Journal of Coastal Life Medicine

journal homepage: www.jclmm.com

Original article doi: 10.12980/jclm.4.2016J6-142

The sero-epidemiology of infectious mononucleosis in Neyshabur, Northeast Iran during 2010–2014

Mohammahd Salehi[1,2], Mahtab Vafaei[3], Abolmajed Ghashim[4], Sayyed Karli Shakuhi Mostafaei[4*]

[1]*Research Center for HIV/AIDS, HTLV and Viral Hepatitis, Iranian Academic Center for Education, Culture and Research, Khorasan Razavi Branch, Mashhad, Iran*

[2]*Medical Diagnostic Laboratory of Neyshabur, Center of Medical, Pathological and Genetic Diagnostic Services, Iranian Academic Center for Education, Culture and Research, Mashhad Branch, Mashhad, Iran*

[3]*Department of Virology Laboratory Sciences, Keyvan Virology Laboratory, Tehran, Iran*

[4]*Department of Microbiology, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran*

ARTICLE INFO

Article history:
Received 9 Aug 2016
Received in revised form 22 Aug 2016
Accepted 14 Sep 2016
Available online 18 Sep 2016

Keywords:
Epstein-Barr virus
Infectious mononucleosis
Neyshabur City
Iran

ABSTRACT

Objective: To detect infectious mononucleosis (IM) prevalence in Neyshabur, Northeast Iran during 2010–2014.

Methods: This cross-sectional descriptive epidemiological survey was performed to reveal the prevalence of IM in Neyshabur between 2010 and 2014. A total of 114 individuals were studied. Briefly, individuals with positive test for specific immunoglobulin G and immunoglobulin M in the agglutination test were determined as positive cases.

Results: The overall prevalence of IM was 14%. Mean ± SD of age for IM test was 18.96 ± 15.79. The age groups of 0–10 and 21–30 were the most positive cases in this period. In addition, 31–40 and over 50 years were not positive cases. Male individuals were significantly more positive and likewise, it was observed that there were significantly higher positive cases of IM in spring and summer.

Conclusions: Among the five years of this study, it was a decreasing status from 2010 (23.1%) to 2014 (9.1%), though a slight fluctuation had occurred. The prevalence of IM was low in Neyshabur City. Moreover, children and male individuals had relatively higher prevalence of the disease. Furthermore, it was observed a higher rate of IM in spring and summer.

1. Introduction

Epstein-Barr virus (EBV) is the herpesvirus infecting more than 90% of the world's population[1]. Although the disease is benign and asymptomatic for the most cases, EBV can cause many nonmalignant and malignant disorders of lymphoid and epithelial origins[2]. EBV infection is mostly asymptomatic in children. However, first exposure during this era and an adolescence may develop itself as an infectious mononucleosis (IM) in 30% to 70% of cases[3,4]. Some individuals are more vulnerable than others to develop clinical symptoms from delayed infection, while there is no reason[5,6]. $CD8^+$ T cells play a key protective role for the control of latent EBV infection. However, they are recognized to be the main mediators of the disease during IM[7,8]. Furthermore, observations suggest that other immune mediators are possibly important for the control and prevention of acute symptomatic EBV infection[9]. Results from a recent Phase II clinical trial revealed that the induction of neutralizing antibodies is effective in the prevention of symptomatic acute IM after primary infection[10]. In spite of these effective results,

*Corresponding author: Sayyed Karli Shakuhi Mostafaei, Department of Microbiology, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran.
Tel: +98 82883440
Fax: 82884555
E-mail: Shokuhi64@gmail.com

The study protocol was performed according to the Helsinki Declaration and approved by Research and Technology Deputy of Iranian Academic Center for Education, Culture and Research, Mashhad Branch. Informed written consent was obtained from Research Center of HIV and AIDs, Mashhad, Iran.

Foundation Project: Suppoted by Medical Diagnostic Laboratory of Neyshabur, Center of Medical, Pathological and Genetic Diagnostic Services, Iranian Academic Center for Education, Culture and Research, Mashhad, Iran (Grant No. 1349536/4743, 2014).

The journal implements double-blind peer review practiced by specially invited international editorial board members.

very little emphasis is noted upon the investigation of humoral immunity during primary infection and defects in antibody level could contribute to the severity of the disease burden during acute IM[11]. The virus can persistently shed in saliva for duration of 6 months[12]. The study in Southern Iran showed that the prevalence of EBV among acute lymphoblastic leukemia individuals was high[13]. Another survey indicated a relationship between EBV and breast cancer among women in Iran[14].

