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Changes in the peripheral blood cell count in pediatric patients with Down syndrome

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Abstract

Objectives: Down syndrome (DS) is associated with multiple complications, including a high risk of leukemia and thyroid dysfunction. This clinical study aimed to examine the complete blood cell count in patients with DS without leukemia or transient abnormal myelopoiesis. We also aimed to evaluate the effect of thyroid dysfunction on hematological anomalies in DS.

Methods: We analyzed the peripheral blood cell count in 23 pediatric patients with DS with and without thyroid dysfunction and in 17 pediatric patients without DS with thyroid dysfunction.

Results: Patients with DS showed greater neutrophilia and lymphopenia than did patients with DS and hypothyroidism and patients with hypothyroidism. Surprisingly, patients with DS showed a significant degree of eosinopenia in the peripheral blood. Interestingly, hypothyroidism had an attenuating effect on different lineages in the complete blood count. However, these anomalies were specific for DS.

Conclusions: Our clinical findings support previous data on DS-associated changes in the complete blood count. Our study also shows novel alterations in the complete blood count in leukemia-free patients with DS in association with hypothyroidism. The attenuating effect of thyroid dysfunction on changes in different lineages in the context of DS is novel and deserves further analysis in larger studies.

Keywords

Down syndrome, thyroid dysfunction, hypothyroidism, eosinophils, peripheral blood, leukemia, myelopoiesis

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Introduction

Down syndrome (DS) is associated with a wide array of phenotypes, including a specific spectrum of malignancies. In DS, there is a low risk of solid tumors and a high risk of childhood leukemia, which is 150 times higher for acute myeloid leukemia (also known as myeloid leukemia associated with DS) and up to 33 times higher for acute B-cell lymphoblastic leukemia.[1–3] Myeloid leukemia associated with DS includes acute megakaryoblastic leukemia and myelodysplastic syndrome, and is preceded in almost all cases by neonatal transient abnormal myelopoiesis (TAM). TAM is unique to neonates and infants with DS. TAM is considered a pre-leukemic condition that is associated with N-terminal truncation of GATA1, but it is not sufficient to induce myeloid leukemia features. However, only 20% to 30% of TAM cases acquire additional mutations and develop into myeloid leukemia.[1,4–7] DS-associated hematological abnormalities are tissue (fetal liver and bonne marrow) and lineage specific and are dependent on the trisomic environment (trisomy of chromosome 21 genes implicated in hematopoiesis: CSTB, DYRK1A, ERG, ETS2, OLIG2, RUNX1, TIAM) and GATA1 mutation.[2] ETS family transcription factors, miR-125b, Runx1/2,[6,8] DYRK1A,[9] and Hmgn1,[10] are also associated with development of leukemia.

Most of the studies on neonates/infants with DS (and to a lesser extent in children with DS) reported macrocytosis,[11,12] quantitative and qualitative anomalies of lymphocytes,[13–17] and an increase in the number of platelets and granulocytes (neutrophils, monocytes, and basophils).[1,18] Thrombocytopenia, leukocytosis, and neutrophilia are commonly associated with TAM.[5,18–20] Interestingly, in 10% to 16% of cases, TAM is associated with various degrees of eosinophilia,[1] but there are no data on the status of eosinophils in patients with DS without leukemia. Notably, GATA1 (along with GATA2 and CCAAT enhancer binding proteins) plays a crucial role in commitment and maturation of the eosinophil lineage.[21]

In patients with DS, the frequency of congenital hypothyroidism is 28 times higher, and up to 60% of patients with DS present with subclinical hypothyroidism.[22] Hypothyroidism is associated with various degrees of normochromic/normocytic or, less commonly, macrocytic anemia, eosinophilia, structural anomalies of neutrophils, monocytosis, and hypoplasia of all myeloid lineages (although monocytosis has also been reported).[23–26]

In this study, we analyzed the complete blood cell count (CBC), including eosinophils, in leukemia-free pediatric patients with DS and evaluated the effect of thyroid dysfunction on hematological anomalies.

Material and methods

We performed a case–control retrospective study. All participants of this study were patients of the Emergency Clinical Hospital for Children, Timisoara. Written consent was obtained from the parents of the children. The study was approved by the Ethical Committee of Paediatric Clinic Nr. 1 Timisoara (no. 70/21.12.2016) and was conducted in accordance with the principles of the Helsinki Declaration of Human Rights. We included patients with DS (DS group), patients with DS and hypothyroidism (DS-ht group), and patients with hypothyroidism (ht group).

The CBC was measured by flow cytometry and included leucocytes (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), erythrocytes, hemoglobin, hematocrit, red blood cell indices, and platelets.

For statistical analysis, we computed Z scores to compare percentages in the three patient groups. The Student's t-test was used to evaluate the statistical

significance of the difference of a specific condition. Specifically, we compared the DS-ht group with the ht group, the DS group with the DS-ht group, and the DS group with the ht group.

Results

There were 10 patients in the DS group, 13 in the DS-ht group, and 17 in the ht group. The demographic characteristics of the three groups of patients are shown in Table 1. Detailed information of the clinical data are shown in Supplemental Tables 1S–3S. There were no significant differences in the mean age and sex ratios among the three groups (Table 2).

