.09, p= 0.67, respectively).

The vaccination rate with two doses was 10.7% (n=128) in the whole study group. The difference between vaccination rates of sexes was statistically significant (13.7% (n= 78) males; 9.5% (n=50) females, respectively; p=0.03). Twenty (9.8%) of the rural area residents and 108 (12.1%) of the urban area residents were vaccinated, residence had no significant effect on vaccination status (p=0.41). One hundred and eighteen (92.2%) of the vaccinated group with two doses (n=128) had seropositivity and the median age was 4 years old (range:2-7), 59.3% (n=70) of them were males. The rate of seropositivity between sexes and residential areas were not statistically significant in the full vaccinated group (p=0.34, p=0.39, respectively). Ten (7.8%) of the vaccinated individuals were detected to be seronegative. Two of them had immune deficiency and one of them had chronic hepatitis B infection.

When we compared the children aged between 2 and 6 years old as “vaccinated” (n=128) and “unvaccinated” (n= 311), the rate of seropositivity was 92.3% (n=118) and 36.7% (n= 114)

respectively. The higher rate of seropositivity in the vaccinated group was statistically significant (p<0.0001). In the unvaccinated group (older than 24 months old), 177 (36%) of the males and 149 (31.2%) of the females were seropositive. The difference in seropositivity rates between sexes was not statistically significant (p=0.11). However, the rate of seropositivity was 25.9% (n=48) in the rural area residents while it was 35.5% (n=278) in urban area population. Seropositivity rate was higher in the urban areas and the difference between groups was significant (p=0.02).

In the 7-17 age group, there were 793 participants, 2.9% (n=23) of them were vaccinated. The rate of seronegativity was found to be 67.2% (n= 533) in this group. All vaccinated children were seropositive which was statistically significant (p<0.0001). The results are summarized in Table 1.

Table 1. The summary of the features of the participants

AGE GROUPS	Vaccinated (at least one dose)	Unvaccinated	Seronegative	Seropositive	TOTAL
12-18 months	0	52; (100%)	31; (59.6%)	21 (40.4%)	52
19-24 months	20;(48.8%)	21; (51.2%)	16; (39%)	25 (61%)	41
2-6 years old	105; (34.7%)	198; (65.3%)	119; (39.3%)	184; (60.7%)	303
>6 years old	23; (2.9%)	770; (97.1%)	533; (67.2%)	260; (32.8%)	793
SEX					
Males	90; (14.6%)	525; (85.4%)	346; (56.3%)	269; (43.7%)	615
Females	58; (10.1%)	516; (89.9%)	353; (61.5%)	221; (38.5%)	574
RESIDENCE					
Urban Areas	124; (12.8%)	847; (87.2%)	552; (56.8%)	419; (43.2%)	971
Rural Areas	24; (11%)	194; (89%)	147; (67.4%)	71; (32.6%)	218

The 1.8% (n=22) of the study group consisted of refugees, their mean age was 7.6± 4.3 years old. All were from urban areas and male to female ratio was 2:1 and 59% (n=13) of them were immune to HAV infection; 22.7% (n=8) by natural infection and 22.7% (n=5) by vaccination.

As supplementary information, we would like to share that during the study period 53 children experienced acute hepatitis A infection with anti HAV IgM seropositivity. Fifty cases were detected between February 2012 and March 2013, with the peak incidence in March 2012. The median age of the cases was 8 years old (min-max: 1-17 years old) and all were unvaccinated. Three cases were diagnosed in September 2018; none of them was vaccinated, either. The rate of acute infection in rural area residents was 47.1% (n=25) which was statistically insignificant.

In this study we reported the seroprevalance status of HAV in our province in the vaccinated and unvaccinated children. The rate of anti HAV IgG seropositivity in this study population was found to be 41.2%. Over 90% of the 7-17 years old group was unvaccinated. The results declared that seronegativity rate against HAV infection was higher in unvaccinated and older members of the study group which were statistically significant.

