ISSN: 2475-6296

Research Article

Journal of Clinical & Experimental Immunology

Association between parvovirus B19 virus and childhood acute lymphoblastic leukemia: A cross-sectional study in Tehran; Iran

Fahimeh Ehsanipour[1], Mohammad Faranoush[2], Samileh Noorbakhsh[*3], Fattaneh Babaei[4] and Azim Mehrvar[5]

[1]*Associate professor in Ped Infectious Diseases ,Department of Pediatric Infectious Disease, Iran University of Medical Sciences, Tehran, Iran*

[2]*Full professor in Ped Oncology, Department of Pediatrics, Iran University of Medical Sciences, Tehran, Iran*

[3]*Full professor in Ped Infectious Diseases , Department of Pediatric Infectious Disease, Iran University of Medical Sciences, Tehran, Iran*

[4]*Pediatric Resident, Iran University of Medical Sciences, Tehran, Iran*

[5]*Associate professor in Ped Oncology, Mahak Hospital, Tehran, Iran*

[*]Corresponding author
Professor Samileh Noorbakhsh, Departement of pediatric infectious diseases, 4th floor, Rasoul-e-Akram Hospital, Niayesh Street, Satarkhan Avenue, Tehran, 14455 Islamic Republic of Iran

Submitted: 30 Dec 2021; **Accepted**: 06 Jan 2022; **Published**: 14 Jan 2022

Citation: *Fahimeh Ehsanipour, Mohammad Faranoush, Samileh Noorbakhsh, Fattaneh Babaei, Azim Mehrvar. (2022). Association between parvovirus B19 virus and childhood acute lymphoblastic leukemia: A cross-sectional study in Tehran; Iran. J Clin Exp Immunol, 7(1): 416 - 422.*

Abstract

Objective: *The propose of study was to determine the viral load of Parvovirus B19 in children with proven acute lymphoblastic leukemia (ALL)*

Methods: *A cross-sectional study designed in pediatric ward of Rasoul-e-Akram Hospital (educational, third referral) in Tehran, Iran (2015 – 2016). Sixty-nine children (mean age: 6.57 ± 4.25 years) in preservative phase of ALL selected. BMA had done, and the viral load for Parvovirus B19 determined by quantitative PCR.*

Results: *Type of ALL was Pre B cell: 76.8%; Pro B cell: 14.5% and T-cell type: 7.8%. Low viral load determined in 18.8% (n=13); intermediate in 39.1% (n=27). High and very high viral load observed in 27.1% 15 (n=15) and 20.3% (n=1) of cases respectively. Viral load was related to Pro B cell type ($p = 0.050$) and lymphadenopathy ($p = 0.040$), but not related to gender ($p = 0.350$) and severity of ALL ($p = 0.403$); like hepatosplenomegaly, anemia, thrombocytopenia or need to transfusion.*

Conclusion: *Parvovirus B19 is a common viral infection in young Iranian population. Near one-third of childbearing age, women in Iran are at risk for primary Parvovirus B19 infection. Here, to evaluate the possible role of parvovirus B19 Infection in the etiology of ALL, 42 % of ALL cases had high and very high viral load (21.7% and 20.3); the low or intermediate viral load is detectable in all cases. The viral load was related to Pro B cell type of ALL ($p = 0.050$) and the presence of lymphadenopathy. However, there is no relationship observed between Parvovirus B19 viral load and the severity of ALL and gender. It probably might be due to viral detection in the early stages of the ALL.*

Keywords: ALL (Acute Lymphoblastic Leukemia); Parvovirus B19; Viral Load, Children

Introduction

Parvovirus B19 is a single-stranded non-enveloped DNA virus with profound tropism for erythroid precursor cells. This virus is an important virus for human one because it induce a wide spectrum of clinical manifestation mild, self-limiting) erythema infectious) normal host to lethal diseases (aplastic crisis) in immunocompromised cases [1]. Indeed, approximately 30–50% of pregnant women are nonimmune. Vertical transmission is common following maternal infection (nonimmune mothers) {2} There is still no evidence of fetal teratogenic effects with parvovirus B19, but fetal infection may be asymptomatic, or severe infection and sequelae like hydrops fetalis, or fetal death [1, 2]. Parvovirus B19-contaminated blood products increases the risk of infection [3]. Nosocomial outbreaks of parvovirus B19 rarely occurred among Thailand healthcare personnel (HCP) with more importance in susceptible pregnant women [3]. Persistent viral infection is responsible for an autoimmune response and clinical symptoms can mimic autoimmune inflammatory disorders [4]. Recently ,some clinical symptoms by parvovirus B19 mimic autoimmune inflammatory disorders (eg rheumatoid arthritis, systemic lupus, antiphospholipid syndrome, systemic sclerosis and vasculitides) reported [4]. Molecular mimicry between Parvovirus B19 and host is the main mechanism in autoimmune response. For viral eradication no immunoglobulins, antiviral or vaccination are available until yet [1, 3, 4]. But intrauterine transfusion in selected hydrops fetalis may be lifesaving. Parvovirus B19 diagnosis is mainly through serology and polymerase chain reaction [1-4].

