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# Elevated blood MxA protein levels in children with newly diagnosed B-ALL: A prospective case-control study

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**Ethics Committee Approval**
The Ethics Committee of the Cemil Taşcıoğlu City Hospital approved the study (date: 19/04/2021 and numeral: 160).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

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## Abstract

**Background/Aim:** Although leukemia is thought to be triggered or initiated by viral infections, it is not clear which viruses are the causative agents for which stage of the disease. Previous studies have shown that the MxA protein is expressed from blood mononuclear cells in reply to inducement of type I interferons in viral infections. Viral infections may trigger childhood B-cell acute lymphoblastic leukemia (B-ALL), and the hypothesis of this study was the detection of the presence of viral infection by measuring MxA expression in blood mononuclear cells of recently diagnosed pediatric B-ALL patients as a surrogate viral marker.

**Methods:** This study consisted two groups; the study group consisted of 30 newly diagnosed B-ALL and the control group consisted of 29 healthy asymptomatic children of similar age. Proven bacterial infection and COVID-19 PCR positivity were exclusion criteria. Bacterial culture of peripheral blood, complete blood count, plasma CRP levels and whole blood MxA levels detected by ELISA (Enzyme-Linked ImmunoSorbent Assay) method were taken.

**Results:** The patients' mean age was 7.42 years in the leukemia group (previously mentioned as study group) and 7.25 years in the control group. Routine serologic studies for newly diagnosed leukemia patients (CMV, EBV VCA and Hepatitis B IgM, anti-HCV and anti-HIV) were negative in all patients without any bacterial infection detected. The MxA levels were found significantly higher in children with B-ALL than in control group (5.84 (2.18-199.38) and 2.45 (1.17-88.65) ngr/ml, respectively, with $P<0.001$). CRP levels were significantly elevated in children with B-ALL than the control group (27.40 (2.60-133.40) and 0.60 (0.12-4.90) mgr/L, respectively, with $P<0.001$).

**Conclusion:** Our study demonstrates that blood MxA levels are increased in children with newly diagnosed B-ALL when compared to healthy asymptomatic children. This study is the first in literature in testing MxA levels in children with B-ALL. This finding may underline the triggering effect of viral infections in the onset of leukemia.

**Keywords:** MxA, Blood, Acute Lymphoblastic Leukemia, Children

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## Introduction

B cell acute lymphoblastic leukemia (B-ALL) is the most common type of pediatric malignancy [1]. Various studies have been designed to retrospectively evaluate the etiological risk factors leading to the development of leukemia [2]. A series of events, including breakage and inaccurate repair of DNA in response to infections, chemical agents, radiation, or other unidentified environmental factors, may be responsible for the occurrence of childhood leukemias [3-9]. These sequential interactions transform a preleukemic clone into leukemia. Infections have long been considered to be one of the possible reasons of pediatric leukemia [10]. There are three different hypotheses concerning infectious etiology of pediatric leukaemia: In utero or perinatal exposure, delayed exposure after the first age to common infectious agent (Greaves) and unusual population mixing (Kinlen) [11, 12]. According to "Greaves hypotheses", regular immune stimulation can lower the risk of leukemic development. In lack of these stimulations, children may overreact to the infectious agents subsequently exposed in school, and this is responsible for a cytokine "storm", which create secondary mutations that may lead to leukemia [11]. Kinlen pointed out that leukemia space-time clusters were occurred often after recent population mixing situations, and such mixing facilitated the transmission of a specific leukemia-initiating virus [12]. More recent studies have noted that ALL patients refer to their physicians for infections at the first year of life more frequently than children who do not develop leukemia [13, 14]. Infection may initiate a preleukemic clone but that may not trigger to leukemia in the absence of abnormal response to delayed infection. Population interaction rises the possibility of contagious exposure in susceptible persons [12]. Some recent studies revealed strong findings to support the hypothesis that exposure to infections may lead to the clonal evolution of preleukemic clones to overt leukemia [15-19]. Due to the detection of viral genomic inclusions in animals with leukemia, some researchers have suggested that childhood leukemia may be initiated by infection. [20-22]. However, it is not entirely clear which specific viral agents may be responsible, and at what stage exposure to these agents triggers leukemia. Human MxA protein (Myxovirus resistance protein 1), the product of the MX1 gene, is an interferon-inducible protein with antiviral activity, responsible for a wide range of viral infections [23, 24]. The expression of viral MxA protein is induced by IFN-alpha and IFN-beta, but not by IFN-gamma, IL-1, TNF-alpha or other cytokines. Several clinical research have suggested the use of MxA protein expression of peripheral blood mononuclear cells as a marker for differential diagnosis of viral and bacterial agents. In a study on children with acute pharyngitis, high blood MxA levels were determined in patients infected with both a respiratory virus and group A streptococcus, but not in only group A streptococcus infection [25]. It has been worked out as a marker of symptomatic viral infections because of its wide antiviral spectrum, long half-life, rapid increase in hours after start of symptoms and low basal levels in asymptomatic children [26, 27]. The purpose of this study was to investigate the presence of viral infection by measuring blood MxA protein levels in children with newly diagnosed B-ALL.

