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[jbpm1@sbpc.org.br](mailto:jbpm1@sbpc.org.br)

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# Hematological parameters in children with Down syndrome

## *Parâmetros hematológicos em crianças com síndrome de Down*

Renato Nishihara<sup>1</sup>; Alana S. C. Souza<sup>1</sup>; Letícia R. Finatti<sup>1</sup>; Nancy O. Palmieri<sup>2</sup>

1. Universidade Positivo. 2. Ambulatório de Síndrome de Down do Hospital de Clínicas da Universidade Federal do Paraná (UFPR).

### ABSTRACT

**Introduction:** There are few studies that investigated whether Down syndrome (DS) interferes with references values for complete blood counts (CBC) test in children with the syndrome. **Objective:** This study aimed to analyze the results of CBC performed in children with DS. **Patients and methods:** Data from CBC of DS children were included; at the time of examination they were aged between 2 and 10 years and had no clinical signs and/or symptoms of infectious disease. The hematological parameters analyzed were: total number of erythrocytes (RBC), hemoglobin (Hb) concentration, hematological indices, platelet count, and total number of leucocytes. Additionally, we compared the collected parameters according to gender and age of the children studied. **Results:** A total of 203 CBC (100 girls and 103 boys) were evaluated. In general, no significant differences were observed in studied parameters between the values found in samples of DS children and the values described in the literature as a reference for children in this age group. No difference in the prevalence of anemia was observed in relation to gender ( $p = 0.33$ ), 14/103 (13.6%) boys, and 11/100 (11%) girls had anemia. However, the Hb and hematological indices values found in boys was significantly lower than in girls ( $p < 0.001$ ). **Conclusion:** This investigation is the first one in Brazil to present and analyze the CBC results of DS children, reporting that their hematological indices are within the expected range for children without DS. Additionally, it was found that 12.3% of them had anemia.

**Key words:** Down syndrome; hematological parameters; blood counts; anemia.

### INTRODUCTION

Down's syndrome (DS), also known as trisomy 21, is the most common chromosomal change in the world population, where about one in every 700 live births may have the syndrome<sup>(1)</sup>.

At birth and during the first years of life, a Down child has already several health problems, among which the most important include congenital heart defect, hypotonia, hearing loss, thyroid disorders, and increased susceptibility to infections. Over the years, the clinical manifestations described in DS patients are similar to those of aging process, with higher prevalence of bacterial and viral infections, autoimmune diseases, and early progression to dementia, after 40 years of age. Due to these features, DS was long considered as a progeroid disease<sup>(2)</sup>. Furthermore, respiratory tract infections are common, and may become recurrent, and still constitute a major cause of death for all ages<sup>(3)</sup>.

Currently, the most accepted hypothesis is that morphological changes of the thymus are the main causes of immune

abnormalities. The thymus is a primary lymphoid organ responsible for the differentiation, selection and maturation of T lymphocytes. As a result, it appears that thymic alterations observed in patients with DS affect the T lymphocytes function, also causing an imbalance in the cytokine network<sup>(3,4)</sup>. DS fetuses shows changes of the parameters used in the evaluation of thymic function: abnormal thymic anatomy and low lymphocyte T receptor excision circles (TREC) count, which are used as thymic function markers. This is likely to occur because some controlling genes of division and proliferation of thymocytes are present on chromosome 21. It is not yet entirely clear, but it is possible that in addition to abnormalities of the thymus, T and B lymphocytes are also functionally defective<sup>(4,5)</sup>.

Anemia are considered common diseases in all countries, mainly affecting children and pregnant women, especially in developing countries<sup>(6)</sup>. Some authors have shown that DS children are more predisposed to develop hematological disorders, such as anemia. This may be related to the involvement of genes located on chromosome 21, participants of folate-methylation

cycle, an essential component for the hemoglobin formation and deoxyribonucleic acid (DNA) synthesis<sup>(7)</sup>. Some of these genes are responsible for coding protein and ribonucleic micro acid (RNAs), and changes may promote not only impair to hematopoietic system, but also change the differentiation of hematopoietic cells<sup>(8)</sup>. Roberts *et al.*<sup>(8)</sup> suggest that trisomy impacts in a complex way on the biology of hematopoietic progenitor cells, disrupting their growth and differentiation during the embryonic stage. It is possible that such disorders would require changes in cells counts in a test such as complete blood counts (CBC). Therefore, it is estimated that DS children are 10% to 20% more likely of developing leukemia and myeloproliferative diseases than those without the syndrome<sup>(9)</sup>.

