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 methods.

Results IHTS was found in 39 (47.56%) patients, 27 of whom (69.23%) had elevated levels of both transaminases and 12 of only one – eight of AST and four of ALT. The increase in relation to the aforementioned reference value for ALT was 1.1–10.08 (1.67 ± 1.73), and for AST it was 1.08–7.91 (1.56 ± 1.29) times. In patients with IHTS compared to those with normal transaminasemia, the age of onset of CD was significantly lower (9.83 ± 3.69 vs. 12.95 ± 4.43 months, p = 0.001), as well as the age of 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 old 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 old
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 classical CD, especially in those of 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 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 one-year gluten-free diet [9–12, 16, 17, 19, 20, 21].

The objective of this study was 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 to the mucosa of the small intestine.

METHODS

The objectives of the study were considered on a sample of 82 children (55 female and 27 male) aged 7–24 (14.28 ± 4.41) months, with clinically classical CD, i.e. disease characterized by 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 was obtained, while in the clinical examination, each patient's body length (BL) and weight (BW) was accurately measured and the obtained values were compared to the standard for the appropriate age and sex [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 were compared with standard reference values. In patients with hypertransaminase, the serum creatine phosphokinase activity was determined, so none of them, in addition to the absence of cholestasis and hemolysis, had no elements for rhabdomyolysis. Also, none received any medication following an increase in the serum level of transaminases, nor did they have an intercurrent infection that would produce this effect. The degree of increase in the 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 onset of 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 the degree of damage to the small intestine with the χ² test.

RESULTS

Of the 82 patients, mild to moderate hypertransaminasemia was found in 39 (47.56%), 27 of which (32.93%) had elevated levels of both transaminases, and 12 of only one – eight of AST and four of ALT (Figure 1). The increase in relation to the upper limit of the reference value for ALT was 1.1–10.08 (1.67 ± 1.73) times, and 1.08–7.91 (1.56 ± 1.29) times for AST.

Although there was no significant difference between patients with IHTS and those with normal serum transaminases at the age of introduction of gluten-containing food (4.76 ± 1.13 vs. 5.06 ± 1.23 months; p = 0.302), nor in the 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 months, average 9.83 ± 3.69 months) was significantly earlier than in those with normal serum transaminase levels (4–21 months, 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 months, mean 12.97 ± 3.88 months) was significantly lower than that in children with normal serum transaminases (7–24 months, mean 15.47 ± 4.56 months) (t = 2.53; p = 0.01) (Figure 2).

No significant differences were found by comparing the differences in percentile BL, the degree of BW deviation compared to the 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 to the small intestine mucosa in patients with IHTS and patients with normal serum transaminase values (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 the time of diagnosis of CD [21]. It is most common in children with classical CD, especially in those of the youngest age [16, 17, 21]. Hypertransaminasemia can sometimes be the first or only sign of CD; therefore, in all cases where its presence is unrecognized, testing in
that sense is recommended [16, 21, 26]. Rarely, CD can be associated with severe autoimmune liver disease [12, 26, 27]. In contrast to IHTS associated with 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 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 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 diet 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 two years with classical CD, mild to moderate IHTS was found in almost half of them. In accordance with the findings of other authors, such a 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 older ones. However, the anticipated more frequent appearance of IHTS in patients with lower BL percentile, a more significant BW deficiency, more pronounced laboratory nutritional deficiency indicators, and a more severe degree of damage to the small intestine mucosa inflicted by enterobiasis, was not found. The same findings were also based on the child population, state, and other parameters [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.

Almost always, CD-associated IHTS disappears within one year on gluten-free diet [16, 17]. If it does not, in addition to poor adherence to the gluten-free diet, autoimmune and other liver disorders associated with CD should be considered [12, 17]. Also, because of the possibility of a later onset of autoimmune liver disease, it is recommended that all patients with CD undergo annual liver tests [17]. Normalization of transaminases in all of our patients was established after two to nine months of gluten-free diet. Normalization of liver test results was preceded by a complete clinical recovery of patients. During further ambulatory monitoring, most of them over the course of several years, none have developed any of the autoimmune liver diseases.

**CONCLUSION**

Isolated hypertransaminasemia is a benign, and with a strict gluten-free diet transient, occurrence found in almost half of children up to two years old 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 CD.

**Conflict of interest:** None declared.
REFERENCES

1. Horton RH, Moran LA, Scrimgour GK, Rerry MD, Rawn DJ. Amino acid metabolism. In: Horton RH, Moran LA, Scrimgour GK, Rerry MD, Rawn DJ, editors. Principles of Biochemistry, 4th ed. London: Pearson Educ Ltd; 2006. p. 520–56.

2. McGill MR. The past and present of serum aminotransferases and the future of liver injury biomarkers. EXCLI J. 2016;15:817–28.

3. Woreta TA, Alqahtani SA. Evaluation of abnormal liver tests. Med Clin North Am. 2014;98(1):1–16.

4. Cuadrado A, Crespo J. Hypertransaminasemia in patients with negative viral markers. Rev Esp Enferm Dig. 2004;96(7):484–500.

5. Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seef LF. Diagnosis and monitoring of hepatic injury. II. Recommendations for use of laboratory tests in screening, diagnosis and monitoring. Clin Chem. 2000;46(12):2050–68.

6. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med. 2002;342(17):1266–71.

7. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol. 2017;112(1):18–35.