## Materials and methods

This study was conducted as a prospective case-control study. 30 children with newly diagnosis of B-ALL and 29 asymptomatic children served as a control group were enrolled in the study. The Ethics Committee of the Cemil Taşcıoğlu City Hospital approved the study (date: 19/04/2021, number: 160). Parents of participating children gave their written informed consent. All patients with B-ALL were diagnosed by histopathological and immunophenotypic examination of bone marrow biopsy. Children with B-ALL were included in the study and samples were taken within the first 24 hours after diagnosis, before chemotherapy was started. Patients with culture-proven bacterial infection or without consent were excluded. The control group consisted of healthy children without any signs or symptoms of chronic or acute disease. COVID-19 PCR test was taken for all patients, for exclusion criteria and were found negative. COVID-19 RT- PCR tests (Direct Detect SARS-CoV-2 Detection Kit; Coyote Bioscience, Beijing, China) were performed with swab samples from nasopharyngeal and throat on children. Blood samples for bacterial culture (only for B-ALL group), complete blood count, plasma C-reactive protein (CRP), and blood MxA protein levels were collected by venous access, and assessed by routine methods in the main laboratory of the hospital. Whole blood samples for MxA protein measurement were collected in EDTA collection tubes and stored at − 80 °C until ELISA (Enzyme-Linked ImmunoSorbent Assay)was performed following the kit user manual (biovender).

**Statistical analysis**

IBM SPSS Statistics 22.0 (SPSS IBM, Turkey) program was used. The normality of distribution of the parameters was evaluated with the Shapiro Wilks test. Descriptive statistical methods (mean, standard deviation, frequency), were used to compare normally distributed parameters between groups for quantitative data. Independent-samples t-test and Mann Whitney U test were used for comparisons between two groups according to the results of the normality test. *P*-values of less than 0.05 indicated significance.

## Results

The mean age of the cases was 7.42 years in the leukemia group and 7.25 years in the control group. The detailed characteristics of leukemia and control are shown in Table 1. One patient had clinically upper respiratory system infection symptoms and, 3 patients had fever. Routine serologic studies for newly diagnosed leukemia patients (CMV, EBV VCA and Hepatitis B IgM, anti HCV and anti-HIV) were negative in all, and bacterial infection was not detected. All children in the control group were asymptomatic. The basal level of blood MxA was significantly higher in children with B-ALL than in asymptomatic children 5.84 (2.18-199.38) vs 2.45 (1.17-88.65) ngr/ml ($P<0.001$). There was a statistically significant difference in MxA levels ($P<0.001$), CRP ($P<0.001$), %LY ($P<0.001$), #LY ($P<0.001$), %EOS ($P=0.045$), #EOS ($P=0.034$), %NEU ($P=0.007$), PLT ($P=0.008$) and HGB ($P=0.001$) values between the control and leukemia groups.

Table 1: Comparison of laboratory values of leukemia and control groups

| | Control (n=29) | B-ALL (n=30) | *P*-value |
|---|---|---|---|
| Age | 7.25 (1.91-17.75) | 7.42 (1-17.66) | 0.282 |
| Gender (Male) | 22 (75.9 %) | 17 (56.7 %) | 0.200 |
| MxA-ElLSA (nonogram/ml) | 2.45 (1.17-88.65) | 5.84 (2.18-199.38) | <0.001 |
| WBC(μL) | 7.65 (4.38-18.05) | 10.46 (2.10-153.87) | 0.120 |
| LY% | 41 (8.20-79.10) | 12 (0.10-70.90) | <0.001 |
| #LY | 3.25 (1.45-7.23) | 1.07 (5-6.82) | <0.001 |
| EOS% | 1.20 (0.11-13.10) | 0.80 (0-7.90) | 0.045 |
| #EOS | 0.11 (0.01-6.56) | 46 (0-6.56) | 0.034 |
| BASO% | 0.02 (0-0.60) | 0.20 (0-0.90) | 0.810 |
| #BASO | 0.01 (0-0.04) | 0.01 (0-0.11) | 0.568 |
| NEU% | 51.40 (8.54-66) | 28.40 (1-64.90) | 0.007 |
| #NEU | 3.07 (1.05-15.62) | 2.37 (0.16-14.55) | 0.110 |
| PLT ($10^3$μL) | 294 (176-475) | 147 (10-688) | 0.008 |
| MPV | 9.46 (1.43) | 9.01 (1.16) | 0.197 |
| MONO% | 6.23(1.65) | 5.41(3.29) | 0.226 |
| MONO | 0.42 (0.18-5.25) | 0.48 (0.05-1.54) | 0.519 |
| HGB (gr/dl) | 12.36 (1.57) | 10.26 (2.64) | 0.001 |
| BLAST% | - | 83.50 (0-100) | - |
| BLAST | - | 3,234.50 (0-153,60) | - |

WBC: White Blood Cell, EOS: Eosinophil, NEU: Neutrophil, BASO: Basophil, PLT: Platelet, MPV: Mean Platelet Volume, MONO: Monocyte, HGB: Hemoglobin