The parvovirus B19 is an erythropoietic virus with high prevalence in bone marrow erythroblasts [2, 3]. The role of infectious agents such as parvovirus B19 in the pathogenesis of different types of leukemia were studied by some authors [5-7]. The clinical and hematological pattern of parvovirus B19 infection in childhood ALL studied by Zakki et al, Heegaard et al reported transient pancytopenia preceding in pre-ALL cases precipitated by parvovirus B19 Also, Zaki et al described that seroprevalence for parvovirus B19 virus among various population is varied between 0% -10%, while in children with acute leukemia exceeds 40% to 45% [8-10]. Lee et al explained the distribution of parvovirus B19 DNA in blood compartments and persistence of virus in blood donors [11]. Tsitsikas et al proposed a possible association between human parvovirus B19 infection and bone marrow necrosis and fat embolism syndrome in sickle cell disease [12]. According to Fisgin et al study, Parvovirus B19 dependent aplastic anemia happened few months before appearing acute leukemia and directly leads to aplastic crisis in near 2% of all aplastic anemia [13]. All above findings emphasize the relationship between parvovirus B19 infection and the risk of ALL in children.

Except viral infection, numerous carcinogenic and mutagenic chemicals might increase the risk of developing leukemia [14-23]. Increased frequency of chromosome translocations or deletion observed in leukemic cases [16-19]. The increscent of childhood ALL in tobacco smoke home pesticide paint and petroleum solvents exposure defined by authors [21-23]. Indeed, Kerr et al reported the cytokine gene polymorphisms associated with symptomatic parvovirus B19 infection [24]. A three-way association between the presence of acute leukemia in children, the presence of some molecule markers , as well as the infection with B19 Gough et al determined progenitor B-1 B-cell acute lymphoblastic leukemia is associated with collaborative mutations in 3 critical pathways [24, 25]. Parvovirus B19 infection induces the production and secretion of certain cytokines and adversely reduction of Interleukin-10 as pro-inflammatory cytokines, at the same time, indeed these markers increase in childhood ALL [24, 25].

Worldwide mortality rate /year for ALL estimated 74% of 300,000 new cases [26-28]. Leukemia is the most common pediatric cancer, affecting 3,800 children per year in the United States [26]. Mousavi et all in a literature review in Iran (1974- 2008) reported the most common cancer in children from 0 to 14 years old were leukemia (incidence rate=8 to 62/million) [27]. Despite progress in ALL treatment, a poor prognosis of acute leukemia in our country reported by Ayremloei et al (2001-2011) during the last decade [28]. It seems that environmental factors have potential influences for incidence of ALL in our young population [29-34]. The previous studies in Iran have identified father's freelance job (such as animal husbandry, agriculture, work in the rubber industry, and work in an oil refinery) as a common risk factor for childhood ALL [32]. Zolala et al determined the inducing factors of childhood ALL in Fars province of Iran Relationship between exposure to pesticides and occurrence of ALL in Iran showed by Zakerinia et al [33, 34].

During last decade the prevalence of Parvovirus B19 in malignancy, blood disorders and Transplant Candidates with Bone Marrow Suppression reported in Iran [35-37]. According to Soltani et al the positive parvovirus B19 DNA detection rate in Thalassemic and Sickle cell group was 4–15.3%. And 4–54% respectively [38].

Parvovirus B19 is a common viral infection in Iran [39-41]. A possible role considered for parvovirus B19 in the pathogenesis of abortion [42]. The infection during pregnancy can affect the fetus due to lack of mother's immunity [43, 44]. The maternal parvovirus B19 infection was not associated with fetal death [45].

Due to probable role for parvovirus B19 Infection in the etiology of ALL, this cross sectional study had done to search the viral load of parvovirus B19 (PCR) in bone marrow samples of confirmed ALL children during 2 years.

