Evaluation of Immunoglobulin-A Level in Children with Acute Lymphoblastic Leukemia

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common type of leukemia among children. Immunoglobulin A is the most numerous immunoglobulin isotype in mucosal secretion. Immunoglobulin A (IgA) deficiency can increase risk of cancer in patients. Since few studies have been done on relation between serum IgA and ALL, this study was attempted to evaluate serum IgA in ALL patients.

Materials and Methods: In this descriptive analytical study, 28 pediatric patients diagnosed with ALL with mean age of 6.75± 3.29 ranged from 1 to11 years old and 28 controls with mean age of 7.31± 4.12 ranged from 2 to 12 years old were chosen from Shahid Sadoughi Hospital. Serum IgA was measured by immunotorbidometric method (Pars Azmoon Kit, Iran). Pearson and Independent t test were used for the analysis of data.

Results: In this study, the mean level of IgA was lower in patients with ALL ($82.5 \pm 21.3 \text{ mg/dl}$) in comparison to control group ($113.2 \pm 26.62 \text{ mg/dl}$). Moreover, there was significant difference between two groups (P<0.01). Regarding patients age, no significant difference was seen either (P>0.05).

Conclusion: According to the results of the present study, the serum level of IgA was significantly lower in ALL pediatric patients than the control group; however, it was in normal range in both groups. More studies are needed to strongly conclude IgA deficiency as a new risk factor or as a new marker of ALL in children. Other immunoglobulins are recommended to be considered in patients with ALL in further studies.

Key Words: Acute Lymphoblastic Leukemia, Immonoglobulin, IgA deficiency

Introduction

One of the most fatal diseases in human beings is cancer with the death of about 30000 persons annually in Iran (1, 2). Leukemia as a common and important starts in blood (3). Acute lymphoblastic leukemia (ALL) is the most common type of leukemia among children (4). So that incidence peak of ALL is between 2 to 5 years old. The survival rate of ALL in children has been improved nearly 90% (5). Moreover, the annual incidence of ALL has increased 0.8% per year from 1975 to 2006 (6). It is estimated that 6000 new cases of ALL are recognized annually in the United States (5). ALL as multi-factorial disease arises from interaction between exogenous or endogenous exposures, genetic susceptibility, and chance (5). These factors account for the approximately 1 out of 2000 risk of childhood ALL (5). Treatment of ALL involves short-term intensive chemotherapy, including highmethotrexate, cytarabine, dose cyclophosphamide, dexamethasone or prednisone, vincristine, L-asparaginase, and/or an anthracyclin and radiation therapy. These treatments are used for patients who show evidence of Central Nervous System (CNS) or testicular leukemia, although this approach is controversial at the current time, especially children Moreover, in **(7)**. immunoglobulin A (IgA) is the most numerous immunoglobulin isotype in mucosal secretion (8). IgA exists in two

isotypes, IgA1 and IgA2 which are glycosylated proteins (10).IgA1 predominates in serum (~80%); while, IgA2 is higher in secretion than serum (11). Prevalence of immunoglobulin-A deficiency (IgA-D) is diverse in different geographical regions (12). This deficiency is altered from 1/500 in Caucasians to 1/18,500 in Asia (13). IgA deficiency as the commonest type of immunodeficiency is associated with autoimmune disease (12). Moreover, it is linked to lymphoma or lymphoproliferative malignancy (LPM) in both rheumatoid arthritis and celiac (CD) (14). Moreover, deficiency in patients increases the risk of cancer and death (14). So that cancer is the most common cause of death in patients with IgA deficiency (14). Since, few studies have been done on the relation between IgA level and ALL in children; the aim of this study was to evaluate immunoglobulin-A level in children with Acute Lymphoblastic Leukemia.

Materials and Methods

Sample Collection

In this descriptive analytical study, 28 children with ALL (newly diagnosed patients) and 28 controls were chosen based on Cochran's formula from Shahid Sadoughi Hospital from 2014 to 2015. Children with ALL who were diagnosed using aspiration of bone marrow were recruited for this study. Informed written consent was taken from the participants. Ethics committee approval was obtained by Yazd University of Medical Sciences (IR.SSU.Medicine.Rec.1395.2).

Blood Collection and immunoglobulin-A (IgA) assay

Blood samples were obtained from patients after at least 8 hours fasting. Serum was separated from the clots after complete coagulation (1 h in room temperature) by low speed centrifugation (15 min at 2000 g) and stored in -70°C refrigerator. Serum IgA was measured by immunotorbidometric method Azmoon Kit, Iran). In this method, IgA concentration was evaluated by photometric reaction between antibodies and IgA.