Most of the studies about HAV seroprevalence in Turkey were dated before vaccination had become mandatory. As mentioned before, in October 2012, Turkish Health Ministry added HAV vaccination to the routine childhood schedule for the infants born after March 1, 2011 and application to be performed as two doses in 18th and 24th months (Turkish Ministry of Health, 2022). According to the previous data in 1990's, more than half of the adolescents had immunity to HAV by natural infection. In 2000's, more than 90% of the adults were immune against HAV, but in urban areas rate of immunity in children under five years old had decreased, revealing the epidemiological shift (K. H. Jacobsen, 2009). A study from Central Anatolia in 2017, dated after immunization, established that 79.1% of the population was immune to HAV; the study group consisted of unvaccinated individuals over six years old. The authors found the seronegativity rate of 6-19 years old age group to be 47.8%, which was higher than the older age groups (Kader et al., 2019). Our results also declared that the rate of seronegativity was higher in children aged between 7-17 years old.

WHO data established that the seroprevalences were high in Africa and South Asia whereas intermediate in Latin America and North Africa (K. H. Jacobsen & Wiersma, 2010). The incidence of confirmed HAV infection cases was reported to be 2.6/100.000 in Europe in 2012, varying between countries (0.1-66.8/100.00). The reason of this great variation was thought to be depending on the recording and surveillance systems as well as socioeconomic features (

European Centre for Disease Prevention and Control, 2014). Socioeconomic development, improvement in sanitation, promotion in hygiene in food production and marketing and vaccination against HAV had reduced seroprevalence among European Union (EU) countries in the last 40 years but increased the "susceptibility" to the complicated infection in adults. A systematic review in 2017, expressed this entity by the epidemiologic shift of the infection and expressed the increased risk of symptomatic infection risk in adults because of changing exposure patterns, such as globalized food markets related with HAV endemic areas and travellers visiting and returning from high endemicity areas. These could pose a risk for susceptible individuals in low endemicity areas by virus circulation or importation (Askling, Rombo, Andersson, Martin, & Ekdahl, 2009; Carrillo-Santisteve et al., 2017; MacDonald et al., 2013; Tavoschi et al., 2015). The authors concluded that increased susceptibility should force the countries to seek tailored control programs to reduce the possibility of symptomatic adulthood infections (Carrillo-Santisteve et al., 2017). In Spain, the rate of seropositivity had increased in 2-5 year age group in 2008 compared to previous studies, revealing the significance of migration trends from high endemicity areas or the effect of vaccination (Garcia-Comas et al., 2016). The rate of immunity had increased in China after the childhood vaccination program, but the same concern about susceptibility in adults was also reported in the study. The decay of antibodies produced by vaccination was thought to be the reason of this problem, but the exact time for this process was not known. A systematic review reported that the duration period of immunity was at least 14 years by the inactivated vaccine (Ott, Irving, & Wiersma, 2012). In our study group, the seropositivity was found to be high in the vaccinated group seven years after the vaccination program (92.2%), the rate of susceptibility in the 7-17 age years old group was 67.2%. The adulthood status of our province was not evaluated in this study which is one of the limitations. The rate of natural immunity in this age group was found to be 32.8% which is lower than the previous reports from our country (Kader et al., 2019; WHO, 2019). As the rate of seropositivity in the vaccinated group was 92.2%, vaccination seems to be most effective way of providing seropositivity according to our results.

The study from Middle East and North Africa (MENA) region assigned the endemicity levels according to the age at midpoint of population immunity (AMPI) which means the youngest age at which at least half of the population has serologic evidence of prior HAV infection (Koroglu et al., 2017; Mohd Hanafiah, Jacobsen, & Wiersma, 2011). According to this study, socioeconomic indicators such as gross national income (GNI) per capita, gross domestic product (GDP) per capita and human development index (HDI) had more significant role in HAV seroprevalence

when compared with water supply and sanitation facilities. Since improved drinking water and sanitation infrastructure were provided, economic variables became more significant[21, 22]. (Koroglu et al., 2017; WHO/UNICEF, 2015). Bahrain, Kuwait, Qatar were predicted to have low endemicity (Koroglu et al., 2017). However, endemicity was very high in Iraq, Palestine, Yemen, Egypt and Syria, the countries where civil wars continue (Koroglu et al., 2017). Wars disrupt the facilities of reaching improved drinking water and sanitation conditions. Protective services of the healthcare systems, such as vaccination and nutrition consultancy are delayed. The civil wars and political conflicts in these countries made residents immigrate to neighbor countries and large outbreaks occurred among Syrian refugees in Turkey and Jordan (Sharara & Kanj, 2014). The outbreaks can potentially change the epidemiological profiles of the host countries. That's why vaccination becomes more important as a protective service. HAV vaccination is recommended in Turkey since 2012 and Saudi Arabia since 2008. There are a few refugees in this study population, and it is difficult make comments about the effect of refugees considering this report.