Materials and Methods

This cross-sectional study had done upon 69 ALL cases admitted in pediatric Ward of Rasoul-e-Akram Hospital (3th level referral hospital) affiliated by Iran University of Medical sciences during 2 years (2015 – 2016) in Tehran, Iran.

Cases selected randomly from ALL patients were referred to

pediatric oncology department. ALL cases were in preservative phase. This study has adhered to the principles of Helsinki and has been approved by the ethics committee in Iran University of Medical Sciences. Informed consent was obtained from parents of all cases. Ethics code number: MS.FMD. REC 1396.931.

A questionnaire was filled for each selected cases including demographic characteristics (age, gender), history of disease, underlying disease, and clinical manifestations. Conducting additional evaluations according to the history and clinical examination, and finally study variables determined. After collecting the information, blood sampling had done on admission day for performing additional tests (like Complete Blood cells and other LAB tests according to necessary). The bone marrow aspiration had done and specimens were transported to the laboratory at Hazrate-Rasool hospital for PCR test.

Inclusion Criteria: All selected children was in preservative phase of ALL (pathologic proved in Bone Marrow Aspiration). Parvovirus B19 infection: defined as the presence of parvovirus B19 DNA viral loading by (qualitative PCR) on bone marrow samples. Exclusion criteria: In first step patients whom not did return for further examination and complementary tests, or did not reach the final diagnosis (preservative phase) were excluded from our study.

LAB Test:

DNA Extraction: Viral DNAs were extracted from BMA samples by using thermal shock (modified protocol). Minimal Essential Medium (MEM, Sigma Aldrich Co, USA) incubated overnight (4°C), and then heated in a thermo cycler with a temperature of 55°C for 60 min, 100°C for 7 min, and 0°C for 2 min (Eppendorf, Germany). Finally, after a centrifugation step (3320×g for 15 min), the supernatant (20 µl) was frozen at −80°C overnight and tested for the presence of viral DNA with an in-house nested PCR assay. DNA extraction was done using a PCR template purification kit (NucleoSorb, Quiagen). The quantification kit for detection of the parvovirus B19 genomes (Primer Design™ using the TaqMan® principle) with sensitivity 10 B19V DNA copies/reaction were used.

The samples with positive amplification were submitted to DNA sequencing of the B19V polymorphic region (VP1u-NS1 gene junction) using an in-house optimized nested-PCR with first round primers: forward JUN1 (5′GGACCAGTTCAGGAGAATCAT3′) and reverse JUN2 (5′CCAGCTTGTAGCTCATTGC3′) and second round primer pair: JUNNF (5′GACCAGTTTCGTGAACTGTTAGT3′) (forward) and JUNNR (5′CAGGCTTGTGTAAGTCTTCACTAG3′) (reverse).

Statistical Analysis: SPSS version 16.0 the statistical software (SPSS Inc., Chicago, IL) was used. The frequencies and percentages for categorical variables ; mean ± standard deviation (SD) for quantitative variables calculated ,quantitative variables were compared with t -test or Mann- Whitney U test. Categorical variables were compared using chi-square test or Fisher's exact test values <0.05 were considered statistically significant

Results

The range of age was between 6 months to 16 year (mean age: 6.57 ± 4.25 years); 37 cases (53.6%) were male and 32 cases (46.4%) were female. Just three cases (4.3%) had Down syndrome.

From 69 children with confirmed ALL; Pre B cell diagnosed in 76.8% (n=53); Pro B cell in 14.5 %(n=10); and T-cell type in 7.8 %(n=6).

Clinical Manifestations: lymphadenopathy observed in 40.6% (n=28), hepatosplenomegaly 7.2% (n=5); anemia (dependent to age) in 87.0% (n=60); thrombocytopenia in 42.0% (n=29) and need for transfusion in 66.7%; (n=46) of cases.

Table 1: The load of parvovirus B19 in children with ALL according to baseline factors

Factor	B19 (+) load
Gender	
Male	4 (10.8)
Female	6 (18.8)
Type of ALL	
Pre B cell	0 (0.0)
Pro B cell	10 (18.9)
T cell	0 (0.0)
Lymphadenopathy	
Positive	7 (25.0)
Negative	3 (7.3)
Hepatosplenomegally	
Positive	2 (40.0)
Negative	8 (12.5)
Anemia	
Positive	9 (15.0)
Negative	1 (11.1)
Thrombocytopenia	
Positive	6 (20.7)
Negative	4 (10.0)
Blood transfusion	
Positive	7 (15.2)
Negative	3 (13.0)
Viral load	
Low	0 (0.0)
Intermediate	5 (18.5)
High	3 (20.0)
Very high	2 (14.3)

The severity of viral load in ALL cases was shown in Figure -1

The load of parvovirus B19 virus in ALL cases: Low viral load determined in 18.8% (n=13); intermediate in 39.1% (n=27); very high and high viral load observed respectively in 15 (n=21.7%); and 20.3% (n=14) of cases. No association found between viral load and ALL (p = 0.403).