Statistical analysis was performed using SPSS (version 19). Pearson and Independent t test were used for analysis of data. P-values< 0.05 were considered statistically significant.

Results

In this study, the mean age of case group was 6.75 ± 3.29 ranged from 1 to11 years and mean age of control group was 7.31 ± 4.12 ranged from 2 to 12 years old. Fifteem patients (53.57%) were female and 13 patients (46.4%) were male.

The normal range of IgA was 70 - 400 mg/dl

The mean level of IgA in patients and control group is shown in Table I.

As shown in Table I, the mean level of IgA was lower in patients with ALL in comparison to control group. However, there was significant difference between IgA in patients with ALL and control (P=0.000).

The mean level of IgA in male patients and control group was 82.5± 21.3 and 113.2± 26.62 mg/dl, respectively.

Moreover, no significant relation between IgA and age was observed (P=0.45).

Table I: The mean level of IgA in patients and control group.

IgA mean in children with ALL n=28	IgA mean in control group n=28	p-value
82.5± 21.3 mg/dl	113.2± 26.62 mg/dl	0.000

Discussion

The result of this study showed that the mean level of IgA was lower in patients with ALL in comparison to control group. Moreover, significant difference was seen in patient and control group in terms of IgA level. Okpala et al., evaluated the level of immunoglobulin A by single radial immunodiffusion method in patients with ALL. They showed that the level of serum IgA was lower than control group, although it was not statistically significant (15). Potapnev et al., in another study evaluated serum IgA in 68 children with primary B-lineage ALL and 46 healthy children. They reported no significant difference between ALL patients and control group regarding mean level of serum IgA (16). Martin Ibanez evaluated serum IgA, IgG, and IgM in 50 patients with ALL and reported immunoglobulin concentration was normal in ALL's onset (17). Ludvigsson et al., reported that individuals with IgA deficiency are at moderately increased risk cancer, especially risk of gastrointestinal cancer (14). They also reported that children with IgA deficiency are not at increased risk of cancer (14). Welch et al., reported that low level of serum IgA is associated with worse prognosis for survival in children (18). Luczynski et al., carried out a study on 40 children with ALL aged 2-15 years old. The level of IgA was measured using flow cytometry. The results of aformentioned study showed reduced level of IgA in patients during maintenance therapy in comparison to healthy children (19).

Haraldsson et al., evaluated serum IgA in 10 patients with acute lymphoblastic leukemia before, during, and after antileukemic therapy. The results showed that concentration of IgA decrease during treatment but recovere slowly after cessation of the therapy in patients with ALL (20). Van Tilburg et al.,, evaluated the level of immunoglobulins in patients with ALL and showed that decreased chemotherapy is advantageous for

recovery of immunoglobulin which may prevent the susceptibility for infections (21)

Ludvigsson et al., reported that IgA deficiency increase risk of infections in individuals (22). They believed that relation between IgA deficiency and infections is due to reduced mucosal defense mechanisms, because IgA is the most important immunoglobulin at mucosal surface (22). Salavoura et al., also reported that IgA deficiency is associated with high frequency of epithelial tumors, because of defective defense of mucosa against pathogens especially in respiratory and gastrointestinal tract (23).

Conclusion

According to the results of the present study, the serum level of IgA was significantly lower in ALL pediatric patients than the control group; however, it was in normal range in both groups. More studies are needed to strongly conclude IgA deficiency as a new risk factor or as a new marker of ALL in children. Other immunoglobulins are recommended to be considered in patients with ALL in further studies.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Zare-Zardini H, Taheri-Kafrani, Amiri A, Shanbedi M 4, Sadri Z, Ghanizadeh F, Neamatzadeh H, Sheikhpour R, Keyvani Boroujeni F. Nanotechnology and Pediatric Cancer: Prevention, Diagnosis

