Hematological disturbances in Down syndrome: single centre experience of thirteen years and review of the literature

Neslihan Karakurt1, Ilker Uslu2, Canan Aygün2, Canan Albayrak1

1Divisions of Hematology and 2Neonatology, Department of Pediatrics, Ondokuz Mayis University School of Medicine, Samsun, Turkey. E-mail: neslihankarakurt@gmail.com

Received: 3rd August 2019, Revised: 21st August 2019, Accepted: 24th August 2019

SUMMARY: Karakurt N, Uslu İ, Aygün C, Albayrak C. Hematological disturbances in Down syndrome: single centre experience of thirteen years and review of the literature. Turk J Pediatr 2019; 61: 664-670.

Neonates with Down syndrome (DS) may have hematological abnormalities such as polycythemia, thrombocytopenia and transient leukemia (TL).

The primary objective of this study was to report the descriptive data of complete blood counts (CBC) of neonates with DS, which were obtained within first week of life. We wanted to focus on neonates with hematological abnormalities and compare them among those with and without TL. The secondary objective was the description of hematological malignancies in the first six years of life.

Medical records of 100 neonates with DS between 2006-2018 were assessed. Hematological abnormalities were present in 73/100. We detected anemia in 16, polycythemia in eight, microcytosis in 10, leukopenia in two, leukocytosis in 11, thrombocytopenia in 26, thrombocytosis in 7 and TL in 11 patients. TL group had higher levels of leukocyte count (115.0±93.0x10^3/mm3) when compared with neonates without TL (11.7±5.6x10^3/mm3) (p<0.001). No other statistically significant difference between groups for hemoglobin, MCV and platelet count levels was detected. In the follow-up period, two patients developed acute lymphoblastic leukemia, one hemophagocytic lymphohistiocytosis and one Burkitt lymphoma. None of the TL survivors developed myeloid leukemia of Down Syndrome (ML-DS).

Thrombocytopenia may be detected frequently in DS and it may not be a part of TL. We suggest that CBC with peripheral blood film should be evaluated for every patient to check for TL and other hematological disturbances. Despite the fact that none of our TL survivors developed overt leukemia (ML-DS), we also suggest that patients with DS be followed due to the risk of developing leukemia.

Key words: Down syndrome, transient leukemia, thrombocytopenia, leukocytosis.

Down syndrome (DS) occurs in one of 800-1200 births depending on the acceptability and availability of prenatal screening, survival and medical termination of DS pregnancies across the world.1 Some studies related to complete blood count (CBC) results of neonates with DS exist and have great importance in defining reference values.2-5 Since neonates with DS may have hematological abnormalities such as polycythemia and thrombocytopenia,2-6 obtaining a CBC is recommended for all neonates with DS.7

Between 5% and 30% of neonates with DS are born with transient leukemia (TL), also known as transient abnormal myelopoiesis and transient myeloproliferative disorder.8-10 Circulating non-erythroid blasts and/or organ infiltration with non-erythroid blasts are characteristics of TL.11 TL can present with a spectrum of abnormalities ranging from a few circulating blast cells in an otherwise well
neonate to hyperleukocytosis and multi-organ failure.

The primary objective of this study was to report the descriptive data of CBC results of neonates with DS, which were obtained within the first week of life. We wanted to focus on hematological abnormalities in DS and compare them among neonates with and without TL. The secondary objective was the description of hematological malignancies and hemophagocytic lymphohistiocytosis (HLH) during the first six years of life.

**Materials and Methods**

The medical records of neonates admitted to neonatal intensive care unit (NICU) between 1st January 2006 and 15th February 2018 with a diagnosis of DS were assessed retrospectively. The diagnosis of DS was made by either prenatally or after birth. The demographic data and major problems associated with DS (cardiac, hematological, gastrointestinal) were recorded. CBC results of neonates (hemoglobin, hematocrit, Mean corpuscular volume (MCV), leukocyte and White blood cell (WBC) count) within first week of life were recorded. Those with hematological disturbances (polycythemia, thrombocytopenia, leukocytosis, TL) were demonstrated.