The viral load was related to Pro B cell type of ALL (p = 0.050) and the presence of lymphadenopathy (p = 0.04) but not related to gender (p = 0.35), hepato splenomegaly (p = 0.150), anemia (p = 0.757), thrombocytopenia (p = 0.302) or need to transfusion (p = 0.809).

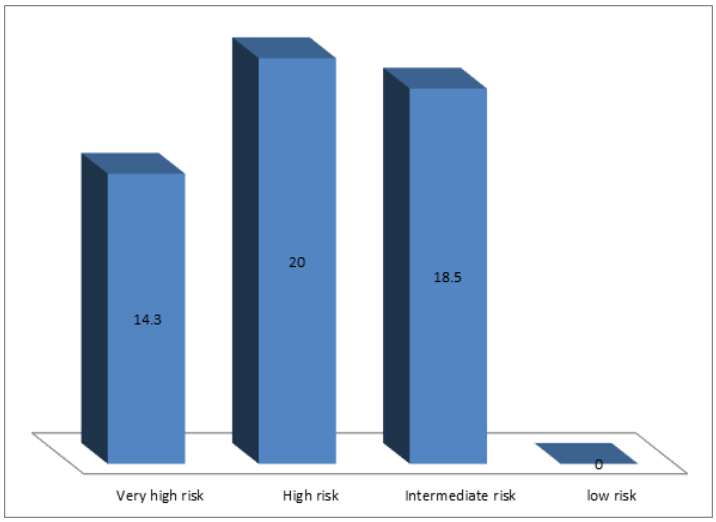

Figure 1: The severity of viral load in ALL cases.

Discussion

Here, we present the viral load of parvovirus B19 in 69 children with various type of ALL (preservative phase) .Mean age of studies cases was 6.57 ± 4.25 years, 53.6% were male and 46.4% were female. Down syndrome just diagnosed in three cases (4.3%) Pre B cell (76.8%) was the most frequent and T-cell type (7.8%) was the less common type of ALL diagnosed.

Despite the low or intermediate parvovirus B19 viral load in all cases, overall, 42 % of ALL cases had high and very high viral load (21.7% and 20.3). The higher viral load was so frequent in Pro B cell type of ALL (p = 0.050) and related to presence of lymphadenopathy (p = 0.040). The viral load of was not related to severity of ALL (p = 0.403); but viral load was not related to gender (p = 0.350), hepatosplenomegaly (p = 0.150), anemia (p = 0.757), thrombocytopenia (p = 0.302) or need to transfusion (p = 0.809).

In recent studies, the physio pathological role of parvovirus B19 virus in the pathogenesis of different types of leukemia, especially in children, has been confirmed [5-15]. However, the role of the parvovirus B19 in the occurrence of ALL is still doubtful. Various studies have indicated that the occurrence of the Pro B cell type of ALL has been accompanied by an increase in the expression of some genes, as well as the activation of some biological pathways such as the Janus kinase (Jak) pathway [16-19]. The percentage of the parvovirus B19 positivity in various studies among children ranged from 14.5% to 47.5%, which indicates that the virus is widely distributed in different types of leukemia [7-15]. Kerr et al reported parvovirus B19 in 33.3% of ALL cases [7]. In Heegaard et al study, specific IgG was positive in 30% of patients [9]. Like us, Ibrahim et al study determined positive parvovirus B19 in 47.5% (vs. 42%) of ALL patients in Basra, Iraq [15]. This viral load is higher than reported by Nikoozad et al in Isfahan, Iran, but lower than Soltani et al study Nikoozad et al compared Parvovirus B19 infection between cases with blood disorders and healthy people [35-38]. Parvovirus B19 DNA was detected in 23.1% of cases. 17.1% and 30% among benign and malignant blood disorder groups vs none of controls parvovirus B19 infection detected in 26% of Transplant Candidates with Bone Marrow Suppression Soltani et al in a literature review showed the seroprevalence (IgG and IgM) of parvovirus B19 infection in β-thalassemia patients [35, 37]. Were 18.2– 81% and 14.5–41.1%, the positive parvovirus B19 DNA was 4–15.3%. In the Sickle cell group, IgG and IgM was 37.6 to 65.9% and was 2.9–30%, DNA detection rate was 4–54% [38].