2. Materials and methods

2.1. Patients and population

This cross-sectional descriptive epidemiological survey was performed to reveal the prevalence of IM in Neyshabur during 2010–2014.

A total of 131 individuals were studied. Travelers (n = 16) and migrants (n = 11) were excluded in this study. Thus, 114 subjects from all age groups were included. The sample size was considered as 5 years of study. The individuals were healthy and no clinical sign was observed. None of subjects had fever, rash, stomach pain and headache symptoms.

2.2. Sample collection

Briefly, blood samples were collected from individuals and the sera samples were prepared. In addition, the examination of white blood cells showed that total lymphocyte count was 4 700. The agglutination test was used with equal amount of serum and reagent. Any individuals with positive test for specific immunoglobulin G and immunoglobulin M (heterophile antibodies) were determined as positive cases[15]. The Oxoid IM kit (Oxoid Ltd, Hampshire, UK) was employed for antibodies detection. Components of the kit included DR0681M test latex that consisted of latex particles sensitised with purified bovine antigen where the kit contained sufficient reagent for 50 tests, DR0682M positive control serum that consisted of rabbit antiserum containing specific antibody reactive with the sufficient test reagent for 15 tests and DR0683M negative control serum that consisted of rabbit antiserum tested for the absence of specific heterophile antibodies with the sufficient reagent for 15 tests.

Bilirubin level of serum was also measured but transaminase and alkaline phosphatase levels were not tested.

2.3. Ethical approve

Approval for this study was obtained from the Research and Technology Deputy of Iranian Academic Center for Education, Culture and Research, Mashhad Branch. Informed written consent was obtained from Research Center of HIV and AIDs, Mashhad, Iran.

2.4. Data analysis

Data were analyzed using SPSS version 20 (IBM SPSS Statistics for Windows, Version 20) and the *Chi*-square test. $P < 0.05$ were considered statistically significant.

3. Results

Mean ± SD of age for IM test was 18.96 ± 15.79. The age range of individuals was 8 months–63 years. As shown in Table 1, the overall prevalence of IM among 5 years was 14%. The age groups of 0–10 and 21–30 were the most positive cases in this period. In addition, 31–40 and over 50 years were not positive cases.

Table 1

The age, sex and seasonal distribution of positive cases of mononucleosis.

Demographic features		No.	Positive cases (%)	Odds ratio	95% confidence interval	*P*
Age	0–10	48	6 (12.5)	Baseline		
	11–20	18	0 (0.0)	0.875	0.786–0.974	0.116
	21–30	28	6 (21.4)	1.909	0.550–6.621	0.303
	31–40	10	0 (0.0)	–	–	–
	41–50	6	2 (33.3)	3.500	0.523–23.418	0.176
	> 51	4	0 (0.0)	–	–	–
Sex	Male	54	10 (18.5)	3.182	0.935–10.831	0.054
	Female	60	4 (6.7)			
Season	Spring and summer	52	10 (19.2)	0.290	0.085–0.987	0.038
	Fall and winter	62	4 (6.5)			

–: Not determined.

Male individuals were significantly more positive and likewise, it was observed that there were significantly higher positive cases of mononucleosis in spring and summer (Table 1 and Figures 1-3).

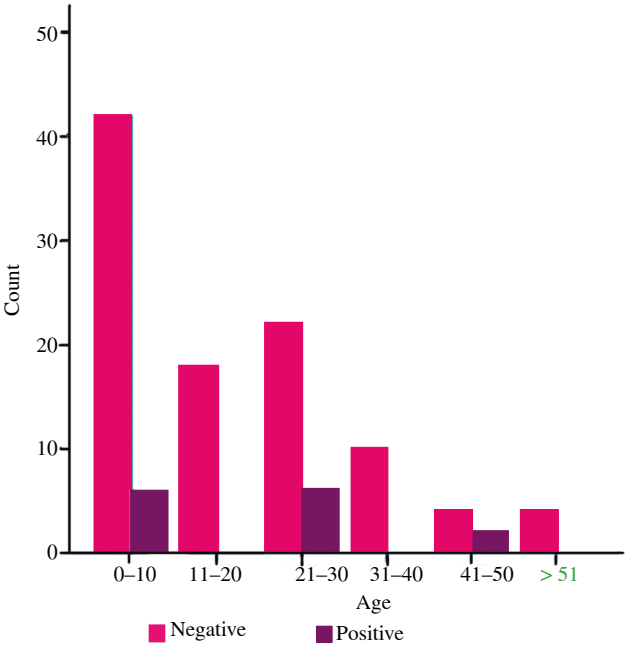

Figure 1. The age distribution of individuals in this study.
The age groups of 0–10 nd 21–30 were more positive for IM, whereas, among age groups of 11–20, 31–40 and > 51, there was no case of IM.