Diagnoses of TL were made by an experienced hematologist by clinical findings (hepatomegaly and/or splenomegaly), laboratory results (leukocytosis, signs of organ infiltration like hepatic or renal failure), examination of peripheral blood smear with and/or bone marrow aspiration (existence of non-erythroid blasts of minimum 6%). Analysis for GATA-1 mutation was not available when the study was conducted. The patients were divided in two groups: Those with TL and those without (regular group). Hemoglobin and MCV values, leukocyte and platelet counts were compared between groups. Anemia, microcytosis, macrocytosis, leukopenia, leukocytosis, thrombocytosis were defined according to the gestational week- matched reference values. Hemoglobin level below 14.5 g/dl in terms and below 110 g in preterms were defined as anemia. MCV level below 95 fl in terms and below 110 fl in preterms were defined as microcytosis. Macrocytosis was defined as MCV level above 130 fl. Polycythemia was defined as venous hematocrit level above 65%. Leukopenia and leukocytosis were defined as WBC count below 5.0 x10^9/mm^3 and above 30.0 x10^9/mm^3, respectively. Thrombocytopenia was defined as platelet count below 100.0 x10^9/mm^3 and thrombocytosis as platelet count above 400.0 x10^9/mm^3.

Data were analyzed statistically with SPSS version 18. Normal distribution of data was assessed by Kolmogorov-Smirnov Test. Scale variables were expressed as mean± standard deviation (SD) and median (minimum – maximum). Categorical data were expressed as number and percentage (%). Student’s t test was used for comparison of means. Categorical variables were compared with Chi- Square. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into logistic regression analysis to determine independent predictors of patient outcome. P<0.05 was assessed as statistically significant.

**Results**

One hundred neonates with DS (Girl/Boy: 51/49) were included. Mean gestational age was 36.8± 2.6 weeks and 38 (38%) were premature (Table I). The average birth weight was 2750± 630 grams and average maternal age was 32±7 years. 37% were born with body weight below 2500 grams.

Cardiac anomalies were detected in 54 (54%), gastrointestinal system anomalies in 10 (10%) and renal anomalies in seven (7%). Eleven (11%) neonates had TL and seven (64%) with TL, who received intervention (partial exchange transfusion or low dose chemotherapy), died related to progressive disease. One TL patient died after resolution of TL, related to congenital cardiac defect. The incidence of neonatal death was 10%. The most common cause of neonatal death was TL (n= 6, 60%), followed by congenital cardiac defects (n= 3, 30%) (Table I).

Table II shows the hematological values of neonates with DS. When groups were
compared, the TL group had higher levels of leukocyte count (115.0±93.0 x10^3 /mm^3) when compared with neonates without TL (11.7± 5.6 x10^3 /mm^3) and this difference was statistically significant (p<0.001). No other statistically significant difference between groups for hemoglobin, MCV and platelet count levels was detected.

Table I. Demographic Data of Neonates with Down Syndrome (n=100).

| Parameter                        | Transient leukemia (n=11) | Regular group (N= 89) | P  |
|----------------------------------|---------------------------|-----------------------|----|
| Gestational age (weeks)          | 36.8± 2.6 (26- 41)        |                       |    |
| 26- 32 weeks                     | 7 (7%)                    |                       |    |
| 33- 36 weeks                     | 31 (31%)                  |                       |    |
| 37- 41 weeks                     | 62 (62%)                  |                       |    |
| Birth weight (g)                 | 2750± 630 (860-4000)      |                       |    |
| Gender (female vs male)          | 51%/ 49%                  |                       |    |
| Mode of delivery (vaginal vs cesarean) | 26%/ 74%               |                       |    |
| Maternal age (years)             | 32±7 (17-56)              |                       |    |
| Cardiac anomalies                | 54%                       |                       |    |
| Gastrointestinal system anomalies| 10%                       |                       |    |
| Renal anomalies                  | 7%                        |                       |    |
| Transient leukemia               | 11%                       |                       |    |
| Death in transient leukemia      | 8/11 (73%)                |                       |    |
| Cause of death in transient leukemia (n=8) | 1/8, 13%                 |                       |    |
| Congenital cardiac defects       | 7/8, 87%                  |                       |    |
| Death in neonatal period         | 10%                       |                       |    |
| Cause of death in neonatal period (n=10) | 6/10, 60%               |                       |    |
| Transient leukemia               | 6/10, 60%                 |                       |    |
| Congenital cardiac defects       | 3/10, 30%                 |                       |    |
| Hydrops fetalis                  | 1/ 10, 10%                |                       |    |