- and Treatment. Iran J Ped Hematol Oncol 2015; 15(4): 227-232.
- 2. Sheikhpour R. The role of ghrelin in cancer. Iranian J blood Canc 2016; 8(1): 1-4.
- 3. Torkaman A, Moghaddam Charkari N, Aghaeipour M. An approach for leukemia classification based on cooperative game theory. Anal Cell Pathol 2011; 34: 235–246.
- 4. Sheikhpour R, Aghaseram M. Diagnosis of acute myeloid and lymphoblastic leukemia using gene selection of microarray data and data mining algorithm. Sci J Iran Blood Transfus Org 2016; 12 (4), 347-357.
- 5. Inaba H, Greaves M, G. Mullighan Ch. Acute lymphoblastic leukaemia. Lancet 2013; 381(9881): 1-26.
- 6.lughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. Ital J Pediater 2012; 38(4):1-11.
- 7. Pui CH. Acute lymphoblastic leukemia. In: Pui CH, editor. Childhood leukemias. New York: Cambridge University Press; 2006; 439–72.
- 8. Fagarasan S, Honjo T. Intestinal IgA synthesis: regulation of front-line body defences. Nat Rev Immunol 2003; 3(1):63-72.
- 9. Burn CH, Ebersole J, Allansmith M. Immunoglobulin A Antibody Levels in Human Tears, Saliva, and Serum. Infect Immun 1982; 36(3): 1019-1022.
- 10. Maverakis E, Kyoungmi K, Michik Sho, Eric G, Forum P, Reason W, et al. Glycans in the immune system and The Altered Glycan Theory of Autoimmunity: A critical review. J Autoimmun 2015; 57-61.
- 11. Delacroix DL, Dive C, Rambaud JC, Vaerman JP. IgA subclasses in various secretions and in serum. Immunology 1982; 47 (2): 383–5.
- 12. Farahnak S, Sheikhpour R, Iranmanesh F. Evaluation of immunoglobulin A and its relation with oral complications. IJDO 2015; 7(2): 82-86.

- 13. Paula França Mantovani A, Perini Monclaro M, Skare Th. Prevalence of IgA deficiency in adult Systemic LupusErythematosus and the study of the associationwith its clinical and autoantibody profiles. Bras J Rheumatol 2010; 50 (3):273-82.
- 14. Ludvigsson JF, Neovius M, Ye W, Hammarström L. IgA deficiency and risk of cancer: a population-based matched cohort study. J ClinImmunol 2015; 35(2): 182-8.
- 15.Okpala IE, Salimonu LS.Immunoglobulin and immune complex levels in Nigerians with acute lymphoblastic leukaemia. Afr J Med Med Sci 1994; 23(2):171-6.
- 16.Potapnev MP, Belevtsev MV, Bortkevich LG, Grinev VV, Martsev SP, Kravchuk ZI, et al. Significance of serum immunoglobulin G for leukocytosis and prognosis in childhood B-lineage acute lymphoblastic leukemia. Pediatr Blood Cancer 2004; 42 (5): 421-6.
- 17.Martín Ibanez I, Arce Casas A, Cruz Martínez O, Estella Aguado J, Martín Mateos MA. Humoral immunity in pediatric patients with acute lymphoblastic leukaemia. Allergol Immunopathol 2003; 31(6): 303-10.
- 18. Welch JC, Lilleyman JS. Immunoglobulin concentrations in untreated lymphoblastic leukemia. Pediatr Hematol Oncol 1995; 12: 545–549.
- 19.Luczyński W, Stasiak-Barmuta A, Krawczuk-Rybak M, Zak J. Immunologic monitoring in children with acute lymphoblastic leukemia during maintenance treatment with regard to coexisting infections. Wiad Lek 2004; 57 (8): 337-42.
- 20. Haraldsson A, de Vaan GA, Van Dijk WJ, Bakkeren JA, Weemaes CM. Light chain ratios and concentrations of immunoglobulins G, A, and M in childhood common acute lymphoblastic leukemia. Pediatr Hematol Oncol 1994; 11(1): 83-90.

21.Van Tilburg CM, Bierings MB, Berbers GA, Wolfs TF, Pieters R, Bloem AC, Sanders EA. Impact of treatment reduction for childhood acute lymphoblastic leukemia on serum immunoglobulins and antibodies against vaccine-preventable diseases. Pediatr Blood Cancer 2012; 58(5): 701-7.

22.Ludvigsson JF, Neovius M, Hammarström L. Risk of Infections

Among 2100 Individuals with IgA Deficiency: a Nationwide Cohort Study. J Clin Immunol 2016; 36(2):134-40.
23. Salavoura K. Kolialexi A, Tsangaris G, Mavrou A. Development of Cancer in Patients with Primary Immunodeficiencies. Anticancer Res 2008; 28: 1263-1270.