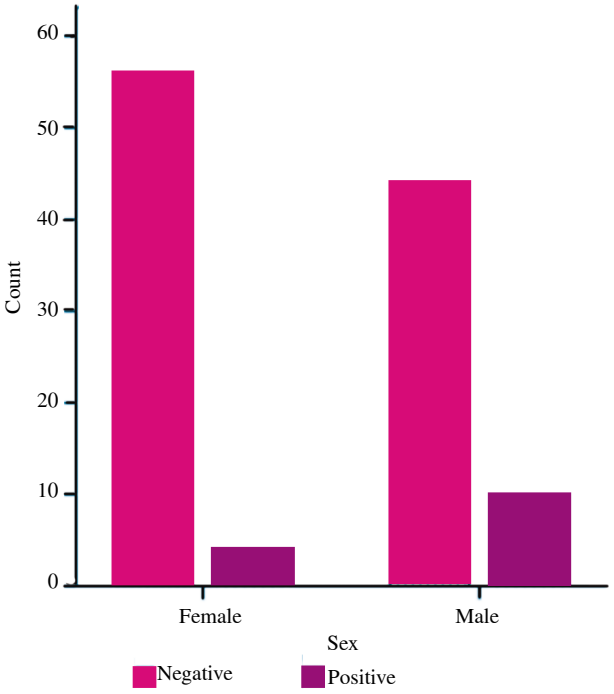

Figure 2. The genders of this study and comparison between the two groups.
Males were significantly more infected with IM.

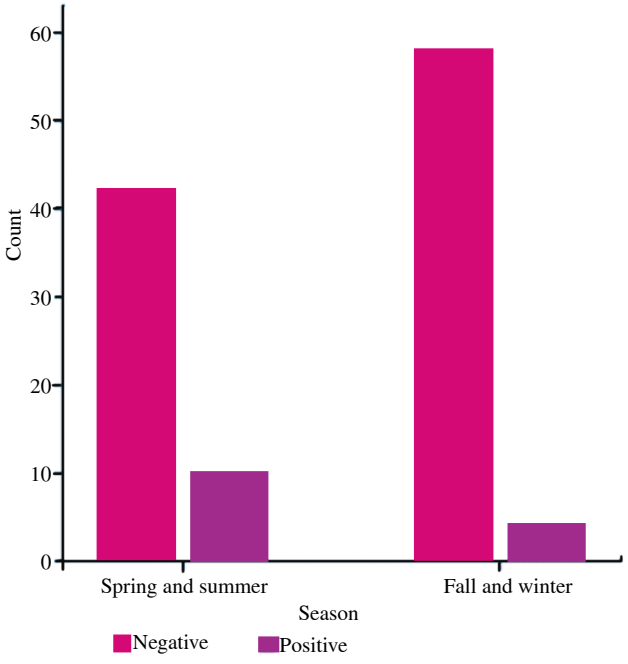

Figure 3. The highest and lowest count of seasons in which the positive cases of mononucleosis were observed.
There was a significant higher positive results in spring and fall (P = 0.038).

There was a declining trend from 2010 to 2014 regarding the prevalence of IM. Moreover, no positive case was detected in 2012. The bilirubin level of 48 (42.10%) out of 114 subjects was higher than normal. As shown in Table 1, there was a significant difference among seasons for the detection of IM. Among the 5 years of this study, it was a decreasing status from 2010 (23.1%) to 2014 (9.1%), though a slight fluctuation was occurred (Table 2 and Figure 4).

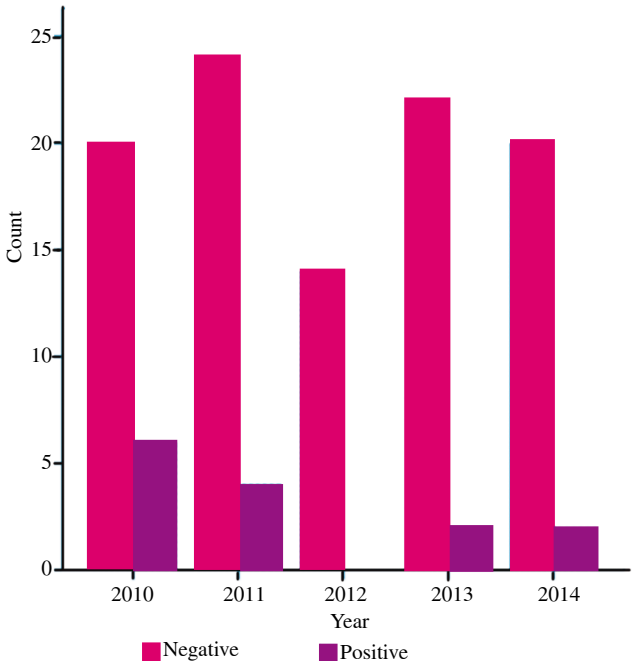

Figure 4. The prevalence of mononucleosis in each year from 2010 to 2014.
In 2010 and 2011, there were higher positive cases of IM, while in 2012, no positive IM case was detected.