Table II. Hematological Values of Neonates with Down Syndrome within the First Week of Life.

| Parameter                              | Transient leukemia (n=11) | Regular group (N= 89) | P  |
|----------------------------------------|---------------------------|-----------------------|----|
| Hb (g/dl) (mean± SD)                   | 15.9± 4.6 (8.0- 23.0)    | 17.6± 3.3 (9.0- 23.0) | >0.05 |
| (range)                                |                           |                       |    |
| Hematocrit (%) (mean± SD)              | 48± 14 (24- 69)           | 54± 10 (27- 74)       | >0.05 |
| (range)                                |                           |                       |    |
| MCV (fl) (mean± SD)                    | 117±12 (101- 144)         | 112± 7 (94- 128)      | >0.05 |
| (range)                                |                           |                       |    |
| WBC (x10^3/mm^3) (mean± SD)            | 115.0± 93.0 (38.0- 314.0) | 11.7± 5.6 (4.5- 29.0) | <0.001 |
| (range)                                |                           |                       |    |
| Platelet (x10^3/mm^3) (mean± SD)       | 160.0± 65.0 (69.0- 249.0) | 195.0± 138.0 (19.0- 752.0) | >0.05 |
| (range)                                |                           |                       |    |

Hb: Hemoglobin MCV: Mean corpuscular volume, WBC: White blood cell
Seventy three neonates out of 100 had hematological anomalies including one or more: anemia, polycythemia, leukopenia, leukocytosis, thrombocytopenia, thrombocytosis and/or TL. Sixteen (16%) neonates had anemia (Table III and IV). However, only 8% had a hemoglobin level below 12 g/dl. Eight (8%) neonates had polycythemia. Microcytosis was detected in 10 (10%) and macrocytosis in only one (1%) patient. All neonates with TL leukocytosis whereas two neonates in regular group had leukopenia. Thrombocytosis was not detected in the TL group whereas it was detected in 7 (8%) of regular group. Twenty six (26%) neonates presented with thrombocytopenia and the frequency of thrombocytopenia was similar in both groups (Table III). Only 4% of neonates presented with platelet count below 50 x10^3/mm^3. When etiology of thrombocytopenia (n=26) was evaluated, TORCH screening was negative for all neonates and no other infection was detected. Three neonates had TL, two neonates were small for gestational age, one was born to a mother with immune thrombocytopenia, two had polycythemia and one was born to a preeclamptic mother. None of patients with thrombocytopenia had skeletal anomaly like radial anomaly nor developed intracranial bleeding.

Regression analysis was performed to identify risk factors for neonatal death in DS. Gender, birth weight, birth week, hemoglobin/leukocyte/platelet level, congenital cardiac defect and TL were detected not to be statistically significant risk factors (p>0.05). Similarly, the same factors were not statistically significant for death in the period of follow-up either (p>0.05).

The mean follow-up time of survivors was six years. None of the neonates were lost to follow-up. Four neonates with DS developed lymphoreticular disorders: Two developed acute lymphoblastic leukemia (ALL) at three and four years of age, one patient developed HLH when he was three years old and one patient developed Burkitt lymphoma at four years of age (Table V). None of the survivors of TL developed leukemia during the follow-up period. The patient diagnosed with HLH, who was otherwise healthy before, presented with protracted fever with unknown origin, hepatomegaly and splenomegaly. She had anemia, thrombocytopenia and leukocytosis with prominent neutrophils. Infectious work up including EBV, CMV, other viral markers were negative. She had hemophagocytosis in marrow and other laboratory findings were consistent with HLH. Assisted ventilation was required in the pediatric intensive care unit. She died seven days after admission, on the second day of chemotherapy for HLH (dexamethasone, etoposide, cyclosporine).

The number of deaths in the follow-up period was 29, at a mean age of 5.1 months (three days- 36 months) (Table V). The most common cause of overall death was congenital cardiac defects (n=15, 52%) followed by TL (n=7, 24%).

