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ORIGINAL ARTICLE

Immunological Evaluation of Patients with Fanconi Anemia

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ABSTRACT

Fanconi anemia (FA) is a progressive bone marrow failure syndrome with multiple congenital anomalies and predisposition to various malignancies. Immune status of these patients has been investigated in a few studies. In our study we prospectively measured serum immunoglobulin (Ig) levels, and lymphocyte subgroup counts in 25 patients with Fanconi anemia. Median age of the patients was 12.5 years (1.5 – 27). Serum IgA and IgM levels were found to be low in 1 out of 25 patients. Lymphocyte subgroups were analyzed in 6 of the patients and two of them were found to have lower natural killer cell count than their age appropriates. In children with Fanconi anemia, natural killer cell counts are more frequently disturbed as the leading cellular defect while these patients usually have normal Ig levels.

Key words: Fanconi anemia, immune deficiency, natural killer cell

INTRODUCTION

Fanconi anemia (FA) is an inherited progressive bone marrow failure syndrome characterized by typical physical findings, congenital anomalies and propensity to malignancy development. Affected patients may present with a wide variety of clinical manifestations [1]. Bone marrow failure is one of the major findings of patients with FA [2]. Neutropenia related to bone marrow failure causes increased risk for infections in these patients, nevertheless immunological abnormalities other than neutropenia may also be detected in patients with FA [3]. There is scarce data on the immune status in patients with FA in both adult and pediatric age groups from North America and Europe [3-6]. Due to rarity of FA, studies included small number of patients [3-7]. In this study we aimed to denote basic immunological findings of children and young adults with FA from Turkey.

MATERIAL and METHODS

This retrospective study was performed in patients with FA (N=25) with a confirmed diagnosis by diepoxybutane testing. During the routine outpatient clinic visit, complete blood count, serum immunoglobulin (Ig) levels, and lymphocyte subgroup analyses were measured. Lymphocyte subgroup phenotyping was performed by a two color flow cytometric analysis of EDTA-preserved whole blood using fluorochrome-labelled monoclonal antibodies to lineage-specific cell surface markers for T cells (CD3, CD4, CD8), B cells (CD19), and natural killer (NK) cells (CD16, CD56) [3]. Data was collected from electronic patient files retrospectively.

RESULTS

Serum immunoglobulin levels were measured in 25 patients. Median age of the patients was 12.5 years (1.5 – 27). Male to female ratio was 14/11. None of the patients underwent hematopoietic stem cell transplantation and five (20%) of the patients were treated by erythrocyte and/or platelet transfusion. Complete blood count and Ig results were summarized in Table 1. None of the patients had infection history ended-up with hospitalization. Except

Table 1. Complete blood count and immunoglobulin results of the patients.

	Median (Range)
Hemoglobin (g/dL)	11.9 (7.6 – 16.1)
White blood cell Count (x10^9/L)	4.5 (2.2 – 11.4)
Platelet count (x10^9/L)	147 (21 – 383)
IgA (mg/dL)	130 (10.8 – 296)
IgG (mg/dL)	1010 (599 – 1660)
IgM (mg/dL)	62.3 (16.2 – 226)

from one patient, Ig levels were in within normal range for age appropriates. In one female patient, IgA and IgM levels were below the normal range. White blood cell count (WBC) of that patient was 3.8 x10^9/L and she was on oxymetaholone treatment. Lymphocyte subgroup phenotyping was performed in six of the patients (Table 2). Total lymphocyte, B lymphocyte, and T lymphocyte counts were within normal range in all patients, however in two patients (33%) natural killer (NK) cell count was less than normal range for age appropriates. One of these patients was a seven-year-old boy whose WBC was 2.4 x10^9/L, and has been previously transfused with platelet and erythrocyte. Other patient was a 5.5 years old boy who hadn't a bone marrow failure yet and WBC was 7.3 x10^9/L.

