Original Research Article

Evaluation of hematological findings in children with Down syndrome

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Received: 21 June 2018
Accepted: 23 July 2018

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ABSTRACT

Background: Various hematological disorders and malignancies may be encountered with Down syndrome. In this article, hematological findings of children with Down syndrome were investigated.

Methods: The hematological results of 106 Down syndrome children aged 3 months to 17 years were assessed retrospectively. The results were compared with a patient group consisting of non-DS and healthy children with a similar age range.

Results: When compared with the control group, a significant difference was found between the frequencies of neutropenia, monocytosis, macrocytosis and anisocytosis. No significant difference was detected between the patients with macrocytosis and those without macrocytosis when the relation of macrocytosis with other hematological disorders was examined. On the other hand, the comparison between the groups with and without macrocytosis showed that the prevalence of acute leukemia was significantly higher in patients with Down syndrome.

Conclusions: DS children with macrocytosis should be more closely monitored for myelodysplastic syndrome and acute leukemia.

Keywords: Down syndrome, Hematological disorders, Macrocytosis

INTRODUCTION

Down syndrome (DS) is a genetic disorder caused by the trisomy of chromosome 21 characterised by congenital anomalies such as typical dysmorphic features, mental retardation, gastrointestinal system abnormalities, congenital heart defects, endocrine disorders and immunodeficiency.1 The incidence of DS is 1 in 700-1000 live births. Increased risk of acute leukemia and a wide range of different hematological disorders may be seen with DS.2 Hematological disorders may be structural as well as due to nutritional deficiencies. Early recognition of nutritional deficiencies is of great importance for mental and motor development processes.3 In this article, hematological findings of DS cases were investigated in order to understand the differences comparison to the normal population and to find out what to look for in their follow-up.

METHODS

The hematological results of 106 DS patients aged 3 months to 17 years were assessed retrospectively who were examined and followed up in pediatric hematology-oncology clinic in 2016 in a period of 9 months. The cases were retrospectively reviewed, and their age, sex, and laboratory results were recorded. In cases who had suspicion of infection in the laboratory and clinical evaluation, laboratory results in non-infectious period were used. The results were compared with a patient group consisting of non-DS and healthy children with a similar age range that have no evidence of infection and nutritional deficiencies. This group consist of children who came to the primary health care clinic for routine control and vaccination. The assessment was based on normal values according to the age range. Blood samplings and results were used for the study at the time.
of the no evidence of infection was detected in patients. Descriptive statistics are used to describe continuous variables (mean, standard deviation, minimum, median, maximum, N (frequency), percent). Chi-Square was used to examine the relationship between categorical variables. Statistical significance was calculated using Fisher’s exact test, continuity correction and Pearson’s chi-squared test.

Limit values for hematological findings: leukopenia <4000/μL, leukocytosis >12,000/μL, neutropenia <1000/μL under 1 year, <1500/μL over 1 year, lymphopenia <1500/μL, monocytosis >800/μL, thrombocytopenia <150,000/μL, thrombocytosis >450,000/μL and anemia below -2 SD according to age.

RESULTS

41 (38.6%) of the patients were female and 65 (61.3%) were male. The mean age was 3.7 (±4.46). Mean and standard deviation values of white blood cell (WBC), hemoglobin, mean corpuscular volume (MCV) and platelet counts were 8428.3±3839.6/μL, 12.4±1.8 gr/dl, 85.8±8.4 fl., 328.81±115.340/μL, respectively.

Leukopenia was present in 4 (3.7%), neutropenia in 17 (16%), lymphocytosis in 8 (7.5%), monocytosis in 18 (16.9%), eosinophilia in 16 (15%), basophilia in 4 (3.7%), anemia in 17 (16%), macrocytosis in 33 (31.1%), anisocytosis in 51 (48.1%) thrombocytopenia in 7 patients (6.6%), and thrombocytosis was detected in 13 patients (12.2%). When compared with the control group, a significant difference was found between the frequencies of neutropenia, monocytosis, macrocytosis and anisocytosis (Table 1).

