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Serum IgG and IgA Level in Children with Acute Lymphoblastic Leukaemia and Its Relationship with Outcome in Induction Chemotherapy

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ABSTRACT

Background: *Immunosuppression in children with Acute Lymphoblastic Leukaemia (ALL) escalates vulnerability to severe infectious complications which leads to higher morbidity and mortality rates among patients. Immunoglobulins are important part of defence mechanism of the body contributing to the humoral immunity. Of all the immunoglobulins, IgG and IgA represents most common type of antibody in blood circulation and provides most long-lived antibody-based immunity against invading pathogens. In earlier years, studies have shown that, serum immunoglobulins are found to be decreased during chemotherapy and this reduction is related with severe sepsis and death in patients. Early identification of immune status can be much useful for assessment of severity and better risk stratification of the patients.* ***Objective:*** *Evaluation of serum IgG and IgA levels in children with ALL and its relationship with sepsis in induction phase of chemotherapy.* ***Method:*** *This prospective observational study was conducted in the Departments of Paediatric Haematology & Oncology and Department of General Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka. During January 2022 to December 2022, a total 60 paediatric patients of newly diagnosed ALL were included as study population. As control, 30 patients were included in this study from General paediatrics and Paediatric Haematology & Oncology, BSMMU to compare baseline immunoglobulin levels with the study group. Complete history and physical examination of all patients were undertaken, and all prior reports were collected. Serum IgG and IgA level assay was done before starting chemotherapy and at the end of induction chemotherapy in the study group. Patients diagnosed with ALL received chemotherapy modified UK-ALL 2003 protocol. History and data of any event of sepsis, along with the symptoms of complications were taken from all patients during the course of induction chemotherapy.* ***Results:*** *The mean age of the cases were 5.49±3.15 (mean±SD) years, which ranged from 1.9 to 15 years. Among the cases, 41 patients (68.3%) were male and 19 (31.7%) females. Seven (11.7%) subjects expired during induction chemotherapy. In comparison to the control group the mean IgG level in the study group was lower at baseline and even lower at the end of induction and it was statistically significant ($p<0.05$). The mean IgG level*

was low in patients with septic events in comparison with the patients with no septic events. Difference of mean of IgG between septic and aseptic patients was significant only at the end of induction chemotherapy (p<0.05). The mean IgA level was low in study group in comparison with the control group and it was statistically significant (p<0.05) only at the end of induction chemotherapy. The mean IgA level was low in patients with septic events in comparison with the patients with no septic events. Difference of mean of IgA between septic and aseptic patients was significant (p<0.05). Based on the receiver-operator characteristic (ROC) curves of change of S. IgG, with a cut off value 50% decreased from baseline having 68.8% sensitivity and 29.7% specificity for prediction of sepsis. Considering change of S. IgA with a cut off value 50% decreased from baseline having 67.6% sensitivity and 27.5% specificity for prediction of sepsis. ***Conclusion:*** *In our study, the mean IgG and IgA level of the cases were low in comparison to the control group. The mean IgG and IgA level of the patients were lower who had infectious complications, and it was more marked after induction chemotherapy. Therefore, evaluation of immunoglobulin profiles is recommended to be considered in patients with ALL in further studies.*

Keywords: ALL, children, chemotherapy, immune status, IgG, IgA

Introduction

Acute Lymphoblastic Leukaemia (ALL) is the most common malignancy of childhood accounting for 25% of cancers in children.[1] With multi-modality therapies and improved supportive care, children with ALL have an excellent chance of survival with five-year survival rate around 93.5%.[2] Despite advancement in treatment, 2-5% of children with ALL still die of causes other than relapse and infection remains major cause of mortality.[3] Immunoglobulins are important part of defence mechanism contributing to humoral immunity of the body. Low serum immunoglobulin levels have been reported to be related with higher rate of sepsis and mortality of the patients.[4] Among the immunoglobulins, IgG and IgA are mostly found to decline significantly and related with death in patients with acute leukemia.[5,6] Further, there is no published data for immunoglobulin status of children with Acute Lymphoblastic Leukaemia (ALL) in Bangladesh. So, the purpose of this study is to evaluate immune status by investigating serum IgG and IgA level in children with ALL and its relationship with sepsis during induction chemotherapy.

