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Original Research Article

Investigation of the incidence of vitamin B12 deficiency in leukopenia and neutropenia secondary to infection

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ABSTRACT

Background: Infections and nutritional deficiencies are the most common causes of the leucopenia and neutropenia. In this study, we aimed to find the incidence of vitamin B12 deficiency in patients with leukopenia and neutropenia secondary to infection.
Methods: Between September 2018 and December 2018, patients who were referred to Diyarbakır Children Hospital's Pediatric Hematology and Oncology Clinic for leukopenia and/ or neutropenia were thought to develop secondary to infection retrospectively evaluated.
Results: Of the 60 patients that evaluated, 23(38.3%) were female and 37(61.7%) were male. The mean age±SD was 4.75±4.5 years. Severe neutropenia was detected in 5(8.3%), moderate neutropenia in 31(51.7%) and mild neutropenia in 17(28.3%) patients. Neutrophil counts were within normal limits in 7(11.7%) patients. When vitamin B12 levels were examined, 17(28.3%) patients had B12 deficiency.
Conclusions: Investigation and treatment of vitamin B12 deficiency in patients with leukopenia and neutropenia may shorten the duration of cytopenia and prevent the development of secondary complications.

Keywords: Ebstein-barr virus, Infections, Leucopenia, Neutropenia, Vitamin B12 deficiency

INTRODUCTION

Leukopenia is a common condition in childhood. Most cases develop due to secondary causes. Infections, nutritional deficiency, drugs, immune neutropenia, neonatal neutropenia, pure white cell aplasia, hypersplenism are the most important secondary causes.[1] Infections are the most common etiology in these conditions. In addition to this virus are the most common cause of infectious agents.[2] Acute transient neutropenia most commonly occur after viral infections and starts in a few days before the onset of infection and continues until viremia ends. Viral infections including influenza, varicella, Ebstein-barr virus, parvovirus B19, rubella, measles, hepatitis A and B, cytomegalovirus, adenovirus and coxsackie lead to neutropenia by causing reduction in production and increase in destruction.[3,4] In addition, sepsis due to gram negative bacteria, may be the cause leukopenia and neutropenia. Bacterial infections secondary to leukopenia and neutropenia due to viral infections may be associated with severe mortality, especially in patients with immunodeficiency or underlying chronic disease.[5] Nutritional deficiencies are other common conditions after infections.

Vitamin B12 and folic acid deficiency cause leukopenia due to abnormal granulocyte series production and decrease in myeloid serie production.[1,6] In this study, we aimed to find the incidence of vitamin B12 deficiency in patients with leukopenia and neutropenia secondary to infection.

METHODS

Between September 2018 and December 2018, patients who were referred to Diyarbakır Children Hospital's Pediatric Hematology and Oncology Clinic for leukopenia and/ or neutropenia were thought to develop secondary to infection included to the study and retrospectively evaluated. Age, gender, diagnosis, leukocyte count, neutrophil count and vitamin B12 levels were evaluated. Mean age, female/ male ratio was calculated. Patients with vitamin B12 levels below 200 pg/ mL were considered to be deficiency. The mean values of leukocyte count and neutrophil count were calculated. The neutrophil count was classified as severe neutropenia of 0-500/ mm^3, moderate neutropenia of 500-1000/ mm^3, and mild neutropenia of 1000-1500/ mm^3. Vitamin B12 deficiency and non-vitamin B12 deficiency were compared in terms of the incidence of severe and moderate neutropenia. The factors that could not be detected due to infection were determined according to the focus of infection.

Exclusion criterion

- Patients with chronic leukopenia and neutropenia and patients with immunodeficiency and in cancer treatment were not included in the study.

Statistical analysis

The normality of distribution of continuous variables was tested by Shaphiro wilk test. Mann-Whitney U test (for non-normal data) was used for comparison of two independent groups and Chi-square test was used to assess relation between categorical variables. Statistical analysis was performed with SPSS for Windows version 24.0 and a p value <0.05 was accepted as statistically significant.

RESULTS

Of the 60 patients that evaluated, 23(38.3%) were female and 37(61.7%) were male. The youngest patient was 3 months old and the oldest patient was 17 years old. The mean age±SD was 4.75±4.5 years. Mean leukocyte count ±SD was 4135±1896/ mm^3 and mean absolute neutrophil count±SD was 982±435/ mm^3. Severe neutropenia was detected in 5(8.3%), moderate neutropenia in 31(51.7%) and mild neutropenia in 17(28.3%) patients. Neutrophil counts were within normal limits in 7(11.7%) patients. When vitamin B12 levels were examined, 17(28.3%) patients had vitamin B12 deficiency. Severe vitamin B12 deficiency (<100 pg/mL) was detected in 6 of these patients. The mean vitamin B12 level was found to be 274±142 pg/mL. There was no significant difference in vitamin B12 values between boys and girls (p=0.294) (Mann Whitney U test) (Figure 1). When the agent or focus of infection causing leukopenia and/ or neutropenia was investigated, 30(50%) patients had upper respiratory tract infection, 12(20%) lower respiratory tract infection, and 9(15%) Ebstein-Barr Virus (EBV) infection, acute gastroenteritis in 7(11.7%), varicella in 1(1.7%) and 5th disease in 1(1.7%). When vitamin B12 deficiency and non-vitamin B12 deficiency were compared in terms of the incidence of moderate and severe neutropenia, no significant correlation was observed between the presence of vitamin B12 deficiency and the development of moderate and severe neutropenia (p=0.293) (Chi-square test) (Table 1).