### Table III. Description and Comparison of Hematological Disturbances in Neonates with Down Syndrome.

|                  | Transient leukemia group | Regular group |
|------------------|--------------------------|---------------|
|                  | N (%)                    | N (%)         |
| Anemia, n (%)    | 1/11 (9)                 | 15/89 (17)    |
| Polycythemia, n (%) | 1/11 (9)               | 7/89 (8)      |
| Microcytosis, n (%) | -                       | 10/89 (11)    |
| Macrocytosis, n (%) | 1/11 (9)              | -             |
| Leukopenia, n (%) | -                       | 2/89 (2)      |
| Leukocytosis, n (%) | 11/11 (100)          | -             |
| Thrombocytopenia, n (%) | 3/11 (27)            | 23/89 (26)    |
| Thrombocytosis, n (%) | -                     | 7/89 (8)      |
The summary of hematological problems in neonates with DS is presented in this study and comparison with past studies is given in Table IV. In this present study we detected anemia in 16% of cases, which is markedly higher than the literature. In fact this might be related to cut off levels of hemoglobin in our study. However only 8% had hemoglobin level below 12 g/dl. Anemia can be mostly related to bleeding, hemolytic disease of newborn, other hemolytic anemias and perinatal infections, which were excluded in our study group. When we compared neonates with and without TL, hemoglobin levels were not different among groups (Table II). Children’s Oncology Group reported 135 patients with DS and TL. They reported that hemoglobin was generally normal, however those who needed intervention for TL had lower levels of hemoglobin, when compared with TL patients with spontaneous resolution. According to the data of the British Society of Hematology, anemia seems to be higher in TL patients (5-10%) when compared to those without TL (1-5%).

Polycythemia was detected in 8% of neonates. In previous studies it was reported to range between 10.8% to 33.0%. Microcytosis and macrocytosis were not frequent findings in the

| Table IV. Review of Hematological Problems in Present Study and Literature. |
|---------------------------------------------------------------|
| **Present study** | **Martinez-Macies et al.** | **Jackson et al.** | **Kim et al.** | **Henry et al.** |
| | N=100 | n=135 | n=232 | n=37 | n=158 |
| Age when CBC was obtained (days) | <7 | <7 | <10 | <28 | <7 |
| Anemia (%) | 16 | 8.2 | - | - | <1 |
| Polycythemia (%) | 8 | 23.7 | 33.2 | 10.8 | 33 |
| Microcytosis (%) | 10 | 15.5 | - | - | - |
| Macrocytosis (%) | 1 | 5.2 | - | - | - |
| Leukopenia (%) | 2 | 2.2 | - | - | - |
| Leukocytosis (%) | 11 | 11.1 | - | 16.4 | - |
| Thrombocytopenia (%) | 26 | 24.4 | 24.8 | 16.2 | 33 |
| Thrombocytosis (%) | 7 | 2.2 | - | 2.7 | <1 |

CBC: Complete blood count

| Table V. Outcomes of children with Down Syndrome. |
|-------------------------------------------------------------|
| Duration of follow-up (years) | 6.0± 3.5 (2 months- 13.1 years) |
| Acute lymphoblastic leukemia | 2% |
| Burkitt Lymphoma | 1% |
| Hemophagocytic syndrome | 1% |
| Death | 29% |
| Age at death (months) | 5.1±8.0 (3 days- 36 months) |
| Cause of death (n=29) | |
| Congenital cardiac defects | 15/29, 52% |
| Transient leukemia | 7/29, 24% |
| Congenital gastrointestinal system defects | 5/29, 18% |
| Hemophagocytic syndrome | 1/29, 3% |
| Hydrops fetalis | 1/29, 3% |

Discussion

The summary of hematological problems in neonates with DS is presented in this study and comparison with past studies is given in Table IV. In this present study we detected anemia in 16% of cases, which is markedly higher than the literature. In fact this might be related to cut off levels of hemoglobin in our study. However only 8% had hemoglobin level below 12 g/dl. Anemia can be mostly related to bleeding, hemolytic disease of newborn, other hemolytic anemias and perinatal infections, which were excluded in our study group. When we compared neonates with and without TL, hemoglobin levels were not different among groups (Table II). Children’s Oncology Group reported 135 patients with DS and TL. They reported that hemoglobin was generally normal, however those who needed intervention for TL had lower levels of hemoglobin, when compared with TL patients with spontaneous resolution. According to the data of the British Society of Hematology, anemia seems to be higher in TL patients (5-10%) when compared to those without TL (1-5%).

Polycythemia was detected in 8% of neonates. In previous studies it was reported to range between 10.8% to 33.0%. Microcytosis and macrocytosis were not frequent findings in the
present study. There is limited data concerning MCV in literature. Martinez-Macias et al.\(^2\) reported that microcytosis was present in 15.5% and macrocytosis in 5.2% of neonates with DS.