Materials and methods:

This prospective observational study was conducted in the Departments of Paediatric Haematology & Oncology and Department of General Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka. Sixty children diagnosed with ALL by standard diagnostic methods (Bone marrow morphology and immunophenotyping) from January 2022 to Dec 2022 were included in this study. Thirty children were identified who came to hospital for general physical checkup or to participate in screening programs, having no fever, cough, runny or other symptomatic acute clinical illness or any chronic illness were selected as control group by clinical evaluation and judgment, from general paediatrics and paediatric haematology oncology OPD, BSMMU. Complete history (present & past) and thorough physical examination of all patients was undertaken. Serum IgG and IgA level was assayed before starting chemotherapy and at the end of induction chemotherapy for the study group. Patients diagnosed with ALL received chemotherapy according to modified UK-ALL 2003 protocol. History and data of any event of sepsis, along with the symptoms of complications were taken from all patients during their course of induction chemotherapy. Sepsis was defined as, SIRS (systemic inflammatory response syndrome) in the presence of or as a result of suspected or proven infection.[7] Statistical analysis was performed by using SPSS (Statistical Package for the Social Sciences) for windows version 22. A p-value of < 0.05 was considered as a significant.

Results:

The mean age of the cases was 5.49±3.15 (mean ± SD) years, which ranged from 1.9 to 15 years. Of total 60 cases, 41 patients (68.3%) were male and 19 (31.7%) were female. Seven (11.7%) subjects expired during induction chemotherapy (Table I). It was observed that 53 (88.3 %) patients bone marrow was on remission on day 28 bone marrow study (Table II). A total of 46 (76.6%) patients developed sepsis during the study (Table II).

Table I: Age and gender distribution of the study subjects (n=60)

Age(years)	Number of patients (n)	Percentage (%)
Total	60	100%
1-5	34	56.7
6-10	2	33.3
11-18	6	10.0
Mean±SD	5.49±3.15	
Range (Min -Max)	1.9-15	
Gender		
Male	41	68.3
Female	19	31.7

Table II: Outcome of the patients after induction chemotherapy.

Variables	Number of patients (n)	Percentage (%)
Bone marrow study at day 28		
On remission	53	88.3
Not Assessed	7	11.7
Septic patients	46	76.6
Aseptic patients	14	23.4
Death		
Yes	7	11.7
No	53	88.3

In comparison to the control group mean IgG level (10.30±1.68 gm/L), the mean IgG level in the study group was lower at baseline (9.12±1.84 gm/L) and even lower at the end of induction (5.55±0.76 gm/L). This difference was statistically significant ($p<0.05$). However, compared to the control group mean IgA level (1.31±0.49 gm/L), the study group's mean IgA level was relatively low at baseline (1.22±0.50 gm/L), and it was only statistically substantially lower ($p<0.05$) at the end of induction chemotherapy (0.76±0.48 gm/L). (Table III & IV)

Table III: Baseline serum IgG and IgA levels in the study group and control group (n=90)

	Study group (n=60) Mean±SD	Control group (n=30) Mean±SD	*p* value
IgG (Baseline)	9.12±1.84	10.30±1.68	0.005 ^{s}
IgA (Baseline)	1.22±0.50	1.31±0.49	0.418 ^{ns}

Table IV: Comparison between serum IgG and IgA Levels at baseline and at the end of induction chemotherapy in the study group.

	Baseline (Mean±SD) (n=60)	At the end of induction (Mean±SD) (n=53)	P-value
Serum IgG	9.12±1.84	5.55±0.76	0.001^{s}
Serum IgA	1.22±0.50	0.76±0.48	0.001^{s}

The mean IgG level was low (8.33±1.31 gm/L at baseline, 5.08±1.63 gm/L at the end of induction) in patients with septic events in comparison with the patients with no septic events (Table V). Difference of mean of IgG between septic and aseptic patients was significant only at the end of induction chemotherapy ($p<0.05$).

Table V: Comparison of serum IgG levels at baseline and at the end of induction chemotherapy in septic and aseptic patients.

	IgG level (gm/L)			
	Baseline Mean±SD	*p* value	At the end of induction Mean±SD	*p* value
Sepsis				
Absent (n=14)	9.36±1.93	0.067^{ns}	7.01±1.07 (n=14)	0.001^{s}
Present (n=46)	8.33±1.31		5.08±1.63 (n=39)	

The mean IgA level was low (1.14±0.47 gm/L at baseline, 0.63±0.37 gm/L at the end of induction) in patients with septic events in comparison with the patients with no septic events (Table VI). Difference of mean of IgA between septic and aseptic patients was significant ($p<0.05$).