Only few studies have investigated whether DS interfere with reference ranges for the assessment of CBC in children with the syndrome. There are no studies in Brazil that show the prevalence of anemia in DS children.

## OBJECTIVE

This study aimed to analyze the results of CBC performed in children with DS who did not show any symptoms of viral or bacterial infection at the time of the examination.

## PATIENTS AND METHODS

This study was approved by the Ethics Committee on Human Research of Positivo University (Comitê de Ética em Pesquisa em Seres Humanos da Universidade Positivo [CEP/UP], number 667.592/2014). The study presents cross-sectional, observational and analytical design with historical data collection, carried out from May to July 2014. Clinical and demographic data were collected by review of medical records. All patients were seen at the pediatric clinic of a single pediatrician who is a reference for DS children care in Curitiba (PR), assisting patients by covenant and private health care.

The study included data taken from CBC, automated methodology with slides review, performed in children diagnosed with DS and confirmed by karyotype, which at the time of examination were aged between 2 and 10 years and had no signs and symptoms infectious disease at the time of clinical examination.

Children who were not in the stipulated age group and those that at the time of medical appointment presented symptoms of

viral or bacterial infection or any complaints that could clearly affect the CBC results, were considered exclusion criteria for participation in the study.

The tests were performed on clinical laboratories in the city of Curitiba (PR), through automated blood cell counting method, using manual analysis as a routine tool to confirm erythrocyte indices changes on slides. Hematological parameters analyzed on the CBC reports were: total number, hemoglobin (Hb) concentration, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, and total number of leukocytes. In addition, an analysis comparing the parameters evaluated in relation to gender and age of the studied children was performed.

Data were submitted in tabular form to statistical analysis, and Kolmogorov-Smirnov test, chi-squared test, Fisher's *p* test, and Mann-Whitney test were performed using Prisma 4.0 Program. We considered significant values less than  $p < 0.05$ .

## RESULTS

A total of 203 CBC were evaluated, including 103 boys and 100 girls with DS, with mean age of  $4.3 \pm 2.08$  years (between 2 and 10 years). The data found in this study were compared with those already established in the literature as a reference<sup>(10)</sup> for children without DS at the same age group. In general, it was observed that the erythrocyte values found in samples from DS children are similar to those described for children without DS<sup>(10)</sup>. The mean of total erythrocyte count was  $4.63 \times 10^6 \pm 0.45$  cells/mm<sup>3</sup>. The mean total leukocyte count was  $7300.5 \pm 2893.92$  cells/mm<sup>3</sup>. The mean hemoglobin was  $13.7 \pm 1.59$  g/dl and the hematological indices, MCV, MCH and MCHC were close/similar to the values reported for children without DS of the same age<sup>(10)</sup>, the same occurs with the total number of platelet count (**Table 1**).

The values found for all parameters were similar for both genders (**Table 2**). There was no significant difference in prevalence of anemia in relation to gender ( $p = 0.33$ ), and 14/103 (13.6%) boys and 11/100 (11%) girls had anemia. However, it was observed that boys presented Hb concentration levels and hematological indices significantly lower than girls ( $p < 0.001$ ). The exception were the MCHC values, for which there was no significant difference ( $p = 0.76$ ). **Table 3** shows that 25/203 (12.3%) of the studied children had anemia, and average age of  $3.3 \pm 1.28$  years (between 2 and 6 years) in this group. Among girls with anemia, 6/11 (54.5%) were younger than two years of age. Concerning the boys,