8. Husby S, Noeke S, Deque G, Cipriano MA, Sofia C. Hypertransaminasemia in celiac disease: Celiac or autoimmune hepatitis? GE Port J Gastroenterol Nutr. 2013;54(1):136–60.

9. Vajro P, Paolella G, Maggiore G, Giordano G. Pediatric celiac disease, cryptogenic hypertransaminasemia, and autoimmune hepatitis. J Pediatr Gastroenterol Nutr. 2013;56(6):663–70.

10. Eliseu L, Lopes S, Duque G, Cipriano MA, Sofia C. Hypertransaminasemia in celiac disease: Celiac or autoimmune hepatitis? GE Port J Gastroenterol. 2013;20(4):162–6.

11. Rubio-Tapia A, Murray JA, Hill ID, Kelly CP, Calderwood AH, Murray JA. Celiac disease-related hepatic involvement in pediatric celiac disease. World J Gastroenterol. 2015;21(19):5813–22.

12. Anania C, De Luca E, De Castro G, Chiesa C, Pacifico L. Liver involvement in pediatric celiac disease. World J Gastroenterol. 2012;18(1):1–16.

13. Lee GJ, Boyle B, Ediger T, Hill I. Hypertransaminasemia in newly diagnosed pediatric patients with celiac disease. J Pediatr Gastroenterol Nutr. 2016;63(3):340–3.

14. Sifford M, Koch A, Lee E, Peña LR. Abnormal liver tests as an initial presentation of celiac disease. Dig Dis Sci. 2007;52(11):3016–8.

15. Arslan N, Buyükgezib B, Öztürk Y, Ozer E. The prevalence of liver function abnormalities in pediatric celiac disease patients and its relation with intestinal biopsy findings. Acta Gastroenterol Belg. 2005;68(4):424–7.

16. Di Biase AR, Colecchia A, Scialo E, Berri R, Viola L, Vestito A, et al. Autoimmune liver diseases in a paediatric population with coeliac disease – a 10-year single-centre experience. Aliment Pharmacol Ther. 2010;31(2):253–60.

17. Anania C, De Luca E, De Castro G, Chiesa C, Pacifico L. Liver involvement in pediatric celiac disease. World J Gastroenterol. 2015;21(19):5813–22.

18. Arslan N, Buyukgezib B, Ozturk Y, Ozer E. The prevalence of liver function abnormalities in pediatric celiac disease patients and its relation with intestinal biopsy findings. Acta Gastroenterol Belg. 2005;68(4):424–7.

19. Walker-Smith JA, Guandalini S, Schmitz J, Shmerling DH, Visakorpi JK. Revised criteria for diagnosis of coeliac disease. Report to working group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child. 1990;65(8):909–11.

20. Needlman RD. Growth and development. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson Textbook of Pediatrics, 17th ed. Philadelphia:WB Saunders Comp; 2004. p. 23–66.

21. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol. 1999;11(10):1185–94.

22. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108(5):656–76; quiz 677.

23. Marciano F, Savoia M, Vajro P. Celiac disease-related hepatic injury: Insights into associated conditions and underlying pathomechanisms. Dig Liver Dis. 2016;48(2):112–9.

24. Necso-Schiavon JL, Schiavon LL. To screen or not to screen? Celiac antibodies in liver diseases. World J Gastroenterol. 2017;23(5):776–91.

25. Parzanese I, Qehajaj D, Patrinicola F, Aralica M, Chiriva-Internati M, Stifter S, et al. Celiac disease: From pathophysiology to treatment. World J Gastrointest Pathophysiol. 2017;8(2):27–38.

26. Hoffmanová I, Sánchez D, Tůcková L, Tlaskalová-Hogenová H. Celiac disease and liver disorders: From putative pathogenesis to clinical implications. Nutrients. 2018;10(7).
Изолована хипертрансаминаземија код деце до две године са класичном целијачком болешћу

Недељко Радловић1, Зоран Лековић2,3, Марија Младеновић4, Владимир Радловић2, Биљана Вулетић5,6, Синиша Дучић2,3, Зоран Голубовић2,3, Мехо Махмутовић7, Снежана Петровић-Тепић8

1 Српско лекарско друштво, Академија медицинских наука, Београд, Србија;
2 Универзитетска дечја клиника, Београд, Србија;
3 Универзитет у Београду, Медицински факултет, Београд, Србија;
4 Медицински центар „Љубо“; Београд, Србија;
5 Клинички центар Крагујевац, Клиника за педијатрију, Крагујевац, Србија;
6 Универзитет у Крагујевцу, Факултет медицинских наука, Крагујевац, Србија;
7 Општа болница Нови Пазар, Нови Пазар, Србија;
8 Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина

САЖЕТАК
Увод/Циљ Изолована хипертрансаминаземија (ИХТС) представља честу, бенигну и пролазну појаву код болесника са целијачком 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.
Методе 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 ESPGAN критеријумима, а активност серумске 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 повишеном нивоима обе трансаминалезе, а код 12 само једне од њих, код осам АЛТ и код четири АСТ. 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 трансаминаземијом узраст појаве првих симптома ЦБ је био знатно мањи (9,83 ± 3,69 месеци наспрам 12,95 ± 4,43 месеца; 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 две године са класичном ЦБ. Хипертрансаминаземија је у већини случајева блага и знатно учесталија код болесника са ранијом клиничком експресијом ЦБ.

Кључне речи: изолована хипертрансаминаземија; класична целијачка болест; деца до две године

DOI: https://doi.org/10.2298/SARH181203026R