Table 2
The positive cases of mononucleosis in each year of this period (2010–2014).

Year	NO.	Positive cases (%)
2010	26	6 (23.1)
2011	28	4 (14.3)
2012	14	0 (0.0)
2013	24	2 (8.3)
2014	22	2 (9.1)
Total	114	14 (12.3)

4. Discussion

In this study, mean ± SD of age of subjects was 18.96 ± 15.79 (8 months–63 years). We observed that the age groups of 0–10 and 21–30 were the most positive cases in this period. The presence of the disease in children has been reported in several previous studies with different disorders and indications, such as enhanced cytotoxicity of specific T-cells, rash following amoxicillin treatment and presence of soluble human leukocyte antigen-G in serum of children[16-18]. In addition, individuals with 31–40 and over 50 years were all negative for the test. Several previous surveys have suggested the lymphocyte count as a valid diagnostic screen test in adults infected with mononucleosis in different results[19,20]. In this study, male individuals were significantly more positive and likewise, it was observed that there were significantly higher positive cases of mononucleosis in spring and summer. Similarly, Ramagopalan *et al.* revealed that males were more frequently infected with IM for all age groups apart from age ranges of 10–14 (false match rate 1.50 and 95% confidence interval)[21]. Regarding differences between genders for infection susceptibility of EBV, there have been several hypotheses, such as different social behaviors and thus interpersonal contact and exposure[22]. Visser *et al.* determined no evidence of relation between seasons and EBV infection in children[23]. Seasonal

fluctuations, sun radiation and vitamin D affect the immune system against EBV and several studies have similarly shown this effect[24,25]. On the other hand, we observed that among the 5 years of this study, it was a decreasing status from 2010 (23.1%) to 2014 (9.1%), though a slight fluctuation was occurred. The limitations of this study were no molecular test for detection and characterization of EBV and subtypes, a limited area of study (Neyshabur city), a low number of subjects and no exact detection of liver enzymes levels among subjects.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

This study was supported by Medical Diagnostic Laboratory of Neyshabur, Center of Medical, Pathological and Genetic Diagnostic Services, Iranian Academic Center for Education, Culture and Research, Mashhad, Iran (Grant No. 1349536/4743, 2014).

References

[1] Kong QL, Hu LJ, Cao JY, Huang YJ, Xu LH, Liang Y, et al. Epstein-Barr virus-encoded LMP2A induces an epithelial-mesenchymal transition and increases the number of side population stem-like cancer cells in nasopharyngeal carcinoma. *PLoS Pathog* 2010; **6**(6): e1000940.

[2] Jenson HB. Epstein-Barr virus. *Pediatr Rev* 2011; **32**: 375-84.

[3] Balfour HH Jr, Sifakis F, Sliman JA, Knight JA, Schmeling DO, Thomas W. Age-specific prevalence of Epstein-Barr virus infection among individuals aged 6–19 years in the United States and factors affecting its acquisition. *J Infect Dis* 2013; **208**(8): 1286-93.

[4] Lorenzetti MA, Gantuz M, Altcheh J, De Matteo E, Chabay PA, Preciado MV. Distinctive Epstein-Barr virus variants associated with benign and malignant pediatric pathologies: LMP1 sequence characterization and linkage with other viral gene polymorphisms. *J Clin Microbiol* 2012; **50**(3): 609-18.

[5] Ozbek SM, Ozbek A, Yavuz MS. Detection of human cytomegalovirus and Epstein-Barr virus in symptomatic and asymptomatic apical periodontitis lesions by real-time PCR. *Med Oral Patol Oral Cir Bucal* 2013; **18**(5): e811-6.

[6] Draborg AH, Duus K, Houen G. Epstein-Barr virus in systemic autoimmune diseases. *Clin Dev Immunol* 2013; **2013**: 535738.

[7] Angelini DF, Serafini B, Piras E, Severa M, Coccia EM, Rosicarelli B, et al. Increased $CD8^+$ T cell response to Epstein-Barr virus lytic antigens in the active phase of multiple sclerosis. *PLoS Pathog* 2013; **9**(4): e1003220.

