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**Isolated hypertransaminasemia in children up to two years
with classical celiac disease**

Изолована хипертрансаминемија код деце до две године
са класичном целијачаном болешћу

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SUMMARY

Introduction/Objective

Isolated hypertransaminasemia (IHTS) is a common, benign and transient appearance in patients with celiac disease (CD).

The aim of this study is to determine the frequency of IHTS in children up to two years old with clinically classical CD, as well as its connection with the onset of the first symptoms of the disease, the age of diagnosis, the clinical and laboratory nutritional parameters and the degree of damage of small intestinal mucosa.

Methods The study was based on a sample of 82 children, 55 female and 27 male, ages 7-24 (14.28 ± 4.41) months. The diagnosis of CD was based on the revised ESPGHAN criteria and the activity of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by standard laboratory method.

Results IHTS was found in 39 (47.56%) patients, of whom 27 (69.23%) had elevated levels of both transaminases and 12 only one, 8 AST and 4 ALT. The increase in relation to the above reference value was for ALT 1.10-10.08 (1.67±1.73), and for AST 1.08-7.91 (1.56±1.29) times. In patients with IHTS compared to those with normal transaminasemia, the age of the first symptom of CD was significantly lower (9.83±3.69 vs. 12.95±4.43 months, $p = 0.001$), as well as age of its diagnosis (12.97±3.88 vs. 15.47±4.56 months; $p = 0.01$), while the differences in the other observed parameters were not significant.

Conclusions IHTS occurs in almost half of children up to two years with classical CD. Hypertransaminasemia is in most cases mild and significantly more frequent in patients with earlier clinical expression of the CD.

Keywords: isolated hypertransaminasemia; classical celiac disease; children up to 2 years

САЖЕТАК

Увод/Циљ

Изолована хипертрансаминаземија (ИХТС) представља честу, бенигну и пролазну појаву код болесника са целијачном болешћу (ЦБ). Циљ ове студије је да се утврди учесталост ИХТС код деце узраста до две године са класичном ЦБ, као и повезаност њене појаве са узрастом настанка првих симптома болести, узрастом постављања дијагнозе, клиничко-лабораторијским параметрима исхрањености и степеном оштећења слузнице танког црева.

Метод Студија је базирана на узорку од 82 детета, 55 женског и 27 мушког пола, узраста 7-24 (14,28±4,41) месеци. Дијагноза ЦБ је заснивана на ревидираним *ESPGHAN* критеријумима, а активност ерумске аланин-аминотрансферазе (АЛТ) и аспартат-аминотрансферазе (АСТ) стандардном лабораторијском методом.

Резултати ИХТС је утврђена код 39 (47,56%) болесника, при чему код 27 (69,23%) са повишеним нивоима обе трансминазе, а код 12 само једне од њих, код 8 АСТ и код 4 АЛТ. Повећање у односу на горњу референтну вредност је износило за АЛТ 1,10-10,08 (1,67±1,73), а за АСТ 1,08-7,91 (1,56±1,29) пута. Код болесника са ИХТС у односу на оне са нормалном трансминаземијом узраст појаве првих симптома ЦБ је био знатно мањи (9,83±3,69 наспрам 12,95±4,43 месеци; $p=0,001$), као и узраст њеног дијагностиковања (12,97±3,88 наспрам 15,47±4,56 месеци; $p=0,01$), док разлике у осталим посматраним параметрима нису биле значајне.

Закључак ИХТС се јавља код близу половине деце узраста до 2 године са класичном ЦБ. Хипертрансаминаземија је у већини случајева блага и знатно учесталије код пацијената са ранијом клиничком експресијом ЦБ.

Кључне речи: изолована хипертрансаминаземија; класична целијачна болест; деца до 2 године

INTRODUCTION

Transaminases (aminotransferases) represent a group of enzymes of essential importance in catabolism and amino acid biosynthesis [1, 2]. They are characterized by high specificity for amino acids from which it performs transamination, as well as presence in all

cells of the organism, mainly in those that are metabolically most active, such as hepatocytes, myocytes, tubulocytes, and others [1, 2]. From the physiological and clinical point of view, the most important are alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [3, 4]. ALT is cytoplasmic, and AST is a cytoplasmic and mitochondrial enzyme [3, 4]. The ALT activity is greatest in hepatocytes, while AST is most active in the heart muscle, and then in the liver, kidney and skeletal muscle cells [4-6]. Due to the limited life span of cells, and reversible damage to their membranes, a small amount of transaminases is normally registered in the serum. Physiological variations of their activities in serum depend on the age, during generative period of gender, level of physical activity, and on the type of test they determine [5, 6]. In conditions followed by extensive cellular damage, serum transaminase activity is multiplying, which is a valuable laboratory indicator of various diseases, primarily liver, skeletal muscle and heart [1, 2, 6]. In liver damage, the elevation of the serum ALT level is usually higher than AST, while in muscular and haemolytic diseases the finding is reversed [4, 7].