Table 1: Comparison of hematological findings in patients with Down syndrome to control group.

| Hematological finding | n (%) Patients with DS | n (%) Control group | p-value |
|-----------------------|-----------------------|---------------------|---------|
| Leukopenia            | 4 (3.7)               | 6 (5.6)             | 0.746   |
| Neutropenia           | 17 (16)               | 2 (1.8)             | <0.001  |
| Lymphopenia           | 8 (7.5)               | 3 (2.8)             | 0.215   |
| Monocytosis           | 18 (16.9)             | 2 (1.8)             | <0.001  |
| Eosinophilia          | 16 (15)               | 9 (8.4)             | 0.201   |
| Basophilia            | 4 (3.7)               | 1 (0.9)             | 0.369   |
| Anemia                | 17 (16)               | 8 (8.4)             | 0.143   |
| Macrocytosis          | 33 (31.1)             | 2 (1.8)             | <0.001  |
| Anisocytosis          | 51 (48.1)             | 7 (6.6)             | <0.001  |
| Thrombocytopenia      | 7 (6.6)               | 4 (3.7)             | 0.536   |
| Thrombocytosis        | 13 (12.2)             | 6 (5.6)             | 0.149   |

P <0.05 significant

One of the patients was diagnosed with Acute Lymphoblastic Leukemia and one of the patients was diagnosed with M6 acute myeloblastic leukemia. Myelofibrosis was detected in the bone marrow biopsy of one patient who developed pancytopenia during follow-up. One patient presented with pancytopenia due to hypersplenism. Values after splenectomy increased to normal limits at 6 months.

Three of the patients were diagnosed with thalassemia minor and one of the patients was diagnosed with hereditary spherocytosis (HS). Out of 17 patients, macrocytic anemia was detected in 3 patients (17.6%), normocytic anemia was detected in 9 patients (52.9%) and microcytic anemia was detected in 5 patients (29.4%).

The most common disorder along with anemia was anisocytosis which was observed in 11 patients with anemia (64.7%). Iron deficiency was detected in 8 out of 46 patients whose iron parameters were investigated while iron deficiency anemia was present in 3 of these cases.

Vitamin B12 levels were investigated in 44 of the patients and a B12 deficiency was detected in 8 patients (18.1%). Folic acid deficiency was detected in 2 (6.4%) of 31 patients whose folic acid levels were measured. Among 8 patients with vitamin B12 deficiency, one patient had macrocytic anemia with iron deficiency anemia, one patient had lymphopenia, and one patient had thrombocytopenia with a folic acid deficiency (Table 2).

Table 2: Characteristics of patients with B12 deficiency.

| Patient | Age/ gender | Additional nutritional disorder | Hematological finding |
|---------|-------------|---------------------------------|-----------------------|
| 1       | 1/ female   | Iron deficiency                 | -                     |
| 2       | 6/ male     | Iron deficiency                 | -                     |
| 3       | 1/ male     | Iron deficiency                 | Microcytic anemia     |
| 4       | 10/ female  | Folate deficiency               | Thrombocytopenia, macrocytosis |
| 5       | 1/ male     | -                               | Lymphopenia           |
| 6       | 1/ male     | -                               | -                     |
| 7       | 17/ male    | -                               | Macrocytosis          |
| 8       | 9 months/ female | -                             | -                     |

No significant difference was detected between the patients with macrocytosis, a frequent disorder in DS, and those without macrocytosis when the relation of macrocytosis with other hematological disorders was examined.
On the other hand, two patients with macrocytosis were diagnosed with AML-M6 and ALL at the time of the first admission. One patient was diagnosed with myelofibrosis based on bone marrow biopsy examined upon cytopenia and hypopcellularity of bone marrow aspiration confirmed at outpatient follow up visit. This patient developed AML-M7, identified at follow up after 7 months. The comparison between the groups with and without macrocytosis showed that the prevalence of acute leukemia was significantly higher in patients with DS (Table 3).

**DISCUSSION**

Hematological disorders are more common in individuals with Down syndrome than in the normal population. Neutropenia, thrombocytopenia, polycythemia, anemia, and macrocytosis are the most common disorders.\(^2,3\) In present study, the incidence of neutropenia, monocytosis, macrocytosis and anisocytosis was significantly higher when compared with the control group. Despite a significant difference in the frequency of macrocytosis and anisocytosis, there was no significant increase in the frequency of anemia. Anemia due to nutritional deficiency is common in DS individuals due to nutritional problems. The early recognition and treatment of iron deficiency in DS children is considered to be important in mental development.\(^4,5\) In the assessment of blood counts performed at the age of 1 in pediatric follow-up, iron deficiency anemia can be missed due to macrocytosis in individuals with DS.\(^5\) Three of cases had iron deficiency anemia in the study. While 2 out of 3 patients with iron deficiency anemia presented with microcytosis, 1 patient had macrocytosis.