In the other hand, we found that viral load did not correlate with other risk factors, such as gender, age, changes in blood count and risk stratification of ALL. However, there is no relationship between load of parvovirus B19 and the extent severity of ALL (p = 0.403). In other words, the virus can be expressed and discovered at any stage and in any severity of the disease, and thus, the presence of positive cases of parvovirus B19 has no significant correlation with the severity of the disease and even the virus in the early stages of the disease may also be discoverable. In the present study, the burden of Parvovirus B19 infection in childhood ALL was estimated close to 42%. This abundance of virus expression has been very diverse in various studies [5-9]. The pathways mentioned above or gene expression may also be activated under the influence of parvovirus B19, which, of course, needs to be further evaluation. There are some underlying factors associated with increasing the B19 virus load in patients with ALL in present study. In fact, the presence of lymphadenopathy, which indicates the extent of the spread of the tumor, is a self-indicative index for the high level of parvovirus B19 .On the other hand, parvovirus B19 virus appears to have a more pathogenic role in certain types of ALL tumors, so that this kind of originality has been evident principally and exclusively in the pro B cell type.

Parvovirus B19 is a common viral infection in Iran [39, 40]. The results of one serologic study (2005) in Shiraz (Fars provinence) published. Overall, 66.5%, 2.2% women of childbearing age had positive IgG and IgM. Positive HPV B19 IgG detected 61.5%, 69%, and 69% of the to-be-married girls. Pregnant women and the neonates respectively. Positive IgM not detected in to-be-married

girls and umbilical cord sera .Just one-third of childbearing age were at risk for primary HPV B19 infection [40]. The results of Sabahi et al showed a relatively high prevalence of the B19V-associated diseases in all age groups of the Iranian population [39]. Recently, Shirvani et al (2019) reported the Parvovirus B19 seropositivity and its laboratory and clinical presentation in PICU admitted children in Tehran [40]. Positive Parvovirus B19 -IgM was associated with anemia, neutropenia, and abnormal liver function tests [41]. The infection during pregnancy can affect the fetus due to lack of mother's immunity but non-immune fetal hydrops and abortion may be caused by vertical transmission of the virus during pregnancy. Habibzadeh et al (2013) reported the prevalence of parvovirus B19 immunity among pregnant women (aged between15 to 34 years) in Ardabil (west provience of Iran). Near 70% of pregnant women (242/350) were immune (positive anti-B19-specific IgG antibody), with a significant correlation with the age of pregnant but without relation with living area, family member, number of commensals, number of living children, and the amount of hemoglobin [42]. They concluded that one-third of the pregnant women are at risk of primary B19 infection had intrauterine fetal infection. They recommend health education of pregnant women and screening of infected pregnant women [42]. In contrast to Habibzadeh et al study, according to Rahbar et al study, from 94 pregnant women (mean age of 28.4 years) with spontaneous abortion, 18.1% had parvovirus B19 specific antibody (IgM), and in 14.9% were suspected for presence of the antibody in their blood sample. No correlation with age, occupation, gestational age, number of previous abortion, presence of children <6 years old and number of pregnancy. These findings revealed that a high percentage of pregnant women are probably non-immune against parvovirus B19, and there might be a number of spontaneous abortions in which parvovirus infection caused fetal death. However, more studies are needed to prove the absolute role of parvovirus B19 in these abortions [43]. Another study (2011) in West Azerbaijan province of Iran determined positive anti-B19-specific IgG antibody in 75.6% of pregnant women (mean age: 25.56 ± 5.30 years); 88.8% of women with a history of abortion were IgG positive, history of blood transfusion obtained in 3 women (2 seropositive) for B19). A possible role of parvovirus B19 considered by authors in the pathogenesis of abortion [44]. Sarfaraz et al (2009) reported the risk of fetal death and low birthweight with parvovirus B19 infection in pregnant women [45]. They found 0.7% of the women with fetal death (vs 0.9% controls) had positive IgM 3.1% of seronegative women with fetal death and 2.6% with a live birth seroconverted. Positive IgG or IgM antibodies in the first trimester, or seroconversion during pregnancy were not associated with lower birthweight or reduced length of gestation in live born children, but was associated with low birthweight in stillborn offspring [45].

