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Original Article

Cytomegalovirus Seroepidemiology: a Population-based Study in Alborz Province, Iran

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ABSTRACT

Cytomegalovirus (CMV) is a type of herpes virus. This virus is one of the most common causes of congenital and prenatal infections. CMV infection in pregnant women, especially in the first trimester, may lead to congenital abnormalities in newborns. The prevalence of CMV infection in developed countries is approximately 40%, and in developing countries, this prevalence may be up to 100%. Because there is no information available related to the seroepidemiological patterns of this infection in different cities of Alborz province, Iran, this study was conducted. This seroprevalence study was based on sera collected from adults who were referred to health care providers or Medical Diagnostic Laboratory Centers (MDLS) in Alborz province, Iran, from 2011 to 2015 for different purposes. Using ELISA (IgG), a retrospective serological survey of CMV antibodies in serum samples was performed in a non-immunized community. Frozen sera from 2001 individuals who were randomly selected by a cluster sampling technique were collected from spring 2013 to winter 2015. Seroprevalence was stratified by age (>1 to <50 years). Mathematical techniques were used to determine whether there is a relationship between CMV seroprevalence and age, sex, and level of education in this community. Data were analyzed using Fisher's exact test and the $\chi 2$ test using SPSS software version 11.5. The mean age of seropositive individuals varied between 15 and 50 years. CMV IgG was found in 1813 (91%) of 2001 individuals. In total, 188 individuals (9%) were negative for CMV IgG. There were significant relationships between seropositivity (CMV IgG) and age, sex, level of education, and level of antibody titer by sex. As in other developing countries, the prevalence of CMV infection in adults in Alborz province is high. Since CMV infection is prevalent and there are potential abnormalities associated with it, we strongly recommend the expansion of preventive measures and the establishment of programs to inform at-risk populations, especially vulnerable populations such as transplant recipients, immunocompromised patients, and school children on how to prevent this infection and its associated consequences.

Keywords: Cytomegalovirus, ELISA, Alborz, Iran

Séroépidémiologie du Cytomégalovirus: une Étude Axée sur la Population dans la Province Iranienne d'Alborz

Résumé: Le cytomégalovirus (CMV) est un type de virus de l'herpès. Ce virus est l'une des causes les plus courantes d'infections congénitales et prénatales. L'infection à CMV chez la femme enceinte, en particulier au cours du premier trimestre, peut entraîner des anomalies congénitales chez le nouveau-né. La prévalence de l'infection à CMV dans les pays développés est d'environ 40% et, dans les pays en développement, cette prévalence peut aller jusqu'à 100%. Cette étude a été menée en raison de l'absence d'informations séro-

épidémiologiques disponibles concernant cette infection dans les différentes villes de la province d'Alborz (Iran). Nos analyses se sont basées sur des sérums de sujets adultes prélevés entre 2011 à 2015 chez des prestataires de santé ou dans des laboratoires de diagnostic médical (MDLS) dans la province d'Alborz. Une étude sérologique rétrospective sur la présence d'anticorps anti-CMV dans les échantillons de sérum a été réalisée par le biais de tests ELISA dans une communauté non immunisée. Les sérums congelés datant de de l'année 2001 ont été collectés du printemps 2013 à l'hiver 2015et sélectionnés au hasard par une technique d'échantillonnage en grappes. La séroprévalence a été stratifiée par âge (> 1 à <50 ans). Des techniques mathématiques ont été utilisées pour sexe et le niveau d'éducation dans cette communauté. Les données ont été analysées à l'aide du test exact de Fisher et du test 2 à l'aide du logiciel SPSS version 11.5. L'âge moyen des individus séropositifs variait entre 15 et 50 ans. Des IgG anti-CMV ont été détectés chez 1813 personnes (2001). Au total, 188 personnes (9%) étaient négatives. Il existait une relation significative entre la séropositivité (IgG anti-CMV) et l'âge, le sexe, le niveau déterminer s'il existait une relation entre la séroprévalence du CMV et l'âge, le d'éducation et le niveau de titre en d'anticorps par sexe. Comme dans d'autres pays en développement, la prévalence de l'infection au CMV chez les adultes dela province d'Alborz est élevée. Etant donnée les taux élevés d' infection au CMV est lesanomalies potentielles que cela peut engendrer, nous recommandons fortement l'extension des mesures préventives et la mise en place de programmes visant à informer les populations à risque, en particulier les populations vulnérables telles que les greffés, les patients immunodéprimés et les écoliers.