Macrocytosis was the most frequent disorder in studies evaluating hematological disorders in DS.\(^6\) Prasher et al found macrocytosis to be the most common disorder in 147 adult patients.\(^7\) In present study, two patients with macrocytosis had low levels of vitamin B12. Since vitamin B12 and folic acid levels were not examined in all cases with macrocytosis in present study, a correlation could not be established between macrocytosis, and vitamin B12 and folic acid in DS patients. Previous studies have determined that vitamin B12 and folic acid deficiency and elevated hemoglobin F are not the cause of macrocytosis seen in individuals with DS.\(^3\)

Thrombocytopenia is seen in children with DS, especially in the neonatal period, and thrombocytosis may develop in the first year after 6 weeks.\(^3,9\) Studies have shown that thrombocytopenia and thrombocytosis are not associated with bleeding disorders and thrombosis in DS patients.\(^10\) No hemorrhagic symptoms were present except for present cases diagnosed with acute leukemia and myelofibrosis and present cases with severe thrombocytopenia due to hypersplenism. No cases of thrombosis were observed in present cases. In the literature, leucocyte counts were found to be reduced in approximately one third of DS patients.\(^11\) In present study, leukopenia was detected in 4 patients (3.7%). While the leukopenia rate was significantly different from previous studies with DS patients, there was no significant difference in the comparison with the control group.

Children with DS have a higher risk of developing acute leukemia and MDS than the normal population.\(^12\) The majority of patients with lymphoid leukemia exhibit immunophenotypic features as precursor B-cell ALL (acute lymphoblastic leukemia). Unlike myeloid leukemias, lymphoid leukemia is not seen in infancy in DS patients. The prognosis was found to be worse than sporadic lymphoid leukemia patients due to intrinsic drug resistance and treatment-related mortality.\(^13,14\) In present cases, only 1 patient developed ALL. In the consolidation treatment of the patient, severe mucositis, elevation of liver function tests and kidney failure developed with methotrexate. The patient who recovered with supportive treatment was given half the dose of methotrexate therapy. The incidence of AML in children with Down syndrome was 150 times higher than in non-DS children. Acute Megakaryoblastic Leukemia (AML-M7) is the most prevalent form of AML in children with DS.\(^15\) AML-M6 and AML-M1-M2 are less frequent in DS patients than AML-M7.\(^16,17\) In acute erythroblastic
leukemia, there are dyserythropoietic disorder such as multinucleated erythroid cells, basophilic stippling, cytoplasmic vacuoles and macronormoblasts belonging to all stages of the erythroid series. The diagnostic criteria are that more than 50% of the cells in the bone marrow are composed of erythroid precursors and that the myeloblasts other than the erythroid series are more than 20%. In present study, one patient was diagnosed with AML-M6. In the bone marrow aspiration, binucleated giant erythroid cells, dysplasia findings with cytoplasmic vacuoles and 78% erythroblasts were observed in the erythroid series, and 50% myeloblasts were observed in non-erythroid series. The cure rate of about 60% in AML increases up to 80-100% in DS myeloid leukemia, especially due to increased sensitivity in cytosine arabinoside (ARA-C). This is considered to be the result of GATA1 mutation.19

One of the cases developed pancytopenia and hepatosplenomegaly in the follow-up. Anisocytosis, poikilocytosis, tear drop cells, myelocytes and erythroblasts were seen in its peripheral smear. The bone marrow biopsy of the patient whose bone marrow aspiration could not be assessed due to being hypocellular was found to be compatible with myelofibrosis. In the literature, myelofibrosis has been identified in patients with Down syndrome. In these cases, transformation to acute leukemia was seen within months and the prognosis was poor. In present patient, this transformed to AML-M7 7 months after diagnosis. The patient with underlying congenital heart and chronic lung disease died. When patients with leukemia were examined, macrocytosis had been also presented in three patients. The comparison between the groups with and without macrocytosis showed that the prevalence of acute leukemia was significantly higher in patients with DS (Table 3). Macrocytosis can therefore be considered a risk criterion for leukemia development, just like the GATA1 mutation.

CONCLUSION

In conclusion, DS children with macrocytosis should be more closely monitored for myelodysplastic syndrome and acute leukemia. For these reasons, routine blood counts, peripheral smear, iron parameters, vitamin B12-folate levels should be evaluated in DS individuals especially those with macrocytosis.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sarbay H. Evaluation of hematological findings in children with Down syndrome. Int J Contemp Pediatr 2018;5:1724-8.