Only two cases in the study group had leukopenia, which is similar when compared with the literature (Table IV). All cases with leukopenia were in the regular group and infections were excluded. Leukocytosis was limited to those with TL, as expected. Children's Oncology Group\(^11\) reported that median WBC at diagnosis was elevated. Leukocytosis was detected in half of neonates with DS and 10-15% of neonates without TL in the literature.\(^10,12,14\) One of limitations of this study was that correction for nucleated red blood cells and non-erythroïd blast percentage was not defined. One other limitation was differential count for leukocyte subgroups was not available.

Thrombocytopenia was a frequent finding in our study (26%), which is consistent with the literature.\(^2,4,6,11-12,15\) In most cases the etiology of thrombocytopenia is unclear. Thrombocytopenia in neonates may result from either decreased production or increased destruction or both.\(^15\) We observed that the incidence of thrombocytopenia among neonates with or without DS were correlative. Similarly, the frequency of thrombocytopenia was constant in both TL or non-TL patients.\(^12\) In other words, we suggest that thrombocytopenia may not be a marker for TL. Thrombocytosis is a very rare finding in neonates with DS which was similar in our study.\(^2,4,5,12\)

We detected that seven (64%) out of 11 neonates with TL died due to progressive disease. Transient leukemia is a preleukemic disorder unique to neonates with DS, which may transform to myeloid leukemia of DS (ML-DS).\(^11\) Transient leukemia is diagnosed in approximately 10-30% of neonates with DS.\(^8\)\(^-\)\(^13\) In most cases, TL resolves spontaneously within the first three months of life but it may result in early death in 21%.\(^11\) The rate of death related to primary disease in TL was higher (7/11, 64%) in our study. All cases were ascertained based on admission to the NICU. This may have biased the disease spectrum of TL in favor of severe cases. The high TL mortality (64%) would be consistent with this.

In this study the diagnosis of TL was based on methods including determination of organ infiltration and investigation of bone marrow aspiration for blasts. Analysis for GATA-1 mutation was not available. Currently, TL is marked by the presence of GATA-1 mutation. Since the description of GATA-1 mutation in DS with TL\(^8\), it became easier to diagnose TL. According to the recent guidelines of The British Journal of Hematology\(^12\) TL of DS is defined as the presence of GATA-1 mutation together with a peripheral blood blast percentage >10% and/ or clinical features suggestive of TL in a neonate with DS. However screening for GATA-1 mutation may not be available in many centers and some challenges like comorbidities of DS may masquerade the clinical picture.

Acquired mutations of GATA-1 with trisomy 21 causes transient expansion of megakaryoblasts in liver resulting in TL\(^12,16\). Despite the high rate of spontaneous regression, TL can be a preleukemic disorder in 20-30% of children with DS and GATA-1 mutation. In our study, none of our survivors in the TL group developed ML-DS.

We reported that two children with DS developed ALL at three and four years of age. Children with DS have a 10 to 20 fold increased risk for developing either lymphoid or myeloid leukemia.\(^15\) Myeloid leukemia of DS is usually acute megakaryocytic leukemia with a peak incidence at age two and occurs before five years of age.\(^15\) In contrast, ALL in DS presents in older children, with a peak frequency between three to six years of age.\(^15\)

One patient with DS in our group developed Burkitt lymphoma at four years of age. Solid tumors are infrequently reported in patients with DS.\(^15\) Some investigators have suggested that DS may predispose to lymphoma, with a predominance of Hodgkin disease.\(^17\) Other studies have found no significant increase in cases of lymphoma among patients with DS.\(^18\)
One of our patients developed HLH at the age of three. Mutation analysis for HLH was not available. The distinction between primary or secondary HLH could not be done. One patient with DS who developed HLH secondary to EBV infection has been reported in literature. Patients with DS are prone to infections, especially respiratory tract infections. We could not identify any infectious agent or underlying pathology like collagen tissue disorders, however we got an impression that our case had HLH, probably secondary to an infection.

To conclude, we presented the CBC results of 100 neonates with DS. Hematological abnormalities were present in 73 of newborns with DS. Thrombocytopenia may be detected frequently in DS and it may not be a part of TL. We suggest that CBC with peripheral blood film should be evaluated for every patient to check for TL and other hematological disturbances. Despite the fact that none of our TL survivors developed overt leukemia (ML-DS), we also suggest that patients with DS should be followed for developing leukemia.