Celiac disease (CD) is a systemic immune-mediated disorder triggered by dietary gluten in genetically predisposed individuals [8]. In addition to gluten-sensitive enteropathy, as a basic component of the disease, it is characterized by numerous extraintestinal manifestations, including isolated hypertransaminasemia (IHTS), i.e. elevated levels of serum transaminases without other signs of hepatic dysfunction [8-12]. Although it was first described in 1977, the basis for IHTS in the CD is not entirely clear [13, 14]. Histological examination of liver tissue in these patients shows mild steatosis and minimal inflammatory changes, with no relation to aminotransferase levels [12, 15]. It is most common in patients with a classic CD, especially those in the youngest age [16, 17]. In a certain number of patients, both children and adults, IHTS may be the first or only sign of this disease [5, 16, 18]. Unlike other diseases that can coexist with a CD, such as autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, and primary biliary cirrhosis, IHTS is a benign disorder that in most cases disappears during a 1-year gluten-free diet [9-12, 16, 17, 19-21].

The aim of this study is to determine the frequency of IHTS in children up to two years old with clinically classical CD, as well as its connection with the onset of the first symptoms of the disease, the duration of the symptoms, the age of diagnosis, the clinical and laboratory nutritional parameters and the degree of damage of small intestinal mucosa.

METHODS

The objectives of the study were considered on a sample of 82 children (55 female and 27 male) ages 7-24 (14.28 ± 4.41) months, with clinically classical CD, i.e. a disease characterized by a chronic diarrhea, poor appetite and failure to thrive [8, 22]. The study protocol was approved by the local ethics committee. The diagnosis of CD was based on the revised criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) from 1989 and on the new ESPGHAN guidelines published in 2012 [8, 23].

In the anamnesis for each patient, exact data related to the onset, duration and severity of the underlying disease are required, while in the clinical examination each of them accurately measured body length (BL) and weight (BW) and the obtained values compared to standard for the appropriate age and gender [24].

The liver function test (bilirubinemia, total and conjugated, ALT, AST and gamma-glutamyl transferase) and laboratory nutritional indicators (blood level of hemoglobin, iron, total proteins, albumin, total cholesterol and 3-glyceride) were determined by standard laboratory methods from the morning portion of the blood before breakfast. The obtained findings are compared with standard reference values. In patients with hypertransaminase, the serum creatine phosphokinase activity was determined, so any of them, in addition to the absence of cholestas and hemolysis, had no elements for rhabdomyolysis. Also, none received any of the medications followed by an increase in the serum level of transaminases, nor did it have an intercurrent infection that would produce this effect. The degree of increase in activity of ALT and AST is expressed by an absolute number of magnitudes in relation to the upper limit of the reference value.

Classification of pathohistological changes of the small intestinal mucosa was performed according to modified Marsh criteria on infiltrative (I), infiltrative-hyperplastic (II) destructive (III) and hypoplastic (IV) type [25]. According to the degree of mucosal damage, destructive enteropathy is additionally classified into partial (IIIa), subtotal (IIIb) and total (IIIc).

The association of the occurrence of hypertransaminase with the age of the child when the first symptoms of the CD began, the duration of the symptoms, the age of diagnosis and the clinical and laboratory nutritional parameters were tested with the Student's t-test, and with the degree of damage of the small intestine of the small intestine χ^2 -test.

RESULTS

Of the 82 patients, mild to moderate hypertransaminasemia was found in 39 (47.56%), of which 27 (32.93%) had elevated levels of both transaminases and 12 only one, 8 AST and 4 ALTs (Figure 1). The increase in relation to the upper limit of the reference value was for ALT 1.10-10.08 (1.67 ± 1.73), and for AST 1.08-7.91 (1.56 ± 1.29) times.

Although there was no significant difference between patients with IHTS and those with normal serum transaminases in the age of introduction of gluten containing food (4.76 ± 1.13 vs 5.06 ± 1.23 months, $p = 0.302$), nor in duration of the disease until diagnosis (3.13 ± 2.75 vs 2.53 ± 1.80 months, $p = 0.248$), occurrence of CD symptoms in children in the first group (4-23, average 9.83 ± 3.69 months) was significantly earlier than those with normal serum transaminase levels (4-21, average 12.95 ± 4.43 months) ($t = 3.447$; $p = 0.001$). Accordingly, the age of diagnosis of CD in children with IHTS (8.5-24, mean 12.97 ± 3.88 months) was significantly lower than that with normal serum transaminases (7-24, mean 15.47 ± 4.56 months) ($t = 2.650$; $p = 0.01$) (Figure 2).