Mots-clés: BLS, Expression génique, Protéine recombinante

INTRODUCTION

Human *Cytomegalovirus* infection is a common global endemic infection that occurs throughout the year and does not exhibit seasonal patterns of infection. CMV infection occurs early in childhood, and natural transmission occurs by either direct or indirect contact. CMV infections usually show no symptoms in healthy peoples. However, these infections in immunocompromised individuals including organ transplant recipients, human immunodeficiency virus (HIV) positive, and fetuses or newborn babies often result in life-threatening health condition. In transplant recipients, CMV is the most dangerous pathogen due to its effects in terms of morbidity and mortality. For HIV/AIDS patients, reactivation and reinfection and in newborns congenital infections are common problems concerning CMV. This infection initially enters the body via the epithelium of the upper alimentary, respiratory, or genitourinary tracts. The most important sources of infection for women are their first (primary) infection during pregnancy and sexual or close contact with young children (Staras et al., 2008). Previous studies of pre-teen children and children ≤5 years of age indicated that CMV is transmitted to children from their mothers in the uterus, or birth canal, through breastfeeding and from others, especially within childcare settings (Mocarski et al., 2013). CMV is one of the most dangerous pathogens affecting immunosuppressed individuals because it remains latent and persists for the lifetime of the organism. These viruses can be reactivated in immunosuppressed individuals and can lead to critical outcomes, such as interstitial pneumonitis, hepatitis, retinitis, and encephalitis (Mocarski et al., 2013). There is a close relationship between socioeconomic status (SES) and health consequences, especially in low and middle-income countries. Exposure and susceptibility to infections are two ways that SES affects long-term health. The main viruses associated with transfusion-related infections are hepatitis viruses, retroviruses, and *Cytomegalovirus* (CMV). The risk of transmitting viruses has been reduced significantly by screening of antibodies before transfusion. This paper evaluates the relationships between the seroprevalence of *Cytomegalovirus* (CMV) infection and education level and sex in

different age groups in a representative sample of the Alborz province population in Iran and investigates potential factors for these relationships. The objectives of this study were a) to study the molecular epidemiology and possible local isolation of virus for designing a primary study related to developing future CMV vaccines for a manufacturer in Iran and b) to assess the sources and the seroprevalence of CMV infection in the population of Alborz province, Iran.

MATERIAL AND METHODS

This descriptive study was carried out using serum blood samples from donors aged 1 to 50 years that were referred to the Medical Laboratory Diagnostic Services (MLDS) from spring 2011 to winter 2015.

Study population. The community chosen was the population of Alborz province, located in northern Iran. Alborz province was introduced as the 31st province of Iran centered in Karadj on June 23, 2010. The population size was approximately 2.712 million during the study period (2011-2015), and the inhabitants were distributed over an area of 5833 km^2, with >10% of the population residing in the urban area (228, 142) and the rest distributed among 4 large cities (Figure 1), (Table 1). The economic activity of Alborzis are centered in various large industries and smaller factories along the expanse between Tehran, which is the capital, and Qazvin, which is another industrial city of Iran. The social structure is highly heterogeneous, which is a characteristic seen in many developed Iranian cities.

Sampling. The population was sampled by including a total of 92 MDLSs in 6 different cities of Alborz province, where blood from donors between 1 and 70 years of age was sampled and divided into the following age groups: <15, 15 to 20, 25 to 29, 30 to 34, 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 60, and >60.In total, 2001 consecutive serum samples were tested for CMV IgG antibodies (Table 1). Prevalence was calculated by age group, level of education, and sex based on the epidemiological study (Figure 1), (Tables 1 and 2).

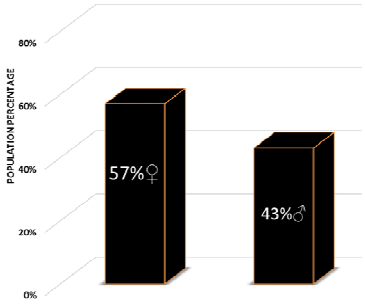

Figure 1. Frequency distribution of sex among patients with cytomegalovirus infection.