Conclusion

Parvovirus B19 is a common viral infection in young Iranian population. Near one-third of childbearing age, women in Iran are at risk for primary Parvovirus B19 infection. Here, to evaluate the possible role of parvovirus B19 Infection in the etiology of ALL, 42 % of ALL cases had high and very high viral load (21.7% and 20.3); the low or intermediate viral load is detectable in all cases. The viral load was related to Pro B cell type of ALL ($p = 0.050$) and the presence of lymphadenopathy. However, there is no relationship observed between Parvovirus B19 viral load and the severity of ALL and gender. It probably might be due to viral detection in the early stages of the ALL.

Acknowledgment

We thanks for support of the Paediatric Infectious Diseases Ward in Rasul hospital.

Funding

This study was supported by the Iran University of medical sciences. This study received no specific grant from any funding agency in the public, institutions or not-for-profit sectors.

This study was approved by the Ethical Committee in Iran University of medical sciences. This study has adhered to the principles of Helsinki and has been approved by the ethics committee in Iran University of Medical Sciences. Ethics code number: MS.FMD. REC 1396.931.

.

References

1. Broliden, K., Tolfvenstam, T., & Norbeck, O. (2006). Clinical aspects of parvovirus B19 infection. Journal of internal medicine, 260(4), 285-304.
2. Lamont, R. F., Sobel, J. D., Vaisbuch, E., Kusanovic, J. P., Mazaki-Tovi, S., Kim, S. K., ... & Romero, R. (2011). Parvovirus B19 infection in human pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology, 118(2), 175-186.
3. Sungkate, S., Phongsamart, W., Rungmaitree, S., Lapphra, K., Wittawatmongkol, O., Pumsuwan, V., ... & Chokephaibulkit, K. (2017). Human parvovirus B19 nosocomial outbreak in healthcare personnel in a paediatric ward at a national tertiary referral centre in Thailand. Journal of Hospital Infection, 96(2), 163-167.
4. Lunardi, C., Tinazzi, E., Bason, C., Dolcino, M., Corrocher, R., & Puccetti, A. (2008). Human parvovirus B19 infection and autoimmunity. Autoimmunity reviews, 8(2): 116-120.
5. Eden T (2010) Etiology of childhood leukemia. Cancer Treat Rev, 36(4): 286-97.
6. Francis, S. S., Selvin, S., Metayer, C., Wallace, A. D., Crouse, V., Moore, T. B., & Buffler, P. A. (2014). Mode of delivery and risk of childhood leukemia. Cancer Epidemiology and Prevention Biomarkers, 23(5), 876-881.
7. Kerr, J. R., Barah, F., Cunniffe, V. S., Smith, J., Vallely, P. J., Will, A. M., & Eden, O. B. (2003). Association of acute parvovirus B19 infection with new onset of acute lymphoblastic and myeloblastic leukaemia. Journal of clinical pathology, 56(11), 873-875.
8. Zaki, M. E. S., & Ashray, R. E. (2010). Clinical and