REFERENCES

1. Agarwal Gupta N, Kabra M. Diagnosis and management of Down syndrome. Indian J Pediatr 2014; 81: 560-567.
2. Martínez-Macías FJ, Bobadilla-Morales L, González-Cruz J, et al. Descriptive study of the complete blood count in newborn infants with Down syndrome. Am J Med Genet A 2017; 173: 897-904.
3. Jackson GL, Sendelbach DM, Rambally B, Manning MD, Engle WD. Circulating blasts and associated hematologic disorders in neonates with Down syndrome. Am J Perinatol 2012; 29: 259-266.
4. Kim DW, Kim HR, Shin MG, et al. Distinctive hematological abnormalities in East Asian neonates and children with Down syndrome. Int J Lab Hematol 2011; 33: 369-377.
5. Henry E, Walker D, Wiedmeier SE, Christensen RD. Hematological abnormalities during the first week of life among neonates with Down syndrome: data from a multihospital healthcare system. Am J Med Genet A 2007; 143A: 42-50.
6. Hord JD, Gay JC, Whitlock JA. Thrombocytopenia in neonates with trisomy 21. Arch Pediatr Adolesc Med 1995; 149: 824-825.
7. Bull MJ; Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics 2011; 128: 393-406. Erratum in: Pediatrics 2011; 128: 1212.
8. Ciovacco WA, Raskind WH, Kacena MA. Human phenotypes associated with GATA-1 mutations. Gene 2008; 427: 1-6.
9. Zipursky A. Transient leukaemia--a benign form of leukaemia in newborn infants with trisomy 21. Br J Haematol 2003; 120: 930-938.
10. Roberts I, Alford K, Hall G, et al; on behalf of the Oxford-Imperial Down Syndrome Cohort Study Group. GATA1-mutant clones are frequent and often unsuspected in babies with Down syndrome: identification of a population at risk of leukemia. Blood 2013; 122: 3908-3917.
11. Gamis AS, Alonzo TA, Gerbing RB, et al. Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children’s Oncology Group Study A2971. Blood 2011; 118: 6752-6759.
12. Tunstall O, Bhatnagar N, James B, et al; British Society for Haematology. Guidelines for the investigation and management of Transient Leukaemia of Down Syndrome. Br J Haematol 2018; 182: 200-211.
13. Appendix I: Hematological Reference Values. In: Lanzkowsky P, Lipton, JM, Fish JD (eds). Lanzkowsky’s Manual of Pediatric Hematology and Oncology(6th ed). UK and USA: Elsevier, 2016: 709-728.
14. Klusmann JH, Creutzig U, Zimmermann M, et al. Treatment and prognostic impact of transient leukemia in neonates with Down syndrome. Blood 2008; 111: 2991-2998.
15. Dixon N, Kishnani PS, Zimmerman S. Clinical manifestations of hematologic and oncologic disorders in patients with Down syndrome. Am J Med Genet C Semin Med Genet 2006; 142C: 149-157.
16. Crispino JD, Horwitz MS. GATA factor mutations in hematologic disease. Blood 2017; 129: 2103-2110.
17. Satgé D, Sommelet D, Geneix A, Nishi M, Maitre P, Vekemans M. A tumor profile in Down syndrome. Am J Med Genet 1998; 78: 207-216.
18. Hasle H, Clemmensen IH, Mikkelensen M. Risks of leukaemia and solid tumours in individuals with Down’s syndrome. Lancet 2000; 355: 165-169.
19. Patja K, Pukkala E, Sund R, livanainen M, Kaski M. Cancer incidence of persons with Down syndrome in Finland: a population-based study. Int J Cancer 2006; 118: 1769-1772.
20. Kuitert PC, Abbink FC, Broers CJ, van der Valk P, van Furth AM, van der Kuip M. Epstein-Barr virus infection with severe consequences. EBV, haemophagocytic lymphohistiocytosis and Hodgkin lymphoma with Down syndrome. Ned Tijdschr Geneeskd 2014; 158: A7608.
21. Patiroglu T, Cansever M, Bektas F. Underlying factors of recurrent infections in patients with Down syndrome. North Clin Istanb 2018; 5: 163-168.