TABLE 1 – Hematological parameters of 203 children with Down Syndrome

	Age (years)	Erythrocytes (1012/l)	Hb (g/dl)	PCV (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)	Platelets (mm <sup>3</sup> )	Leucocytes (mm <sup>3</sup> )
Minimum	2	2.97	7.5	25	64.03	21.2	30.1	150000	2500
Maximum	10	5.66	19	51.8	107.1	34.8	38.5	528000	18900
Mean	4.3	4.63	13.68	39.9	86.5	29.4	34.1	312768	7300.5
Standard deviation	2.08	0.45	1.59	4.22	4.93	1.96	1.31	74951	2893.92
Reference values*		4.5 to 6.5	12 to 16	37 to 44	80 to 100	27 to 32	32 to 36	150000 to 400000	4000 to 11000

\* Reference values for the age group, according to Hoffbrand AV, Moss PAH (2013)<sup>(1)</sup>.

Hb: hemoglobin; PCV: packed-cell volume; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration.

TABLE 2 – Hematological parameters in DS children, according to gender

Boys (n = 103)									Girls (n = 100)							
	Age (years)	Hb	PCV%	MCV	MCH	MCHC	Platelets	Leucocytes	Age	Hb	PCV%	MCV	MCH	MCHC	Platelets	Leucocytes
Minimum	2	9.7	28	64.03	21.83	30.3	162.000	2.580	2	7.5	25	71	21.2	30.1	150000	2500
Maximum	10	17.3	50	97	34.6	38.5	504.000	18.900	10	19	51.8	107.1	34.8	36.6	528000	20230
Mean	4.1	13.4 *	39.3	85.5	29	34	314.049	7195.3	4.51	13.9	40.5	87.4	29.7	34.1	311448	7495
Standard deviation	1.97	1.44	3.88	4.87	1.9	1.41	74803.8	3060.94	2.21	1.71	4.48	4.83	1.98	1.19	75456	3087

Student t-test comparing girls and boys \*p < 0.001.

DS: Down syndrome; Hb: hemoglobin; PCV: packed-cell volume; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration.

TABLE 3 – DS patients with anemia, according to gender

Boys with anemia								Girls with anemia							
Age	Hb	PCV%	MCV	MCH	MCHC	Platelets	Leucocytes	Age	Hb	PCV%	MCV	MCH	MCHC	Platelets	Leucocytes
4	11.1	32.1	90.4	31.3	34.6	315000	10310	3	11.5	34.3	87.1	29.2	33.5	250000	9120
2	11.2	33	84	28.7	33.9	162000	11300	2	11.6	33.8	85.4	29.3	34.3	183000	15900
6	10	30.2	86.2	31.2	35.5	279000	9100	3	11.8	36.2	84.6	27.7	32.7	218800	6040
4	9.7	28.4	83	28	34	178000	7300	2	10.9	35.4	82.5	25.5	30.9	447000	14900
5	11.1	39.5	85.7	28.9	33.7	262000	5450	2	7.5	25	71	21.2	30.1	256000	7200
2	11.3	39.6	85.5	28.7	33.6	279000	6300	2	8.5	27.6	71	21.8	30.9	314000	6700
5	11.5	35.4	95	29.3	34	233000	9850	4	11.7	36.9	86.7	27.4	35.9	463000	5770
5	11	34.4	97	30.8	31.9	252000	4300	5	8.9	27.2	91.6	30	32.7	363000	3810
4	11	32.3	64.0	21.8	34.0	312000	4300	2	11.8	35.1	83.6	28.1	36.6	356000	6590
3	11.4	33	83.1	28.7	34.5	310000	5180	3	11.8	35.4	86.3	28.8	33.3	346000	8560
2	11	36.2	79.6	24.1	30.3	238000	6200	2	11.2	34.5	107.1	34.8	32.5	242000	9020
3	10.9	35.3	76.1	23.7	30.8	320000	7600								
3	11.6	35.5	86.4	28.2	32.6	274000	10920								
5	11.6	37.9	89	27.2	30.6	264000	6300								

DS: Down syndrome; Hb: hemoglobin; PCV: packed-cell volume; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration.

prevalence of age regarding the presence of the condition was not observed. When evaluating the hematological indices of patients with anemia, it was found that 5/25 (20%) presented microcytic hypochromic anemia, while the other 80% presented normocytic

normochromic anemia. As expected, increasing age resulted in increased hemoglobin values in children. However, the same does not apply to the number of leukocytes, since it does not significantly change with increasing age.