High socioeconomic status, increased sanitary facilities of urban areas decrease the rate of infection (K. Jacobsen & Koopman, 2005). The socioeconomic status of our study group was not mentioned, which is one of the limitations of this study. However, in our study, the epidemiologic difference between rural and urban areas was not similar with the reports in the literature. In the vaccinated group there was no statistical difference between residences, which established that disseminated and qualified vaccination services can eliminate some limitations. But seropositivity was significantly higher in the urban areas in the unvaccinated group. This result was not compatible with the literature and thought to be the outcome of high migration rates causing inadequate infrastructure services and crowded life settings in our city.

In this study, 1.8% of the children were refugees aged 13 (59%) of them were immunized. Seropositivity rate was higher than the other children at the same age group, but the little proportion of the population may not reflect the real data. A study from İzmir reported that 41 of 86 (47%) of the refugee children had seropositivity, the result was similar to eastern and southeastern parts of our country, but higher than western parts. The reason for this result was thought to be the regional similarities in living and health conditions with MENA countries in some parts of Turkey. The rate of seropositivity with natural infection was the result of poor sanitation, nutrition and low socioeconomic status which are the effects of wars; the threat of humanity and children (Köse et al., 2017).

The transplasental maternal antibodies protect the infant from many infections passively, including hepatitis A. A study from southern Turkey declared that the infants had detectable amount of antibodies till 12 months, but the seropositivity rate was 36.1% although 93.9% of the mothers had immunity (Derya, Necmi, Emre, & Akgun, 2005). Another report established the rate of seropositivity to be 29.6% and 14.8% in 12th and 18th months (Guzelkucuk et al., 2019). The rate of immunity before the first dose of the vaccine was 40.4% (n=21) in our study and median age of the seronegative participants was 14 months. The differences may be the result of maternal immunity status, asymptomatic natural infection rate or technical variations between the studies, but the data about mothers were not mentioned in this study. Furthermore, the number of participants is not sufficient enough to make generalized comments.

HAV vaccines are inactive and well tolerated with long duration of immunity. The immunogenity is over 90% four weeks after the first dose (WHO, 2019). The rate of immunity was lower in this study group which may be result of timing of analyses, but the rate was increased to 92.2% after the second dose. This means that completed immunization scheme provides high immunogenity and contributes herd immunity.

Limitations and Strengths: This is a retrospective study based on hospital records. The number of participants is limited, and the data reflect only the pediatric age group of a small city in northern Anatolia, that's why it is difficult to generalize the results of the study to whole population. The data of infants younger than 1 year old were not evaluated. The rate of immunity in adults and mothers were not mentioned. The socioeconomic status of the study group was ignored. However, there are a few studies about HAV status after the routine vaccination program in Turkey; most of the studies reflect the data before the program onset although publication dates are later. Our study reflects the pediatric data only after universal childhood vaccination program in our country.

4. Conclusion

In conclusion, we established that hepatitis A vaccination program goes on successfully in our province, as the whole Extended Immunization Program (EIP) in Turkey. The 7-17 age group seemed to be susceptible to the acute infection. Turkey is on the intersection ways of travel routes between continents. The high rate of migration burden from Middle East and Asia makes our population susceptible to many infectious diseases. The susceptibility of adolescents seems to be a disseminated problem (WHO, 2016). Although our study sample is small, we would like to

attract attention that such changes may occur in epidemiologic features of infectious diseases. Migration and social burden with lack of infrastructure may result in common and challenging problems. We recommend a catch up dose of HAV vaccine for 7-17 age group to prevent acute infection outbreaks and provide immunity for the kids of these individuals in the future, until their routine immunization age. Tailored precautions for each country should be designed to provide herd immunity, which is the only chance of the susceptible population.

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Conflicts of interest

None

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