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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Frequency, severity and type of anemia in children with classical celiac disease

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SUMMARY

Introduction/Objective Anemia is the most common extraintestinal manifestation of celiac disease (CD) in children.

The aim of this study was to determine the frequency, severity and type of anemia in children with a classical CD, as well as the differences between anemic and non-anemic patients in their age, duration of illness, percentile body length or height, percentage of body weight (BW) deviation compared to ideal, and the degree of damage to the small intestine mucosa.

Methods The study was based on a sample of 90 children, 56 females and 34 males, ages 7–90 (18.23 ± 12.7) months with classical CD. The diagnosis of CD is based on the ESPGHAN criteria from 1990 and 2012, and of anemia on the 2011 WHO reference values.

Results Anemia was found in 47 (52.22%) patients, of which it was mild in 23 cases [hemoglobin (Hb) 100–109 g/L] and moderately severe in 24 (Hb 70–99 g/L), in 34 (72.34%) it was microcytic [mean cell volume (MCV) < 70 fl] and normocytic (MCV 70–87 fl) in 13 patients. Low serum iron levels (< 10.7 μmol/L) were found in 68 (75.56%), and hypoferritinemia (< 16 ng/ml) in 77 (85.56%) patients. Except for a greater deficit of BW in patients with anemia compared to those without anemia (-14.64 ± 9.60 *vs*. -8.56 ± 11.87%, p < 0.01), differences in other defined features were not significant.

Conclusion Mild or moderate iron deficiency anemia occurs in slightly more than half of children with a classical type CD. In anemic compared to non-anemic patients, there is a significantly higher BW deficit, while differences in other characteristics typical for this type of disease are not significant.

Keywords: classical celiac disease; children; anemia

INTRODUCTION

Anemia is the most common extraintestinal manifestation of celiac disease (CD) [1–5]. Depending on the study, it is found in 16–84% of newly detected patients, more often and more pronounced in severe and prolonged forms of the disease [4–8]. A key role in the pathogenesis of anemia in CD, both in children and adults, is iron deficiency, while the lack of folic acid, vitamin B12, copper, and protein results in a lesser expression [4, 9, 1–12]. In a significant number of cases anemia can be the main, and often the only sign of the disease [9, 13–19]. This clinical presentation of CD is commonly seen in adults and adolescents, although it is not rare in school and preschool children [9]. According to the results of some studies, CD as the etiological factor of sideropenic anemia participates with a prevalence of 6–21.3% [9, 17–19]. Hence, some authors recommend that all patients with sideropenic anemia of unclear etiology, especially those resistant to oral iron therapy, should be tested for CD [13, 17, 19].

The aim of our study was to determine the frequency, severity and type of anemia in children with classical CD. In addition, the objective was to analyze the differences between anemic and non-anemic patients at the age of diagnosis of the basic disease and its previous duration, percentile body length (BL) or body height (BH), percentage of body weight (BW) deviation compared to the ideal, and the degree of damage to the small intestine mucosa.

METHODS

The objectives of the study were analyzed on a sample of 90 children (56 female and 34 male) ages 7–90 (18.23 ± 12.70) months with classical CD, i.e. type of the disease followed by chronic diarrhea (> 2 weeks) and failure to thrive. The diagnosis of CD was based on the European Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines published in 1990 and 2012 [20, 21]. The diagnosis was preceded by a detailed medical history, complete

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clinical examination, and appropriate laboratory tests. The study protocol was approved by the local ethics committee.

History of the disease for each patient contained exact data related to the onset, duration, and the severity of the underlying disease. According to the data from parents, all respondents had optimally progressed and had normal blood counts before the onset of the disease. During the clinical examination, each patient's BL/BH and BW was measured and the obtained values were compared with the standard for the appropriate age and sex. The values of BL/BH are expressed in percentiles, and deviations in BW in relation to the ideal in percentages.

In accordance with the modified Marsh criteria, small intestinal mucosal damage is classified into infiltrative (I), infiltrative-hyperplastic (II), destructive (III), and hypoplastic (IV) [22]. Depending on the degree of destruction of villi, destructive enteropathies are additionally differentiated into partial (IIIa), subtotal (IIIb), and total (IIIc).

Blood count and serum iron and ferritin concentrations were determined by standard laboratory methods from a blood portion taken in the morning and before breakfast. The diagnostic criterion for anemia was the level of Hb for children up to five years old below 110 g/L, and for children 5–11 years old below 115 g/L [23]. The Hb value of 100–109 g/L was classified as a slight anemia, from 70 to 99 g/L moderate, and below 70 g/L severe [23]. The reference value for red blood cells count (RBCs) was $3.90–5.10 \times 10^{12}$/L, for MCV it was 70–87 fl, for mean cell Hb (MCH) 25–31 pg, and for iron serum concentration 10.7–31.3 μmol/L, of ferritin 16–100 ng/ml [24]. The differentiation of anemia types is based on the values of MCV, MCH, and serum iron concentration.