By comparing the differences in percentile BL, the degree of BW deviation compared to ideal for the appropriate length, age and sex, Hb level, total proteins, total cholesterol, and 3-glyceride in the blood, as well as the severity of damage the small intestine mucosa in patients with IHTS and patients with normal serum transaminase values, no significant differences were found (Table 1).

DISCUSSION

IHTS is a common finding in patients with active CD. It occurs in patients of all ages and all types of illness, something often in children than adults. According to systematic reviews, it is found in 39-47% of adults and in 26-57% of children at diagnosis of CD [21]. It

is most common in children with a classic CD, especially those of the youngest age [16, 17, 21]. Hypertransaminasemia can sometimes be the first or only sign of CD, therefore in all cases of its unrecognized presence it is recommended testing in that sense [16, 21, 26]. Rarely, CD can be associated with severe autoimmune liver disease [12, 26, 27]. In contrast to IHTS associated with the CD, which disappears on gluten-free diet, autoimmune diseases of the liver in these patients are gluten-independent [12, 26, 28].

Although the presence of IHTS in the CD is long known, its pathogenetic basis has not been fully clarified. It is assumed that the possible mechanism leading to hepatic damage in patients with untreated CD is related to the entry of toxins, inflammatory molecules and antigens in the portal circulation [9, 29]. In any case, it is a generally asymptomatic, benign and with a strict gluten-free diet transient condition [9, 21, 26]. There is, however, evidence that IHTS in patients with CD in cases of an inconsistent gluten-free child can evolve into serious liver disorders, such as chronic hepatitis and consequent liver cirrhosis [30].

In our study, based on a sample of 82 children under the age of 2 years with a classical CD, a mild to moderate IHTS was found in almost any other of them. In accordance with the findings of other authors, the so high prevalence of IHTS explains the average age of our patients at the diagnosis of CD, which was less than 15 months, as well as its clinical form, which was classical in all [16, 17]. Accordingly, there was a significantly higher incidence of IHTS in younger patients compared to the elderly. However, the anticipated more frequent appearance of IHTS in patients with lower percental BL, a more significant BW deficiency, more pronounced laboratory nutritional deficiency indicators and more severe damage degree of small intestinal mucosae obtained by enterobiope, was not found. The same findings, also based on the child population, state and other. [17, 19]. The explanation for the absence of this link is most likely to lie in the identical type of CD and the close age of our patients.

In almost all of the cases, CD associated IHTS disappears within 1 year on gluten-free diet [16, 17]. If this does not happen, in addition to poor adherence with the gluten free diet, it should be considered autoimmune and other liver disorders associated with CD [12, 17]. Also, because of the possibility of a later onset of autoimmune liver disease, it is recommended for all patients with CD once a year control of the liver tests [17]. In all our patients normalization of transaminases was established after 2-9 months of gluten-free diet. Normalization of liver tests was preceded by a complete clinical recovery of patients. During

further ambulatory monitoring, most of them over the course of several years, none has developed any of the autoimmune liver diseases.

CONCLUSION

IHTS is a benign and with a strictly gluten-free diet transient occurrence that finds in almost half of children up to two years with active classical type of CD. The increase in serum transaminase levels is in most cases mild and significantly more frequent in patients with earlier clinical expression of the CD.

Conflict of interest: None declared

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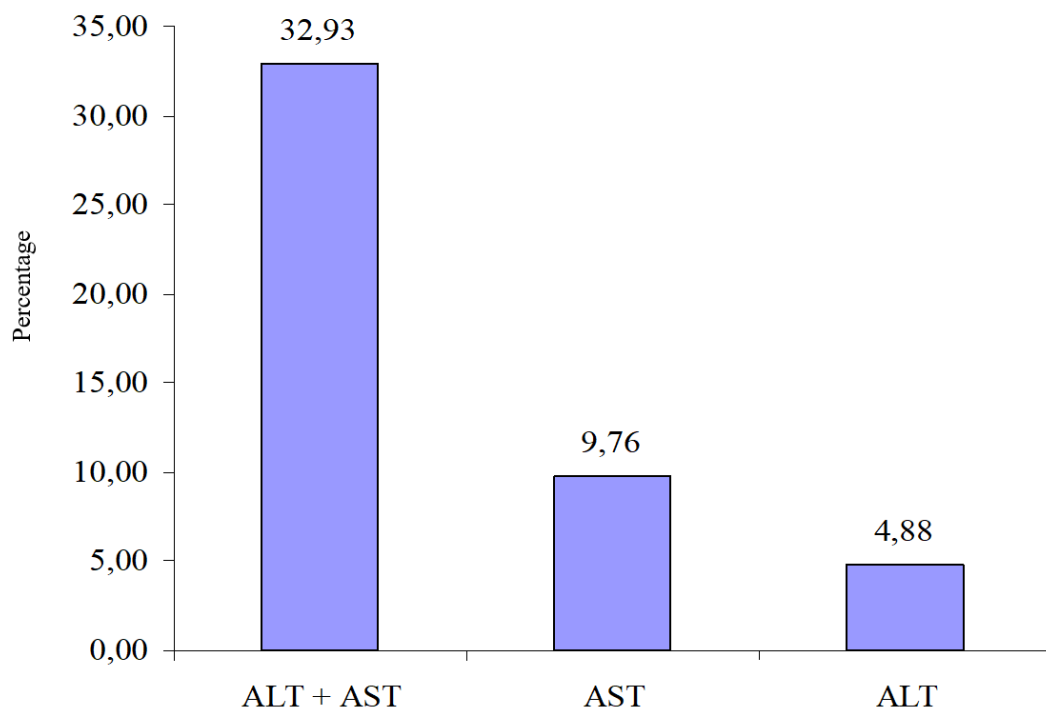