Table 1. Demographic characteristics of serum sample donors and cytomegalovirus seropositives in Alborz, Iran

Age	SEX		Total no of positives	OR	P-value
	Male	Female	(%)	(95%CI)	
>15	223	297.9	521 (92%)*	1.2 (0.5-1.7)	0.15
15-20	106	142	249 (89%)	1	0.15
20-30	355	471	827 (87%)	1.3 (0.6-1.9	0.13
30-40	129	171	300 (95%)	1.4 (0.8-2.1)	0.09
40-50	22	29	51 (100%)	1.2 (0.5-1.7)	0.15
>50	23	30	53 (100%)	1	--------
Total	858	1140	(90.4%)	1.5 (0.9-2.4	0.07

*. Figures in parentheses indicate the percentage X2= 0.17

Table 2. Frequency distribution of CMV-IgG according to educational level

Educational level	CMV-IgG		Total
	Negative (%)	Positive (%)	(percentage)
Illiterate (preschool)	0 (0%)	75 (3.7%)	75 (100%)
Primary school	0 (0%)	212 (10/59%)	212 (100%)
Secondary school	42 (8%)	466 (23.28%)	507 (100%)
High School	91 (11%)	738 (36.88%)	829 (100%)
University	59 (15%)	322 (16.09%)	378 (100%)
Total (percentage)	188 (9.4%)	1813 (90.6%)	2001 (100%)

Serum samples were collected using the Excel simple random sampling function and an epidemiological study (see formula) on distributions of populations. A total of 2001 serum samples were collected from 72 of 131 confirmed medical diagnostic laboratories throughout Alborz province. These laboratories submitted the sample for diagnostic testing, and remnant sera would have otherwise been discarded. The samples were coded by the name of the city, referring laboratory, date of collection, sample number, sex, age or date of birth, date of collection, and level of

education. All serum samples were stored at -20 °C until use.

Enzyme Immunoassay (ELISA) Tests. An enzyme immunoassay (ELISA)(Enzygnost Anti-CMV/IgG, Behringwerke AG, Marburg, Germany) kit for the determination of human CMV IgG antibodies was used. The cut-off value was 0.2, as recommended by the manufacturer.

Statistical Analysis. The data were analyzed using SPSS software version 21.0 for Windows (SPSS Inc., Chicago IL., USA), using Fisher's exact test for qualitative variables and a chi-squared test. Descriptive data were presented as the means ± standard deviation (SD), median (range), or frequency (valid percent). A value <0.05 was considered statistically significant.

RESULTS

The detailed characteristics of the serum sample donors and *Cytomegalovirus*-seropositive patients in different age groups are shown in Table 1. After retrieving the archived results of the experiment, the population was stratified based on age, level of education, and sex. The results are presented in Table 1. Overall, 2001 sera samples were analyzed for CMV antibodies. In total, 1881 samples (90.6%) were positive, and 188 (9.4%) were negative for *Cytomegalovirus* IgG antibodies as determined by ELISA. Moreover, 3% of the serum samples were positive for CMV IgM antibodies (data not shown). The distribution frequency of disease related to the education level in the population showed that the number of positive cases for individuals with high school level education was 738 (89%). The number of individuals with post-graduate or university level education that tested positive for CMV IgG Ab was 322 (16.09%). The number of positive serum samples in the illiterate population was 75, and for secondary and primary school levels, these values were 466 and 212, respectively, with 100% of the serum samples positive for CMV IgG in individuals with these three education levels (Table 3). The distribution of the CMV IgG Ab for all age groups in the population is shown in Figure 2. The distribution of CMV IgG-positive samples in different age groups showed that the majority of individuals sampled (827, 41.60%) were between 20 and 30 years of age. The mean age of seropositive individuals was 24.20±3.36 years. The lowest age for positive individuals was <1 year, and the highest was 70 years. Unfortunately, this average in other countries is 51 years. It seems that in the younger age groups (24.20±3.36) the antibody level was positive in the study population. In terms of the geographical distribution of seropositivity, the highest number was in Karaj. This high number may be due to the large population size in this city. The prevalence of anti-IgG antibodies was 57% in women and 43% in men (Figure 1). There was a significant correlation between IgG CMV Ab and gender. This result indicates a higher representation of women in terms of percentage in comparison with other countries. Most CMV IgG-positive serum samples over the three years (2011-2014) were collected in 2013. The following results were obtained from the statistical analysis of the ELISA data by calculating the odds ratio using the SPSS software. To determine the relationship between sex and serum sample CMV IgG positivity, the chi-squared test was performed, and the results showed a statistically significant relationship between sex and the number of positive serum samples detected by ELISA. The relationship between CMV IgG positivity and age was determined by performing a chi-squared test. The minimum age was 1 year, and the maximum was 71 years. Intervals of 10 years were established for the samples. The P-value showed no statistical relationship. The seropositivity distribution and its relationship with age in Alborz province are presented in (Figure 2). The reduction in CMV IgG prevalence in the population over 50 years old can be linked to the volume of sample collected in these age groups. The age and sex distribution of CMV IgG in Alborz province according to levels of Ab titers revealed that of the samples taken, 1140 cases were female, and 858 were male. Four categories for sample titer were obtained: 1.2, 1.4, 1.8, and 1.16 (Table 3). The results showed that 461 (46.1%) males and 369 (56.5%) females had a titer of