DISCUSSION

Fanconi aplastic anemia is a rare inherited disease characterized with congenital dysmorphic findings, progressive bone marrow failure, endocrinopathies and increased risk of cancer development [1]. Among the multiple problems encountered in patients with FA, immunological abnormalities are less known and obscure. Immunological findings of patients with FA have been investigated in previous studies and ended-up with controversial results. Myers et. al assessed immunological functions of 10 children with FA in their study. They found reduced number of B and NK cell count in FA compared to control group, also cytotoxic activities of NK cells were significantly lower than control group [3]. Korthof et. al. analyzed immunological status of 61 patients with FA and severe bone marrow failure. They revealed decreased total absolute lymphocyte, B cell and NK cell count compared to control group. When they studied Ig levels IgG and M were significantly lower, whereas IgA was higher than control group [6]. In that study patients with advanced bone marrow failure were included so these results may not be relevant for patients with earlier phase of disease. Giri et. al. studied 26 patients with FA for Ig levels and found that 11 patients had at least one low Ig value. Three of the patients with low Ig values were children and all of these children had only low IgM level. In that study they claimed that adult patients with FA were more prone to have low Ig levels. Furthermore, they tested 14 patients for lymphocyte subsets and 11 of patients had lower than normal T, B, or NK cells [4]. Justo et. al. investigated total number of NK cells and subtypes, CD4 and CD8 T lymphocytes and ratios in 42 patients with FA. They exhibited defective cytotoxic response due to decreased number of cytotoxic cells and impaired differentiation of NK cell subsets [5].In our study, we detected low Ig level (IgA and IgM) only in one of the 25 patients. When compared with literature incidence of decreased Ig level may be assumed lower [4]. Median age of our patients was 12.5 years and only five of the patients had transfusion requirement. Normal Ig levels of our patients

Table 2. Lymphocyte and subgroup counts of five patients. Normal range for age was shown in parenthesis.

Patient number	Age (year)	Lymphocyte count (x10^9/L)	T lymphocyte count (x10^9/L)	B lymphocyte count (x10^9/L)	NK lymphocyte count (x10^9/L)
1	7	1.8 (1.2- 4.7)	1.33 (0.77-4)	0.39 (0.1-0.8)	0.054 (0.07-0.59)
2	5.5	3.3 (1.2- 4.7)	3.2 (0.77-4)	0.66 (0.1-0.8)	0,165 (0.07-0.59)
3	5.5	4.3 (1.2- 4.7)	2.58 (0.77-4)	0.94 (0.1-0.8)	0.043 (0.07-0.59)
4	6	3 (1.2- 4.7)	2.28 (0.77-4)	0.45 (0.1-0.8)	0.12 (0.07-0.59)
5	1.5	2.6 (1,4-12.1)	1.92 (0.7-8.8)	0.31 (0.16-3.7)	0.18 (0.055 – 4)
6	9	4 (1.2- 4.7)	2.88 (0.77-4)	0.44 (0.1-0.8)	0.44 (0.07-0.59)

may be explained with younger age and much lower bone marrow failure findings in our cohort. Immunological abnormalities may be expected to be more prominent with increased age, reflecting the progressive bone marrow failure. We could perform lymphocyte phenotyping in six patients and in two of them NK lymphocyte count was lower than normal range for their age. In literature decreased NK cell count and/or impaired NK cell activity is leading immunological abnormality in patients with FA [3-6]. Similarly, in our study decreased NK cell count was detected 33% of tested six patients. Sample size of our study for Ig level measurements was comparable with previous studies, however for lymphocyte subgroup phenotyping, we investigated a limited number of patients. Nevertheless, to our knowledge this study is the first one from Turkey about immune status of patients with FA, therefore we think that our results may be valuable for our national data. In conclusion, Ig levels may be generally normal in children with FA, but decreased NK cell count may be a major immunological abnormality and further studies with larger number of patients should be designed.

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