Notably, at the time of inclusion in our study, all patients in the DS-ht and ht groups had already been diagnosed with thyroid dysfunction/hypothyroidism. Five patients in the DS-ht group and six patients in the ht group received substitutive therapy with levothyroxine, which corrected thyroid function (Supplementary Table 1).

CBC data for the three groups of patients are shown in Supplemental Tables 4S–6S. Patients in the DS group were the most affected; 70% of them showed eosinopenia, 50% showed lymphopenia (none with lymphocytosis), and 10% showed erythropenia. Basophil, monocyte, neutrophil, and platelet counts were within the normal range in the DS group. In the DS-ht group, 38.5% of patients had eosinopenia and 7.7% had lymphopenia. All of the other cell counts were within the normal range in the DS-ht group. In the ht group, only 11.8% of patients showed eosinopenia, none showed lymphopenia, and 5.8% showed neutropenia. Surprisingly, 23.5% of these patients showed erythropenia (all other CBC counts were within the normal range).

Statistical analysis of the CBC counts showed that eosinopenia was significantly more frequent in the DS-ht group compared with the ht group ($P = 0.034$) and in the DS group compared with the ht group ($P = 0.002$). The eosinophil count was not significantly different between the DS and the DS-ht groups (both groups showed eosinopenia in most of the cases). However, the degree of eosinopenia was significantly lower in the DS group compared with the DS-ht group (one-tailed Student's t-test, $P = 0.048$). Neutrophilia and lymphopenia were significantly more frequent in

Table 1. Demographics of patients in the DS, DS-ht, and ht groups.

Clinical data	DS	DS-ht	ht
Female/male, n	5/5	5/8	11/6
Age (months)			
mean ± standard deviation	87.2 ± 50.13	92.15 ± 66.74	52.64 ± 60.66
Minimum/maximum	22/177	3/209	1/170

DS: Down syndrome; DS-ht: Down syndrome with hypothyroidism; ht: hypothyroidism.

Table 2. Comparison of the sex ratio and age among the groups.

	DS-ht vs ht	DS vs DS-ht	DS vs ht
Sex ratio	−1.4278	−0.5534	0.751
Z score (P value)	(0.15272)	(0.58232)	(0.45326)
Age (P value)	0.1	0.84	0.12

DS: Down syndrome; DS-ht: Down syndrome with hypothyroidism; ht: hypothyroidism; vs: versus.

Table 3. Differences in the complete blood count among the groups using the Z score.

	DS-ht vs ht			DS vs DS-ht			DS vs ht		
Blood cells	Z score (P value)	%DS-ht	%ht	Z score (P value)	%DS	%Ds-ht	Z score (P value)	%DS	%ht
Eosinophils	↓ 2.11 (0.034)	46.2	11.8	–	–	–	↓ 3.09 (0.002)	70	11.8
Neutrophils	–	–	–	↑ 2.88 (0.003)	50	0	↑ 2.66 (0.007)	50	5.9
Lymphocytes	–	–	–	↓ 2.29 (0.022)	50	7.7	↓ 3.22 (0.001)	50	0

ht: hypothyroidism; DS-ht: Down syndrome with hypothyroidism; DS: Down syndrome; ↑: increased complete blood cell count; ↓: decreased complete blood cell count; –: no significant difference.

the DS group compared with the DS-ht (both $P < 0.05$) and ht (both $P < 0.01$) groups (Table 3).

Discussion

The most important finding in our study regarding changes in the CBC was the attenuating effect of hypothyroidism on the DS lymphopenic phenotype. This finding suggested that this phenotype was not due to hypothyroidism. This possibility is further supported by the significantly higher incidence of lymphopenia in DS group than in the ht group. DS-associated lymphopenia is thought to be due to dysfunction of the trisomic thymus associated with severe dysregulation in cytokine production.[27,28] Naturally occurring and experimentally induced hypothyroidism are associated with immunodeficiency due to severe lymphopenia.[29] This reflects genomic and non-genomic action of thyroid hormones on lymphopoiesis.[30,31] With regard to neutrophilia and lymphopenia in DS, our results are consistent with those found in the literature because these are common manifestations in DS.[1,2,18,32]

Intriguingly, 70% of patients with DS showed significant eosinopenia, and association of hypothyroidism tended to reduce its incidence (not significant). However, the incidence of eosinopenia was significantly higher in the DS group than in the ht group. This finding suggests a DS-dependent mechanism excluding the involvement of hypothyroidism. More important, our clinical findings support data from Gata1$^{\Delta e2}$ knock-in mice by Maroz et al.[5] These authors showed expansion of eosinophil progenitors due to arrest of their terminal maturation in mice that only expressed N-terminal truncation of GATA1.

We failed to observe a significant difference between the incidence of erythropenia among the three groups of patients. This finding might be attributable to the small size of the groups of patients who were analyzed. Nevertheless, our results suggest that the effect of a lack of thyroid hormones is not just due to pancytopenia, but there are differences in the responses of the different cell lineages.

Conclusions

Our data on changes in eosinophils in the peripheral blood of patients with DS support previous findings.[5] However, the attenuating effect of thyroid dysfunction on changes in different cell lineages in the context of DS is a novel finding that deserves further analysis in larger studies.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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