## DISCUSSION

Although the number of children born per woman in recent years has significantly decreased, the birth rate of DS children remains constant<sup>(12)</sup>. This is, in part, due to the increase of average maternal age observed in the population<sup>(12)</sup>. Because of the increased knowledge on all aspects involving the syndrome, in the last two decades the life expectancy of individuals with DS exceeds double<sup>(12)</sup>.

DS is a challenge for the clinician due to the diverse and complex health problems that affect the SD child, so the appropriate care to this type of patient regards constant attention and awareness of possible complications. It is also known that in childhood, a major complication is related to the number of recurrent infections, especially pneumonia, which can result in serious damage to the patient. Many authors have investigated the SD patient's immune system, mainly focusing on the cellular functions and humoral response<sup>(5)</sup>. Few studies have addressed the presence of anemia in this population. Also there are few studies that provide parameters for laboratory tests interpretation for DS children.

The World Health Organization (WHO)<sup>(13)</sup> defines anemia when the Hb content is below normal values for the age, gender, physiological status, and altitude. The main signs that characterize it are skin and mucosal changes, in addition to gastrointestinal and metabolic symptoms, such as fatigue, palpitations, weakness, growth reduction, and reduction of cognitive function; moreover, it can also affect immunity and thermoregulation<sup>(14, 15)</sup>. Anemic children may have delayed neuromotor development that does not change, even after prolonged treatment<sup>(15, 16)</sup>. It is worthful to mention that some of these symptoms can be confused with those observed in the spectrum of DS characteristics.

WHO estimates that in developing countries half of children under the age 4 years present anemia. In the study of Rodrigues *et al.*<sup>(6)</sup>, which investigates 256 children in 25 of early childhood education municipal centers (centros municipais de educação infantil [CMEI]) in the city of Cascavel (PR), aged from 6 to 24 months, of both genders, the prevalence of anemia was 29.7%. According to Monteiro *et al.*<sup>(17)</sup> there is no data on the exact scale of the problem. These authors investigated 912 children under the age of five years in São Paulo and showed that in the 1980s the prevalence of anemia was 35.6%, increasing to 47.8% in the 90s. In 2001, Silva *et al.*<sup>(18)</sup> studied 557 children between 0-36 months of age in municipal schools of Porto Alegre (RS) and reported the presence of anemia in 47.8%. Santos *et al.*<sup>(19)</sup> investigated 306 children under the age of 6 years who were part of communities served by the Ministry for Children (Pastoral da Criança), on the outskirts of Pelotas (RS), and reported prevalence of anemia in 53% of them. In this study, we was observed that 12.3% (25/203) of the patients had anemia, with 14/103 boys and 11/100 girls. All children with anemia were aged between 2 and 6 years, showing that this would be the age group with higher risk. This fact is

demonstrated in the study of Santos *et al.*<sup>(19)</sup>, with the children from Pelotas (RS); the authors also showed that among children under the age of 12 months, the prevalence was 81.1%, falling to 75.5% among children between 12-24 months of age, for 60.3% in the third year of life, 41.5% in the fourth year, 40.4% in the fifth, and 25.6% in the sixth year of age.

In southern Brazil, Neumann *et al.*<sup>(20)</sup> observed a prevalence of 30.8% of anemia in 476 children studied. In Israel, Tenenbaum *et al.*<sup>(21)</sup> have established that 8.1% of children and adolescents with DS ( $n = 149$ ) had anemia, such prevalence did not differ much of the studied population. It is important to emphasize that the sample analyzed in this study consisted of patients from pediatric office attended by covenant and private health care.