hematological study for parvovirus B19 infection in children with acute leukemia. International journal of laboratory hematology, 32(2), 159-166.
9. Heegaard ED, Madsen HO, Schmiegelow K (2001) Transient pancytopenia preceding acute lymphoblastic leukemia (pre-ALL) precipitated by parvovirus B19. Br J Haematol. 114(4): 810-813.
10. El Sayed Zaki, M. (2007). Relevance of specific immunoglobulin M and immunoglobulin G for parvovirus B19 diagnosis in patients with acute lymphoblastic leukemia receiving chemotherapy: prospective study. Archives of pathology & laboratory medicine, 131(11), 1697-1699.
11. Lee, T. H., Kleinman, S. H., Wen, L., Montalvo, L., Todd, D. S., Wright, D. J., & NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II). (2011). Distribution of parvovirus B19 DNA in blood compartments and persistence of virus in blood donors. Transfusion, 51(9), 1896-1908.
12. Tsitsikas, D. A., Gallinella, G., Patel, S., Seligman, H., Greaves, P., & Amos, R. J. (2014). Bone marrow necrosis and fat embolism syndrome in sickle cell disease: increased susceptibility of patients with non-SS genotypes and a possible association with human parvovirus B19 infection. Blood reviews, 28(1), 23-30.
13. Fisgin, T., Yarali, N., Duru, F., & Kara, A. (2002). Parvovirus-B19 infection preceding acute myeloid leukemia with orbital granulocytic sarcoma. Leukemia & lymphoma, 43(10), 2059-2061.
14. Lee, S. M., Kim, D. G., & Bang, D. (1994). Persistent erythema infectiosum-like rash as a prodrome of acute lymphocytic leukemia. Pediatric dermatology, 11(2), 156-159.
15. Ibrahem, W. N., Hasony, H. J., & Hassan, J. G. (2014). Human parvovirus B19 in childhood acute lymphoblastic leukaemia in Basrah. J Pak Med Assoc, 64(1), 9-12.
16. Mori, H., Colman, S. M., Xiao, Z., Ford, A. M., Healy, L. E., Donaldson, C., & Greaves, M. (2002). Chromosome translocations and covert leukemic clones are generated during normal fetal development. Proceedings of the National Academy of Sciences, 99(12), 8242-8247.
17. Zuna, J., Ford, A. M., Peham, M., Patel, N., Saha, V., Eckert, C., & Greaves, M. (2004). TEL deletion analysis supports a novel view of relapse in childhood acute lymphoblastic leukemia. Clinical cancer research, 10(16), 5355-5360.
18. Tsai, A. G., & Lieber, M. R. (2010). Mechanisms of chromosomal rearrangement in the human genome. BMC genomics, 11(1), 1-9.
19. Papaemmanuil, E., Hosking, F. J., Vijayakrishnan, J., Price, A., Olver, B., Sheridan, E., & Houlston, R. S. (2009). Loci on 7p12. 2, 10q21. 2 and 14q11. 2 are associated with risk of childhood acute lymphoblastic leukemia. Nature genetics, 41(9), 1006-1010.
20. Munthe-Kaas, M. C., Tierens, A., Bechensteen, A. G., & Zeller, B. (2015). Myeloid Leukemia of Down Syndrome: Relation to Parvovirus B19 Infection and Wilms Tumor Gene (WT1) Expression. Journal of pediatric hematology/oncology, 37(1), e67-e68.
21. Metayer, C., Zhang, L., Wiemels, J. L., Bartley, K., Schiffman, J., Ma, X., & Buffler, P. A. (2013). Tobacco smoke exposure and the risk of childhood acute lymphoblastic and myeloid leukemias by cytogenetic subtype. Cancer Epidemiology and Prevention Biomarkers, 22(9), 1600-1611.
22. Scélo, G., Metayer, C., Zhang, L., Wiemels, J. L., Aldrich, M. C., Selvin, S., & Buffler, P. A. (2009). Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. Environmental health perspectives, 117(1), 133-139.
23. Bailey, H. D., Infante-Rivard, C., Metayer, C., Clavel, J., Lightfoot, T., Kaatsch, P., & Schüz, J. (2015). Home pesticide exposures and risk of childhood leukemia: Findings from the childhood leukemia international consortium. International journal of cancer, 137(11), 2644-2663.
24. Kerr, J. R., McCoy, M., Burke, B., Mattey, D. L., Pravica, V., & Hutchinson, I. V. (2003). Cytokine gene polymorphisms associated with symptomatic parvovirus B19 infection. Journal of clinical pathology, 56(10), 725-727.
25. Gough, S. M., Goldberg, L., Pineda, M., Walker, R. L., Zhu, Y. J., Bilke, S., & Aplan, P. D. (2017). Progenitor B-1 B-cell acute lymphoblastic leukemia is associated with collaborative mutations in 3 critical pathways. Blood advances, 1(20), 1749-1759.
26. Whitehead, T. P., Metayer, C., Wiemels, J. L., Singer, A. W., & Miller, M. D. (2016). Childhood leukemia and primary prevention. Current problems in pediatric and adolescent health care, 46(10), 317-352.
27. Mousavi, S. M., Pourfeizi, A., & Dastgiri, S. (2010). Childhood cancer in Iran. Journal of pediatric hematology/oncology, 32(5), 376-382.
28. Ayremlou, P., Razavi, S. M., Solaymani-Dodaran, M., Vakili, M., & Asadi-Lari, M. (2012). Demographic and prognostic factors of 455 patients with acute leukemia admitted to two referral hospitals in tehran-iran during ten years (2001-2011). Iranian journal of cancer prevention, 5(3), 157.
29. Gholami, A., Salarilak, S., Hejazi, S., & KHALKHALI, H. (2011). Parental risk factors of childhood acute leukemia: a case-control study.
30. Hashemizadeh, H., Boroumand, H., Noori, R., & Darabian, M. (2013). Socioeconomic status and other characteristics in childhood leukemia. Iranian journal of pediatric hematology and oncology, 3(1), 182.
31. Rafieemehr, H., Calhor, F., Esfahani, H., & Gholiabad, S. G. (2019). Risk of acute lymphoblastic leukemia: Results of a case-control study. Asian Pacific journal of cancer prevention: APJCP, 20(8), 2477.
32. Veisani, Y., & Delpisheh, A. (2018). A meta-analysis of prenatal and maternal risk factors for childhood leukemia in iran, case-control studies approach. Journal of Pediatrics Review, 6(1), 1-7.
33. Zolala, F., Ayatollahi, S. A. R., Ayatollahi, S. M. T., & Shahriary, M. (2004). Determination the inducing factors