[8] Grywalska E, Markowicz J, Grabarczyk P, Pasiarski M, Roliński J. Epstein-Barr virus-associated lymphoproliferative disorders. *Postepy Hig Med Dosw (Online)* 2013; **67**: 481-90.

[9] Rickinson AB, Long HM, Palendira U, Münz C, Hislop AD. Cellular immune controls over Epstein-Barr virus infection: new lessons from the clinic and the laboratory. *Trends Immunol* 2014; **35**(4): 159-69.

[10] Simon KC, O'Reilly EJ, Munger KL, Finerty S, Morgan AJ, Ascherio A. Epstein-Barr virus neutralizing antibody levels and risk of multiple sclerosis. *Mult Scler* 2012; **18**(8): 1185-7.

[11] Nagarajan T, Marissen WE, Rupprecht CE. Monoclonal antibodies for the prevention of rabies: theory and clinical practice. *Antibody Technol J* 2014; **4**: 1-12.

[12] Balfour HH Jr, Verghese P. Primary Epstein-Barr virus infection: impact of age at acquisition, coinfection, and viral load. *J Infect Dis* 2013; **207**(12): 1787-9.

[13] Mahjour SB, Ghaffarpasand F, Fattahi MJ, Ghaderi A, Fotouhi Ghiam A, Karimi M. Seroprevalence of human herpes simplex, hepatitis B and Epstein-Barr viruses in children with acute lymphoblastic leukemia in Southern Iran. *Pathol Oncol Res* 2010; **16**(4): 579-82.

[14] Kadivar M, Monabati A, Joulaee A, Hosseini N. Epstein-Barr virus and breast cancer: lack of evidence for an association in Iranian women. *Pathol Oncol Res* 2011; **17**(3): 489-92.

[15] Luka J, Chase RC, Pearson GR. A sensitive enzyme-linked immunosorbent assay (ELISA) against the major EBV-associated antigens. I. Correlation between ELISA and immunofluorescence titers using purified antigens. *J Immunol Methods* 1984; **67**(1): 145-56.

[16] Chiang AKS, Ning J, Chan KH. Emergence of highly functional antigen-specific T cells towards Epstein-Barr virus corresponds to viral control and enhanced cytotoxicity in children with infectous mononucleosis and primary asymptomatic infection. The 16th International Symposium on EBV and Associated Diseases; 2014 Jul 16–19; Brisbane, Australia.

[17] Chovel-Sella A, Ben Tov A, Lahav E, Mor O, Rudich H, Paret G, et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. *Pediatrics* 2013; **131**(5): e1424-7.

[18] Wang HY, Tian KG, Fu M, Zheng XQ. Detection of plasma soluble HLA-G and lymphocyte subsets in peripheral blood of children with infectious mononucleosis. *Chin J Nosocomiol* 2012; **5**: 011.

[19] Biggs TC, Hayes SM, Bird JH, Harries PG, Salib RJ. Use of the lymphocyte count as a diagnostic screen in adults with suspected Epstein-Barr virus infectious mononucleosis. *Laryngoscope* 2013; **123**(10): 2401-4.

[20] Biggs T, Hayes S, Harries P, Salib R, Bird J. In response to "use of the lymphocyte count as a diagnostic screen in adults with suspected Epstein-Barr virus infectious mononucleosis". *Laryngoscope* 2014; **124**(11): E448.

[21] Ramagopalan SV, Giovannoni G, Yeates DG, Seagroatt V, Goldacre MJ. Sex ratio of infectious mononucleosis and possible relevance to multiple sclerosis. *Mult Scler* 2013; **19**(3): 359-61.

[22] Hwang AE, Hamilton AS, Cockburn MG, Ambinder R, Zadnick J, Brown EE, et al. Evidence of genetic susceptibility to infectious mononucleosis: a twin study. *Epidemiol Infect* 2012; **140**(11): 2089-95.

[23] Visser E, Milne D, Collacott I, McLernon D, Counsell C, Vickers M. The epidemiology of infectious mononucleosis in Northern Scotland: a decreasing incidence and winter peak. *BMC Infect Dis* 2014; **14**: 151.

[24] Lossius A, Riise T, Pugliatti M, Bjørnevik K, Casetta I, Drulovic J, et al. Season of infectious mononucleosis and risk of multiple sclerosis at different latitudes; the EnvIMS Study. *Mult Scler* 2014; **20**(6): 669-74.

[25] Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K. Season of birth and risk of Hodgkin and non-Hodgkin lymphoma. *Int J Cancer* 2014; **135**(11): 2735-9.