Table VI: Comparison of serum IgA levels at baseline and at the end of induction chemotherapy in septic and aseptic patients.

	IgA level (gm/L)			
	Baseline Mean±SD	*p* value	At the end of induction Mean±SD	*p* value
Sepsis				
Absent (n=14)	1.50±0.52	0.017[s]	1.19±0.55 (n=14)	0.001[s]
Present (n=46)	1.14±0.47		0.63±0.37 (n=39)	

Based on the receiver-operator characteristic (ROC) curves of change of S. IgG, with a cut off value 50% decreased from baseline having 68.8% sensitivity and 29.7% specificity for prediction of sepsis (Figure 1). Considering change of S. IgA with a cut off value 50% decreased from baseline having 67.6% sensitivity and 27.5% specificity for prediction of sepsis (Figure 2).

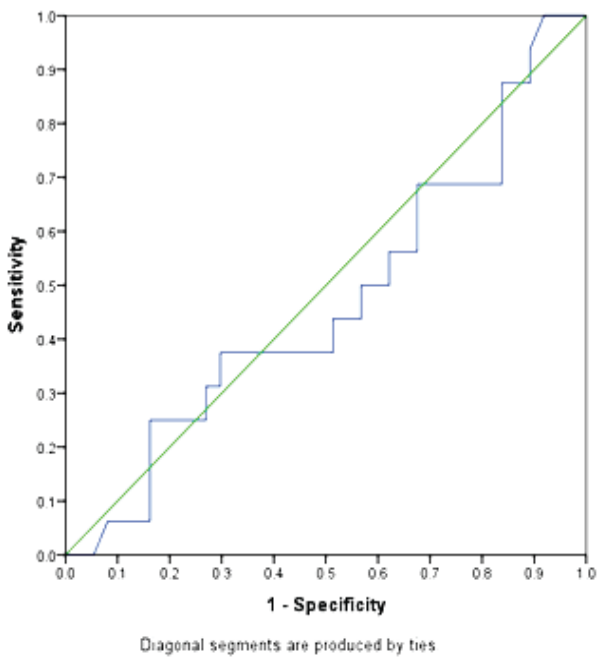

Figure 1. Receiver-operator characteristic (ROC) curve of change of S. IgG at the end of induction chemotherapy from baseline for prediction of sepsis.

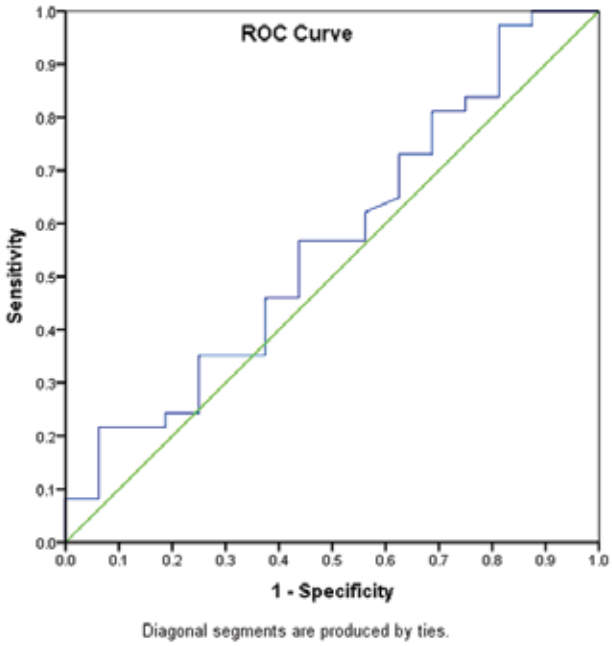

Figure 2. Receiver-operator characteristic (ROC) curve of change of S. IgA at the end of induction chemotherapy from baseline for prediction of sepsis.