1.2. In sum, 999 males and females have titer levels of 1.2. Titre levels of 1.4 were obtained in 319 (56.5%) females and 246 (43.5%) males. The females accounted for 10% more than males at this titer level. However, for the titer level of 1.8, the number of females was 221 (63.1%) and 129 for males (36.9%), indicating nearly two times more females in this category than males.

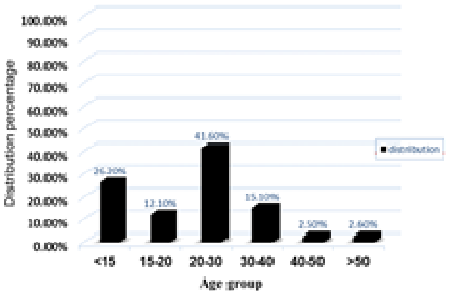

Figure 2. Distribution of Antibody IgG-CMV in all of different age groups

Additionally, at the titer level of 16, of 84 serum samples, 62 (73.8%) were female and 22 (26.2%) were male. As detailed in Table 4, the number of females compared to males was more than double at 1.8 and tripled for the titer level of 16. This finding indicates that as the titer increases, the number of females in comparison to males also significantly increases. The results of the chi-squared test differ and are shown in Table 3. The results obtained from this study of the population of Alborz province in Iran indicate that seropositivity is higher in the female population than in the male population.

Table 3. Frequency distribution (CMV-IgG) for different titers of the antibody in both males and females

Ab Titer (% within changetiter)		SEX		Total
		Female	Male	
1/2	No of samples	538	461	999
	% within changetiter	53.9%	46.1%	100%
1/4	No of samples	319	246	565
	% within changetiter	56.5%	43.5%	100%
1/8	No of samples	221	129	350
	% within changetiter	63.1%	36.9%	100%
1/16	No of samples	62	22	84
	% within changetiter	73.8%	26.2%	100%
Total positive	No of samples	1140	858	1998
	% within changetiter	57.1%	42.9%	100%

DISCUSSION

Cytomegalovirus is a member of the Herpesviridae family and is transmitted by close contact, blood transfusion, saliva, urine, breast-feeding, and sexual contact. Primary infection in adults is usually asymptomatic but can sometimes produce a syndrome similar to mononucleosis. Infection can be transmitted to the fetus via the placenta, which is common in the case of primary maternal infection. One percent of pregnant women have a primary infection, of which 40 percent present congenital fetal infections and 10% of the newborns will become increasingly symptomatic and continue to develop this disease. A total of 30% of infants will die with severe infection, and 80% will show severe neurological morbidity. Globally, 12% of live births show infection with CMV. After the primary infection, the virus is excreted for weeks to years and then becomes a latent infection (Mocarski et al., 2013).

Table 4. Summary of seroepidemiological studies included in this article by outcome in 15 different locations in Iran.

Population under study	CMV IgG%	Method (SC SP GMT Cellular avidity	place	References
College women	92.8	ELISA	Bushehr	Barazesh et al., 2014
Healthy community	98.2	ELISA	Isfahan	Mostafavi et al., 2013
Blood donor	99.2	ELISA	Mashhad	Moniri et al., 2004
Pregnant women	72.1	ELISA	Gonabad	Bagheri et al., 2012
Pregnant women	94-86	ELISA	Khorramabad	Delfan-Beiranvand et al., 2012
Spontaneous abortion	5.2	ELISA	South of Iran	Sotoodeh-Jahromi et al., 2010
Pregnant women recurrent & primary infection	34.4 and 65.6	ELISA	Fars	Arabpour et al., 2007
Blood donor	89.2	ELISA	Zanjan	Asadi et al., 2004