The differences between the anemic and non-anemic groups of children according to the age of diagnosis and the duration of the underlying disease were tested by Oneway ANOVA (on-the-clock analysis of variance), according to sex by the χ^2 test, according to the degree of small intestinal mucosal damage by the Kruskal–Wallis and Mann–Whitney tests, and the percentile BL/BH and the percentage of BW deviation was compared to the ideal by Student's T-test.

RESULTS

Anemia with Hb values of 71–109 (96.62 ± 9.33) g/L was observed in 47 of 90 or 52.22% of patients. None of them had severe anemia, while the incidence of mild and moderately severe anemia was almost the same (24 *vs.* 23). The number of RBCs in the blood in the whole group of subjects varied 2.56–5.19 (4.29 ± 0.73) $\times 10^{12}$/L, while the MCV value was 50.5–88.0 (64.76 ± 9.18) fl, concentrations of serum iron were 2.1–15.5 (5.96 ± 3.32) μmol/L, and of ferritin 2–18 (7 ± 4.20) ng/ml. In the group of children with anemia, the number of RBCs was low in 15 (31.91%) of them, normal in 27 (57.45%), and elevated in five ($5.11–5.70 \times 10^{12}$/L). In the same group of patients, MCV was decreased in 34 (72.34%) and normal in 13, while MCH was low in 35 (74.47%), and normal in 12. In the entire group of subjects, low serum iron levels were determined in 68 (75.56%) cases, while low ferritin levels were determined in 77 (85.56%) cases. Granulocyte and platelet counts in the blood were normal in all.

The duration of symptoms before the diagnosis was 1–6 (2.21 ± 1.48) months. The majority, 50 children (55.56%), were at the age of 1–2 years, 28 were younger than one year, and 12 were older than two years. The values of BL/BH percentile ranged 5–90 (37.62 ± 26.26), and the BW percentage deviation compared to the ideal for the appropriate age and sex from +18.5 to -33 (-11.58 ± 10.80). Destructive enteropathy (type III) was found in all the patients, seven of which partial (IIIa), 41 subtotal (IIIb), and 42 total (IIIc).

The differences in the age and the duration of the disease, sex, percentile BL/BH, percentage of BW deviation in relation to ideal, and the degree of damage of the obtained small intestine samples among patients with anemia and without anemia are shown in Table 1. As it can be seen, with the exception of significantly higher BW deficit in patients with anemia than in those without it, there were no significant differences.

Table 1. Differences in the age of diagnosis of celiac disease, duration of symptoms, BL/BH percentile, BW percentage deviation compared to the ideal, and the degree of damage of the small intestine mucosa in patients with anemia and in those without it

Observed features	Patients with anemia (No 47)	Patients without anemia (No 43)	Statistical significance
Age (months)	7.5–60 (16.42 ± 10.72)	7.5–90 (16.52 ± 5.96)	n.s.
Duration of symptoms (months)	1–6 (2.37 ± 1.54)	1–6 (2.03 ± 1.42)	n.s.
Percentile of BL/BH	5–90 (40.0 ± 26.37)	5–90 (35.25 ± 16.22)	n.s.
% deviation of BW	+9–-33 (-14.64 ± 9.60)	+18.5–-28 (-8.56 ± 11.87)	$p < 0.01$
Enteropathy (No) IIIa:IIIb:IIIc	2:21:24	5:20:18	n.s.

BL – body length; BH – body height; BW – body weight; n.s. – not significant

DISCUSSION

Anemia in CD is primarily caused by iron deficiency, but also by the lack of other nutritional factors necessary for normal erythropoiesis, such as folic acid, vitamin B12, proteins and copper [10, 12, 25, 26]. Hence, viewed pathogenically, it belongs to the group of nutritive or hypoproliferative anemia [10]. Deficit of iron, protein, and copper results in insufficient Hb synthesis and causes anemia of hypochromic and microcytic type, where the number of RBCs can be normal and elevated, while folic acid and vitamin B_{12} deficiency block normal regeneration of RBCs and result in macrocytic anemia [27]. In the state of a combined deficit of a factor of essential importance for normal erythropoiesis, anemia acquires normocytic features [10]. Folic acid deficiency, in addition to a smaller number of Er and low Hb and the number of reticulocytes, is characterized by high values of MCV and MCH and a reduced number of granulocytes and platelets [10]. An

identical hematological image also has a lack of vitamin B_{12}, but it is, except in the heavy form of the classical CD, rarely seen [4, 27, 28].