Studies carried out in different locations and populations indicated high prevalence of iron deficiency anemia in Brazil. Unlike to malnutrition, the prevalence of iron deficiency anemia has increased in recent decades<sup>(22)</sup>. According to the present study records, PCV and Hb levels of the boys was lower than that observed in girls. Prado *et al.*<sup>(23)</sup> reported in 2009, in the state of São Paulo, the anthropometric profile of 187 DS children, asserting that 80.2% of them had low weight and height in relation to age in both sexes, but more frequent among boys. In addition, the study determined that males have higher nutritional needs than females. Moreira *et al.*<sup>(24)</sup>, evaluated 17 DS children aged between 3-18 years in Minas Gerais, they showed that 12% of girls were overweight and 6% of boys were low-weight.

According to current knowledge, the total number of leukocytes of a child under 13 years of age range from 4000-11000 cells/mm<sup>3</sup><sup>(11)</sup>. There are few authors who have investigated the number of leukocyte in the DS. Boy *et al.*<sup>(25)</sup> studied 165 DS children in 1995 and reported that 13.6% of them had leukopenia ( $< 5.000$  cells/mm<sup>3</sup>). In this study, the average number of leukocytes for children from 2-10 years of age was  $7300 \pm 2893$  cells/mm<sup>3</sup>, which is within the parameters defined as normal white blood cell (WBC) count for children without DS. In addition, we observed no change in leukocyte values in relation to increasing age.

In the present study, due to the sample size, we decided not to evaluate the differential CBC count, since it suffers greater influence of age and other uncontrollable conditions, such as allergies, worm infestation, and viruses, which can cause difficulties in interpreting and analysis of data.

## CONCLUSION

This research is the first in Brazil to present and analyze the CBC results of DS children, reporting that, despite all the changes caused by the syndrome, their hematological indexes are within the expected range for the same age children without DS. Additionally, we found that 12.3% of them had anemia.



## RESUMO

**Introdução:** São escassos os estudos que investigaram se a síndrome de Down (SD) interfere nos valores de referência para a avaliação do hemograma em crianças com a síndrome. **Objetivo:** Analisar os resultados dos hemogramas realizados em crianças com SD. **Casística e métodos:** Foram incluídos os dados retirados dos hemogramas realizados em crianças com SD que, no momento do exame, tinham idade entre 2 e 10 anos e não apresentavam no exame clínico sinais e/ou sintomas de doença infecciosa. Os parâmetros hematológicos analisados foram número total de eritrócitos, concentração de hemoglobina (Hb), índices hematimétricos e número total de plaquetas e de leucócitos. Adicionalmente, foram comparados os parâmetros coletados em relação ao gênero e à idade das crianças estudadas. **Resultados:** No total, foram avaliados 203 hemogramas (100 meninas e 103 meninos). De maneira geral, comparando-se os valores encontrados nas amostras das crianças com SD e os valores já descritos na literatura como sendo de referência para crianças nessa faixa etária, não foram observadas diferenças significativas nos parâmetros estudados. Não se observou diferença na prevalência de anemia em relação aos gêneros ( $p = 0,33$ ), sendo 14/103 (13,6%) meninos e 11/100 (11%) meninas com anemia. No entanto, na comparação entre os gêneros, observou-se que os meninos apresentaram Hb e índices hematimétricos significativamente menores que as meninas ( $p < 0,001$ ). **Conclusão:** Esta investigação é pioneira no Brasil ao apresentar e analisar os resultados dos hemogramas das crianças com SD, relatando que seus índices hematológicos encontram-se dentro do esperado para crianças sem a SD. Adicionalmente, foi possível verificar que 12,3% delas apresentavam anemia.

**Unitermos:** Síndrome de Down; parâmetros hematológicos; hemograma, anemia.

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**MAILING ADDRESS**

**Renato Nisihara**

Universidade Positivo; Rua Professor Pedro Viriato Parigot de Souza, 5300; Campo Comprido; CEP: 81280-330; Curitiba-PR, Brazil; e-mail: [renatonisihara@up.com.br](mailto:renatonisihara@up.com.br)