Then, the virus remains latent for some time, after which CMV revascularization episodes may cause reoccurrence of the latent virus or re-infection with different antigenicity. Maternal infection during pregnancy can lead to severe and permanent complications in the fetus. Cell-mediated immunity is the most important defense against active CMV. Active

T-lymphocytes are necessary to control latent CMV. Toddlers are also a significant source of infection. CMV virus transmission is widespread in kindergartens, in which the virus is transferred to childcare facilities or pregnant nursing staff. CMV patients present symptoms consistent with other illnesses such as mononucleosis. The disease lasts from several to a few hundred days and is characterized by excessive fatigue, mild pharyngitis, coughing, nausea, diarrhea, headache and fever from 39 to 40 °C that may last up to two weeks. In a clinical examination, cervical or generalized lymphadenopathy may be present but is rarely seen in hepatocellular, venous, or rash forms. Liver enzymes show a slight increase in 90% of patients and remain high for several months. Other symptoms of acute infection in pregnancy include lymphopenia or lymphocytosis with atypical thrombocytopenic lymphocytes. Most pre-school aged children in Africa and Asia are seropositive, while less than 20% of children in the United States and England are seropositive. Approximately 40,000–300,000 infants are born with congenital CMV each year, with 10% of them having a classic illness. Approximately 90% of these newborns at birth have a neurological disorder with hearing impairment (Mocarski et al., 2013). The presence of CMV IgG indicates that an individual has been infected with CMV postnatally, and the antibody remains intact throughout life and protects the individual against subsequent infection. Because of the high prevalence of CMV IgG, this test has little value for diagnosis, but it is very useful for identifying individuals with negative serum. Serological and molecular methods are two basic pillars for detecting *Cytomegalovirus* infection in mothers and fetuses, and these methods are commonly used in most studies, although serological methods are more commonly used. Multiple studies have shown that ELISA is a suitable method for the diagnosis of congenital *Cytomegalovirus* infection, which was also used in this study. CMV IgM antibodies are typically produced after primary infection, but non-primary infections also appear; therefore, there is no diagnostic value. However, the presence of CMV IgM with CMV IgG with low avidity is an effective serological test for primary infection. The serum cytometric index of CMV IgG titers provides useful clinical information for the determination of the epidemiology of *Cytomegalovirus* infection in the community. This CMV serological survey is the first study conducted in the community of Alborz province of Iran and was carried out by random sampling in terms of the population of each city. Since there has not been any published demographic information on patients with CMV in Alborz, the data were compared with global statistics and other studies in different parts of Iran. The analysis of the results from the published articles in Iran is presented in Table 4. These results reported that 90–95% of the healthy people, 23–37% of pregnant women, and 82–89% of blood donors showed positivity for CMV IgG in different parts of Iran. According to previous studies, the prevalence of CMV is related to race, age, number of births, sexual behavior, and occupational activity (Mocarski et al., 2013). The results of the present study in Alborz showed an overall prevalence rate of 91.2% for CMV IgG among the population under study. On the other hand, 3% of the samples tested positive for CMV IgM, indicating the presence of primary infection (data not presented). The high seroprevalence rate reported in this study is comparable to the rates reported in India (97%) (Kothair et al., 2002), Brazil (96%–98%) (Suassuna et al., 1995), France (97.14%) (Smith and Robinson, 2002), Spain (Madrid; 62.8%–79.1%) (de Ory et al., 2004), in Finnish children up to the age 8 (41%) (Aarnisalo et al., 2003), Turkey (90.6%–99%) (Dolar et al., 2006), for the age group of 6–11 (36.3%) and 80 years (90.8%) in the United States (Staras et al., 2008), healthy children in Cameroon (90.8%) (Stroffolini et al., 1993), Saudi Arabia (90.8%) (Ghazi et al., 2002), Italy (73%) (de Mattia et al., 1991), and Jordan (77.2%) (Abuharfeil and Meqdam, 2000). In this study, the seroprevalence of CMV IgG among the sera varied with age ranging from 92% in the group aged <15, 82% in the ages of 15 to 20, 60% in the ages of 21 to 30, 95% in the ages of