The basis of the deficit of the factors necessary for erythropoiesis is the absorption disorder caused by the inflammation of the small bowel mucosa [29]. The morphological and functional damage to the small intestine mucosa to the CD is most pronounced in its proximal part, i.e. in the segment where most of the nutrients are absorbed [29]. Negative nutritional balance in the classical type of CD is also significantly contributed to by insufficient intake caused by anorexia and vomiting [30]. As with other inflammatory diseases, additional involvement in iron malabsorption also has a suppressive effect of hepcidin [12, 30].

The consequences of the disease are more pronounced in children in the first two years of life, i.e. in the period of the most intensive growth and development, especially in the cases of its prolonged duration [4, 9, 29]. The age of our patients was 18.23 ± 12.70 months, and the length of the symptoms until the diagnosis was 2.21 ± 1.48 months, resulting in a significant deficit of BW (-11.58 ± 10.80%), reduced percentage of BL/BH (37.62 ± 26.26) and high representation of subtotal and total enteropathy (92.22%). In accordance with these facts, the prevalence of anemia in our patients was high (52.22%). The mean Hb value in anemic patients was 96.62 ± 9.33 g/L. None of them had severe anemia (Hb < 70 g/L), while the incidence of mild and moderate anemia was almost the same (24 *vs.* 23). According to morphological features, anemia was microcytic and hypochromic in three quarters of cases and normocytic and normochromic in others. In the whole group of subjects, low levels of serum iron were determined in 68 (75.56%) cases, and of ferritin in 77 (85.56%) cases.

Patients with anemia compared to non-anemic ones had a significantly higher deficit of BW. However, the differences in the age of diagnosing the underlying disease, its previous duration, the percentile of BL/BH, and the severity of the histological lesion of the small intestine mucosa were not significant. The explanation for this finding is probably in severe clinical expression of the underlying disease and/or before its onset in lower values of Hb, RBCs, and iron reserves in anemic patients compared to non-anemic ones. In support of the second hypothesis is the fact that the length of time the symptoms had presented themselves before the diagnosis in this sample of patients was almost twice shorter than the average life of RBCs (2:21 ± 1:48 *vs.* four months).

CONCLUSION

Mild or moderate iron deficiency anemia occurs in slightly more than one half of children with the classical type CD. In anemic patients compared to non-anemic ones there is a significantly higher BW deficit, while differences in other characteristics typical for this type of disease, such as its duration, age at which the diagnosis is set, percentile of BL/BH, and the degree of damage to the small intestine mucosa, are not significant.

Conflict of interest: None declared.

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Учесталост, тежина и тип анемије код деце са класичном целијачном болешћу

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САЖЕТАК

Увод/Циљ Анемија је најчешћа екстраинтестинална манифестација целијачне болести (ЦБ) у дечјој доби.

Циљ рада је био да се утврде учесталост, тежина и тип анемије код деце са класичном ЦД, као и разлике између анемичних и неанемичних болесника у узрасту, дужини трајања болести, перцентилу телесне дужине или висине, проценту одступања телесне тежине (ТТ) у односу на идеалну и степену оштећења слузнице танког црева.

Метод Студијом је обухваћен узорак од 90 деце, 56 женског и 34 мушког пола, узраста 7–90 (18,23 ± 12,70) месеци са класичним ЦД. Дијагноза ЦД је базирана на *ESPGHAN* критеријумима из 1990. и 2012. године, а анемије на референтним вредностима *WHO* из 2011. године.

Резултати Анемија је констатована код 47 (52,22%) болесника и то код 23 лака (*Hb* 100–109 *g/L*) и код 24 средње тешка (*Hb* 70–99 *g/L*), при чему код 34 (72,34%) микроцитна (*MCV* < 70 *fl*) и код 13 нормоцитна (*MCV* 70–87 *fl*). Снижен ниво гвожђа у серуму (< 10,7 *μmol/L*) утврђен је код 68 (75,56%), а феритина (< 16 *ng/ml*) код 77 (85,56%) болесника. Изузимајући већи дефицит *BW* код болесника са анемијом у односу на оне без анемије (-14,64 ± 9,60 односно -8,56 ± 11,87%, *p* < 0,01), разлике у другим дефинисаним обележјима између анемичних и неанемичних испитаника нису биле значајне.

Закључак Лака или умерено тешка сидеропенијска анемија се јавља код нешто више од половине деце са ЦБ. Код анемичности у поређењу са неанемичним болесницима регистрован је значајно већи дефицит ТТ, док разлике у другим карактеристикама типичним за ову врсту болести нису биле значајне.

Кључне речи: класична целијачна болест; деца; анемија