Discussion:

Infection is the major cause of mortality in children with ALL which might be linked to immune status of the patients. So, we prospectively followed the infectious complications to address this issue in newly diagnosed 60 patients. The mean age was 5.49±3.15 (mean ± SD) years, age ranged from 1.9 to 15 years with male predominance, 68.3 % of patients were male (Table I). In this study 11.7% subjects expired during induction chemotherapy (Table II), Rabia et al. (2021) reported 10 % death in ALL patients during the course of induction chemotherapy in a tertiary care cancer hospital.[8] This study states, sepsis occurred in 76.6% patients (46/60). In an Indian study, Prasoon et al, (2021) reported the 20% incidence of sepsis in case of ALL during induction chemotherapy.[9]

In this study, the comparison of serum IgG and IgA levels between the control group and the study population showed that the mean IgG during baseline

was statistically significant ($p<0.05$) between two groups (Table III) and mean IgA was not statistically significant ($p>0.05$) between two groups.

In a study, Lange CS et al. (2020) reported that 13 (25.0%) patients had at least one low IgG level documented (hypogammaglobulinemia), whereas 7(13.5%) had normal IgG level(s) throughout treatment and the overall incidence of hypogammaglobulinemia was 65.0% (13/20).[10]

Potapnev et al (2004) in another study evaluated serum IgA in 68 children with primary B-lineage ALL and 46 healthy children.[11] They reported no significant difference between ALL patients and control group regarding mean level of serum IgA. Sheikhpour R et al (2017) reported that the mean level of IgA in male patients and control group was 82.5±21.3 and 113.2±6.62 mg/dl respectively which keep well with our study.[12]

When comparison of serum IgG and IgA levels of study group between baseline and at the end of induction chemotherapy was done (Table IV), results showed significant decrease of both IgG and IgA level among the study group ($p<0.05$). Chemotherapy and immunotherapy induced hypogammaglobulinemia have been previously described in paediatric ALL patients (El-Chennawi FA et al., 2008).[13]

The mean IgG level was low (8.33±1.31 gm/L at baseline, 5.08±1.63 gm/L at the end of induction) in patients with septic events in comparison with the patients with no septic events (Table V). Difference of mean of IgG between septic and aseptic patients was significant only at the end of induction chemotherapy ($p<0.05$). Holmes EA et al (2019) found a higher number of febrile episodes in paediatric ALL patients who had at least one IgG level checked (IgG levels <500 mg/dL in 39/63 of these patients) compared with patients who did not have IgG levels checked.[13] However, El-Chennawi FA et al (2008) found no correlation between IgG levels and the frequency of infectious events during maintenance in ALL patients.[14]

The mean IgA level was low (1.14±0.47 gm/L at baseline, 0.63±0.37 gm/L at the end of induction) in patients with septic events in comparison with the patients with no septic events (Table VI). Difference of mean of IgA between septic and aseptic patients was significant ($p<0.05$).

Ludvigsson et al., reported that IgA deficiency increase risk of infections in individuals. They believed that there is relation between IgA deficiency and infections is due to reduced mucosal protection, because in mucosal surface defence, immunoglobulin A (IgA) plays a vital role.[15]

Van Tilburg CM et al (2012) 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.[16] Immunoglobulin supplementation with intravenous immunoglobulin (IVIG) for primary immunodeficiencies is a well-established practice known to reduce the risk of serious infection (Busse PJ et al., 2002).[17]

Our study revealed the area under the receiver-operator characteristic (ROC) curves for prediction of sepsis is depicted in Figure 1 and Figure 2. Based on the receiver-operator characteristic (ROC) curves of change of S. IgG at the end of induction from baseline had area under curve 0.470, with a cut off value 50% changed from baseline having 68.8% sensitivity and 29.7% specificity for prediction of sepsis. Based on the receiver-operator characteristic (ROC) curves of change of S. IgA at the end of induction from baseline had area under curve 0.565, with a cut off value 50% changed from baseline having 67.6% sensitivity and 27.5% specificity for prediction of sepsis.

It is trustworthy that the results obtained from receiver-operator characteristic (ROC) curve appeared as baseline data in our research work and has opened an arena for future study in this field both at national and international level.

Conclusion:

In our study, the mean IgG and IgA level of the cases were low in comparison to the control group. The mean IgG and IgA level of the patients were lower who had infectious complications, and it was more marked after induction chemotherapy. Therefore, evaluation of immunoglobulin profiles is recommended to be considered in patients with ALL in further studies.

Limitation and recommendations:

Small sample size and single centre study is considered as the limitation of this study. So, we recommend, multicentre study with larger sample size and more standardized clinical trials are required to verify the serum immunoglobulin levels in children with acute lymphoblastic leukaemia and its relationship with infectious complications.

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Conflict of interest: The authors declare that there is no conflict of interest.

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