Figure 1. Frequency of isolated hypertransaminasemia in our patients with celiac disease (No 82);

ALT –alanine aminotransferase; AST – aspartate aminotransferase

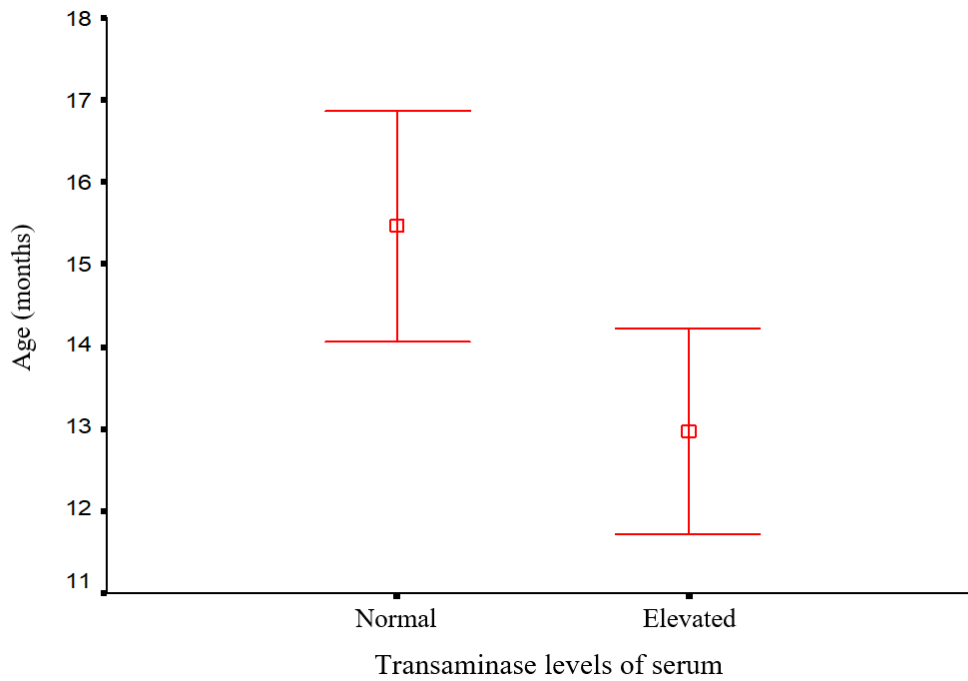


Figure 2. Age of patients with normal and elevated serum transaminase levels during the diagnosis of celiac disease

Paper accepted

Table 1. Differences in percentile of body length, weight deficiency, laboratory nutritional parameters and degree of small intestine mucosal damage in children with celiac disease according to the level of serum transaminases

Observed parameters	Patients without IHTS (No 43)	Patients with IHTS (No 39)	Statistical significance
BL (percentile)	44.24 ± 27.07	35.21 ± 23.29)	ns
Percentage of deviation BW in relation to the ideal	-13.84 ± 9.43	-16.67 ± 8.58	ns
Blood tests			.
Hemoglobin (g/L)	108.07 ± 14.33	102.81 ± 21.22	ns
Iron (µmol/L)	6.18 ± 3.49	6.30 ± 3.73	ns
Total protein (g/L)	58.90 ± 10.00	56.80 ± 8.10	ns
Cholesterol (mmol/L)	3.31 ± 0.70	2.95 ± 0.77	ns
3-glycerides (mmol/L)	1.41 ± 0.48	1.39 ± 0.55	ns
Enteropathy			
Partial (IIIa)	4 (9.30%)	1 (2.56%)	ns
Subtotal (IIIb)	19 (44.19%)	22 (56.41%)	
Total (IIIc)	20 (46.51%)	16 (41.03%)	

BL – body length; BW – body weight; ns – not significant