31 to 40, to 100% in the <50-year age group (Figure 2). These results are comparable to other studies that showed seropositivity increased with age of sample donors (Table 1, Figure 2). Most adults (61.51%) older than 20 have serological evidence of previous infections by CMV, while this rate in the adult population over 40 years of age worldwide ranges from 60 to 100%. The seroprevalence rate for the overall 20 years age group is already high in comparison with other countries. This finding means that in the population under study, the over 20 years age groups may spend more years infected with CMV on average by the time they get older. This rate of seropositivity could be related to environmental, cultural, or socio-economic factors such as family size or population density, transmission through breastfeeding, sexual contact, transmission from children to mothers, and other unknown factors such as blood transfusion. This high prevalence rate in the current study population indicates the endemicity of the infection, which, of course, is consistent with many studies in other parts of the country and especially in other developing countries. With regard to the frequency of CMV in this country and the clinical significance of the disease especially in the context of high prevalence in women, CMV should be given priority over other infectious agents. The broad perspective from this analytical study highlights the need to focus on diagnosis, epidemiology, identification, and isolation of CMV infections in mothers and their newborns. Another study suggested that screening of blood donors or pregnant women through urine specimens by PCR can be a useful method for identifying primary infection and reducing CMV transmission in chemotherapy or immunosuppressed recipients (Mocarski et al., 2013). This screening has two of the most significant benefits in terms of preventing TT CMV. First, identification of the high neutralizing antibody titers in CMV-seropositive samples may permit the extraction of immunoglobulin for treatment of CMV infections in immunosuppressed individuals and, when necessary, for the CMV-seronegative population in emergencies. Second, identification of the low percentage of CMV-seronegative individuals is necessary to alert and educate them on the importance of their status and should include counselling them about their CMV-seronegative status and how to use it with the purpose of enabling rapid recall in times of need since more than 90% of surveys in different parts of Iran recorded samples that were seropositive for CMV (Table 4). However, this procedure is not efficient in terms of cost/benefit; thus, another alternative such as leukoreduction filtration or gamma irradiation might be helpful to decrease risks, especially in immunocompromised or susceptible recipients. This paper examined differences in CMV seropositivity by education level, age, sex, and titer by sex and then explained the relationship between these criteria and infection status. The present survey showed 90–100% seropositivity in teenage, adult, and elderly populations. Recent research has shown that latent CMV infection in the elderly is associated with significant changes in immunological parameters, a condition called the immunological risk phenotype. The signs including high CD8, low CD4 cell percentages, and poor T-cell proliferation are a predisposing factor of mortality among healthy adults. Several studies have noticed increases in herpes virus antibody titers are linked to academic stress in pre-university and university students and military cadets (Glaser, 2005), Alzheimer's disease, poor-quality marriage, and traumatic life events, as well as loneliness and anxiety (Dowd et al., 2008). These studies suggest that psychological stress can reduce cellular immune response, thereby increasing susceptibility to infection. This study has several limitations, some variables such as socioeconomic status of serum donors, housing crowdedness and family size, and family behavior, information for medical conditions of patients such as HIV or immunocompromised cases that was not measured may factor into the transmission dynamics and determination of the individual risk of exposure. The

other limitation is that although this survey provides the most recent data on CMV prevalence in the Alborz population, a definitive inference cannot be made based on cross-sectional data. We recommend future planning for a constant CMV-immune population that would likely focus on early life. The other important consideration for future planning for Razi as a vaccine manufacturer is research on the development of a locally effective CMV vaccine. Alborz province, Karaj in particular, has problems and deficiencies that cannot be eliminated without nationalization and implementation of large-scale projects at the national level. Currently, the province's most pressing problems are due to the over-growth of the population, which is due to the Alborz migratory status. Alborz province has ranked first among immigrants throughout the country, and its proximity to Tehran has caused many problems for this city. Alborz province has only 3% of the country's land and is the smallest province but currently holds 4% of the total population of the country, even though immigration to Alborz is continuing every day. The problems of CMV and related side effect seem to be a global and national problem and will require national and global effort and public resolve; especially at the national level, we hope to overcome these issues as soon as possible. In conclusion, we found high seropositivity for CMV infection in the study population that is evident as early as age 1 and persists through middle and elderly ages. The results indicated that the population under study showed seropositivity, 25 years sooner and longer than other populations of the world. This study showed that females not only have significantly higher CMV IgG titers but also showed 2–3 times more rates of seropositivity than males.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare that they have no conflict of interest.

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