## Discussion

B cell acute lymphoblastic leukaemia (B-ALL) is the most prevalent type of pediatric malignancies [28]. Existence of a clinically silent preleukaemic condition is a biological feature of many types of pediatric B-ALLs [28]. However, most likely owing to the presence of an environmental trigger, a small percentage of those preleukaemic children will develop B-ALL. One of these environmental risk factors that may trigger childhood leukemia is the exposure to viral infections [28]. The relationship between infection and the development of B-ALL has been the subject of many studies over the years. [28, 29]. Findings such as the seasonal increase in leukemia after viral epidemics or the detection of viral genomes in leukemic animals in experimental studies drew attention to this relationship [30-33]. At what stage viral infections play a role in the development of leukemia or which viruses are responsible are controversial issues [28-30, 33]. In a newly diagnosed B-ALL patient, there may be several viruses that may have triggered the disease, and detection of these viruses is time-consuming and not cost-effective. In this study, we tried to detect the presence of viral infection in children with newly diagnosed B-ALL by measuring MxA expression in blood mononuclear cells as a surrogate viral marker. MxA protein has previously been found to be expressed in circulating mononuclear cells in response to stimulation by type I interferons in the presence of viral infections [34, 35]. Interferons are difficult to detect in patients due to their short half-life (1-2 hours), but MxA is quite long (2.3–2.5 days) [34, 35]. The detection of an elevated level of MxA should be diagnostic for viral infection. This is supported by studies showing increased MxA protein concentrations in patients with suspected or proven viral infections [34, 36-41]. Although MxA levels were investigated in many patient groups (infections, autoimmune diseases), we could not find a study that determined MxA levels in children with newly diagnosed B-ALL. In our study, we found that blood MxA levels were increased in newly diagnosed B-ALL patients compared to age-matched healthy asymptomatic children. There are only two publications that have studied MxA in children with pediatric malignancies. Koskenvue et al. observed MxA protein expression in blood leukocytes of 26 febrile and nonfebrile pediatric patients receiving chemotherapy and showed that determination of MxA protein expression provides a promising parameter to distinguish viral infections from bacterial infections in immunosuppressed children with malignancy [42]. The patient group consisted of various malignancies, not just a certain subtype of leukemia as in our study. They determined that some patients have elevated MxA expression after administration of chemotherapy agents and concluded that the reason of this could be cytotoxically mediated or direct effect on mononuclear cells or reactivation of unknown viruses [42]. In our study we collected samples before administration of cytotoxic therapy to avoid this effect of chemotherapy. Manabe et al. studied the cellular expression of MxA protein, as a reliable marker of viral infection, at diagnosis in children with juvenile myelomonocytic leukemia (JMML) to estimate the prevalence of viral infections [43]. They found 67% of 18 patients had increased levels of the MxA protein, with viral infections proven in three patients and concluded that the possibility of viral contribution to JMML pathogenesis by stimulating malignant clones necessitates more research [43]. Although a homogeneous disease group (pediatric patients with JMML) was selected in this study, the number of patients was low and there was no control group.

Many methods have been tried for the measurement of MxA [39, 40]. Manabe et al. studied MxA by flow cytometry in children with JMML [43]. Vallittu et al. evaluated MxA in whole blood by enzyme immunoassay (EIA) in multiple sclerosis (MS) patients treated with interferon [44]. The MxA-EIA was considered by the researchers as a faster and more reliable method compared with flow cytometric analysis of MxA in peripheral blood mononuclear cells [45]. We consider the MxA-EIA as a more reliable and practical method in pediatric patients.

C-reactive protein (CRP) is an acute phase biomarker which is used in routine clinical practice and increased in inflammatory processes such as severe infections [46]. In general, CRP levels were found to be elevated in all infections, quite higher in acute bacterial infections than viral infections [46]. It has been reported that CRP is more valuable than white blood cell counts and ESR in detecting bacterial infections [47]. We used CRP assay to rule out subclinical infections in the control group and detected low levels of CRP in these healthy children compared to the patient group. CRP is increased not only in infections but also in malignancies as an acute phase marker [48]. Therefore, it is expected to be higher in patient group than control group.

In this study, since we wanted to test the hypothesis that viral infections may trigger childhood B-ALL, we tried to detect the presence of viral infection by measuring MxA expression in blood mononuclear cells as a surrogate viral marker. As it was practically impossible to specifically test large number of viruses in pediatric patients that may trigger leukemia, we tried to determine the presence of a viral infection using a surrogate viral marker. To our knowledge, MxA protein was tested for the first time and found to be increased in such a group of newly diagnosed pediatric B-ALL patients.

The small number of cases was the limitation of this study.

### Conclusion

In this prospective case-control study, MxA levels are increased in patients with newly diagnosed B-ALL compared to age-matched healthy children, which supports the relationship

between leukemia and viral infection. Further studies with larger patient groups are necessary to explain the significance of MxA protein expression in pediatric patients with newly diagnosed B-ALL. The understanding of the interaction between preleukaemic cells and exposure to infections may provide us new strategies to prevent childhood B-ALL development.

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