Table 1: Correlation between the presence of vitamin B12 deficiency and the development of moderate and severe neutropenia.

	B12 values				
	>=200 (n=43)		<200 (n=17)		
	n	%	n	%	P
Neutropenia					
>1000/mm^3	19	44.2	5	29.4	0.293
<1000/mm^3	24	55.8	12	70.6	

Chi-square test

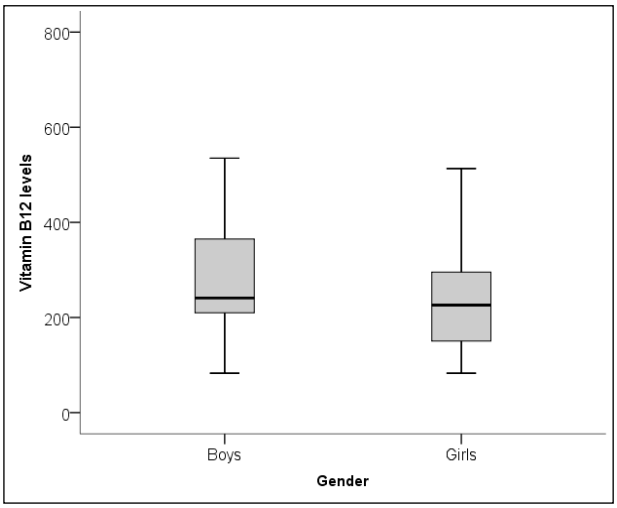

Figure 1: Vitamin B12 levels according to gender.

DISCUSSION

Infections play an important role in leukopenia and neutropenia in childhood. Among the infections, viral agents are the most important and most common agents in the etiology.[1] EBV infections are the most common infectious agents in hematology practice due to hepatosplenomegaly, lymph adenomegaly and cytopenia. In EBV infections, lymphocytosis, monocytosis, anemia and thrombocytopenia can be seen besides neutropenia and leukopenia. Membranous tonsillitis, lymphadenopathy, splenomegaly, atypical lymphocytosis and cytopenia are among the first diseases to be considered.[7,8] In this study, (15%) of patients had EBV infection.[9]

Viral-induced upper and lower respiratory tract infections are among the most common diseases of childhood.[9]

Transient leukopenia and neutropenia are common in respiratory infections caused by influenza, respiratory syncytial virus and rhinovirus. There are studies in the literature that show different hematological findings especially in influenza infections. Respiratory and multiorgan failure is an important cause of mortality in influenza outbreaks. Severe neutropenia in influenza outbreaks also plays an important role in the development of secondary bacterial infections.[10,11] In this patients, respiratory tract infections played an important role in the etiology. Since the patients had non-specific symptoms and the clinic had a mild course, no examinations were performed to determine the causative agent.

Parvovirus replicates in the bone marrow in erythroid precursors, so erythroid series is affected commonly. Aplastic crises due to parvovirus infection can be seen especially in chronic hemolytic anemias.[12,13] However, cases of neutropenia secondary to parvovirus infection have been reported in the literature.[14,15] This patient was diagnosed with typical 5. Disease rash and positive for parvovirus B19 IgM antibody.

Gastrointestinal infections are common in developing countries where hygiene and health systems are backward, and infrastructure and food sanitation are inadequate. While the incidence of diarrhea in children under 3 years in Europe is 0.5-1.9 per child per year, it can be one of the causes of childhood death in developing countries. Among these, Rotavirus, Adenovirus, Noroviruses are the most common agents.[16,17] Rotaviruses are the leading cause of diarrhea in infants and young children worldwide, especially in severe gastroenteritis, leading to hospitalizations and infant mortality. While they cause morbidity in developed countries, they cause both morbidity and mortality in developing countries.[18,19] Acute gastroenteritis was the reason in 7(11.7%) of this patient and 3 of them were diagnosed with rotavirus diarrhea. Author think that secondary leukopenia and neutropenia may increase mortality and morbidity especially in rotavirus infections. Stool microscopy, culture and viral antigen tests were studied in cases where gastroenteritis was the focus of infection in this patient, and no findings that suggesting bacterial or parasitic agents were found.

In addition, Brucella, Salmonella, Leishmania, Tularemia and Rickettsia may be the cause of leukopenia. Bicytopenia and pancytopenia develop more frequently in Brucella and Leishmania infections which are frequently encountered in hematology practice. Zoonoses are the first diseases that should be considered in the differential diagnosis, especially in the case of animal husbandry in anamnesis, fever, cytopenia, hepatosplenomegaly.[20] These factors were not detected in the etiology of this patients.

In developing countries, B12 deficiency and associated megaloblastic anemia are often the problem of children, pregnant women and the elderly patients, and the cause is usually nutritional. In studies conducted in regions with low socioeconomic status in the world, B12 deficiency is found between 22-65%.[21-24] Vitamin B12 levels of this patients were examined in 17(28.3%) patients. Laboratory findings may reveal different clinical findings ranging from mild anemia to pancytopenia. Vitamin B12 deficiency should be considered in cases with anemia or cytopenia or delayed neurological development in childhood.[25]

CONCLUSION

Vitamin B12 deficiency is one of the most important causes of pancytopenia-bicytopenia and anemia. However, in patients with leukopenia-neutropenia secondary to infection, underlying vitamin B12 deficiency may be an important cause of increased susceptibility to cytopenia. Investigation and treatment of vitamin B12 deficiency in these patients may shorten the duration of cytopenia and prevent the development of secondary complications.

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