of acute lymphoblastic leukemia in children under 15 years old in Fars province in the year 2001. Journal of Rafsanjan University of Medical Sciences, 3(4), 267-275.
34. Maryam, Z., Sajad, A., Maral, N., Zahra, L., Sima, P., Zeinab, A., & Davood, M. (2015). Relationship between exposure to pesticides and occurrence of acute leukemia in Iran. Asian Pacific Journal of Cancer Prevention, 16(1), 239-244.
35. Nikoozad, R., Mahzounieh, M. R., & Naghavi, N. S. (2014). Genomic detection of parvovirus B19 in patients suffered from chronic anemia, leukemia/lymphoma in Isfahan, Iran. Scientific Journal of Iran Blood Transfus Organ, 10(4), 364-371.
36. K Tari, A Atashi, HReza Ghafari, M Shahjahani (2016) Parvovirus B19 Infection And Transient Aplastic Crisis. Int J Med Lab Res, 1(2): 48-54.
37. Mohammadi, B., Yaghobi, R., Dehghani, M., & Behbahani, A. B. (2013). The molecular prevalence of viral infections in transplant candidates with bone marrow suppression, Shiraz, southern Iran, 2010. International journal of organ transplantation medicine, 4(2), 87.
38. Soltani, S., Zakeri, A., Tabibzadeh, A., Zandi, M., Ershadi, E., Rezayat, S. A., & Farahani, A. (2020). A literature review on the parvovirus B19 infection in sickle cell anemia and β-thalassemia patients. Tropical Medicine and Health, 48(1), 1-8.
39. Sabahi, M., Salehipour, A., Kazemi, A., Sadeghi, M., Decaro, N., Mozhgani, S. H., & Yaghoobi, M. H. (2019). Prevalence and disease association of human parvovirus B19 in Iran: a systematic review. Future Virology, 14(8), 561-570.
40. Ziyaeyan, M., Rasouli, M., & Alborzi, A. (2005). The seroprevalence of parvovirus B19 infection among to-be-married girls, pregnant women, and their neonates in Shiraz, Iran. Jpn J Infect Dis, 58(2), 95-7.
41. Shirvani, F., Karimi, A., Karbasian, F., & Sanaei Dashti, A. (2019). Parvovirus B19 Seropositivity and Its Laboratory and Clinical Effects in PICU Admitted Children at Mofid Children Hospital. Journal of Iranian Medical Council, 2(5), 161-166.
42. Habibzadeh, S., Peeri-Doghaheh, H., Mohammad-Shahi, J., Mobini, E., & Shahbazzadegan, S. (2016). The prevalence of parvovirus B19 infection among pregnant women of Ardabil in 2013. Iranian journal of microbiology, 8(3), 214.
43. Rahbar, N., Zadeh, S. V., Ghorbani, R., & Kheradmand, P. (2015). Prevalence of parvovirus B19 specific antibody in pregnant women with spontaneous abortion. Acta Medica Iranica, 168-172.
44. Khameneh, Z. R., Hanifian, H., Barzegari, R., & Sepehrvand, N. (2014). Human parvovirus B19 in Iranian pregnant women: a serologic survey. Indian Journal of Pathology and Microbiology, 57(3), 442.
45. Sarfraz, A. A., Samuelsen, S. O., Bruu, A. L., Jenum, P. A., & Eskild, A. (2009). Maternal human parvovirus B19 infection and the risk of fetal death and low birthweight: a case–control study within 35 940 pregnant women. BJOG: An International Journal of Obstetrics & Gynaecology, 116(11), 1492-1498.