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ORIGINAL ARTICLE

Clinical significance of low transaminase levels in children with inflammatory bowel disease

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Abstract

Background Low alanine aminotransaminase (LALT) levels may be seen in patients with inflammatory bowel disease (IBD), but there has been no study about the frequency and its clinical significance. We aimed to analyze the frequency of LALT, and its clinical significance in children with IBD.

Methods The study included the 89 patients with IBD without hepatobiliary involvement. LALT was defined as ALT levels < 5 U/L. Demographic and clinical findings and outcome of the patients with and without LALT were compared.

Results LALT was found 47.1% of the patients. At initial examination, it was more common in female patients (92.3 vs. 41.3%, $P<0.001$) and patients with CD (57.7 vs. 30.2%, $P=0.01$). 75% of the patients with penetrating Crohn's disease (CD) had LALT ($P=0.002$). Hemoglobin (10.4 ± 2.1 vs. 11.7 ± 1.9 g/dL, $P=0.01$), folic acid (5.2 ± 3.3 vs. 8.6 ± 5.9 ng/mL, $P=0.02$) and serum albumin levels (3.6 ± 0.8 vs. 4.7 ± 5 g/dL, $P=0.002$) were significantly low in patients with LALT. LALT was associted with the disease relapse within 2 weeks in 12 of the 16 patients with LALT whereas it was seen in 16 of the 73 patients without LALT during the follow-up (75 vs. 21.9%, $P<0.001$). Additionally, steroid dependency was more common in patients with LALT during the follow-up (62.5 vs. 12.3%, $P<0.001$).

Conclusions LALT is common in children with IBD especially in CD and associated with low hemoglobin, albumin and folic acid levels. It may be a marker of relapse and steroid dependency.

Keywords Children · Inflammatory bowel disease · Low transaminase levels · Vitamin B6

Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is characterized by chronic intestinal inflammation due to a complex interaction between genetic factors, disturbed epithelial barriers, uncontrolled inflammatory signals, loss of tolerance and environmental triggers [1]. Its incidence is increasing in recent years especially in children younger than 6 years-old-age. Classical symptoms of pediatric IBD include bloody diarrhea, abdominal pain and weight loss. Extraintestinal manifestations such as uveitis, arthritis, hepatobiliary and skin involvement are commonly present during the initial admission process or follow-up in patients with IBD. Hepatobiliary involvement is found approximately in 20–30% of the patients. Elevated aminotransferases are the main diagnostic feature of hepatobiliary involvement in IBD, and mainly related with immune-related conditions (such as primary sclerosing cholangitis, autoimmune hepatitis), medication toxicity, thrombotic disorders or underlying primary hepatic disorder unrelated to IBD (such as viral hepatitis, cholelithiasis, IgG4 cholangiopathy) [2].

On the other hand; according to our clinical practice, low alanine aminotransaminase (LALT) levels (ALT < 5 U/L) are generally seen in patients with IBD during the initial diagnostic process or on the follow-up in outpatient clinics. LALT levels is a well-defined clinical entity in patients with chronic kidney disease on hemodialysis due to pyridoxine deficiency, hemodilution and hyperhomocysteinemia.

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Additionally, ALT levels were lower in chronic kidney disease patients on hemodialysis infected with hepatitis C compared to hepatitis C patients without chronic kidney disease. It is mainly related with decreased viremia due to hemodialysis, but other factors such as increased production of hepatocyte growth factor and interferon α, and activation of CD69+ lymphocytes were also shown to reduce the aminotransferase levels in hepatitis Cinfected chronic kidney disease patients on hemodialysis [3]. In a laboratory-based study, LALT levels (< 10 U/L) were found 4.1% of all enzymerequested samples, and associated with alcoholic liver disease, uremia, malnutrition, diabetes, malignancy and infections [4]. In population-based studies, LALT levels were associated with higher mortality risk from all causes in long-term [5, 6].

Pyridoxine deficiency (25–30%) and associated hyperhomocysteinemia have been reported commonly in patients with IBD [7, 8]. Therefore, LALT levels may be seen commonly in patients with IBD. But, there have been no study about the frequency and its clinical significance in children with IBD. Therefore, we aimed to analyze (1) frequency of LALT levels and (2) its clinical significance in children with IBD.

Methods

The study included the 98 patients with IBD in three centers. Nine patients were excluded from study due to hepatobiliary involvement during the initial admission or follow-up. Finally, 89 patients (55 UC, 34 CD) were analyzed. The diagnosis of IBD was made according to Porto criteria [9]. Demographic features, laboratory parameters, disease behavior, medical treatments and outcome of the patients were recorded from the hospital files.

ALT levels measured by an enzymatic calorimetric method that was used in a Roche brand Cobas 8000 biochemical analyzer. LALT was defined as ALT levels < 5 U/L. The presence of LALT was analyzed in two periods; initial diagnostic process (within the 3 months after diagnosis) and follow-up period (3 months after diagnosis). Parameters were compared between the patients with and without LALT.

Steroid-dependency is defined as steroid-dependent if glucocorticoids cannot be tapered to less than 10 mg per day within 3 months of starting steroids, without recurrent disease, or if relapse occurs within 3 months of stopping glucocorticoids [10].

The study was approved by the Karadeniz Technical University, Faculty of Medicine, Scientific Research Ethic Committee, reference number 2018/270.

All calculations were performed using the SPSS 16.0 software, and the continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentage (%). Comparison of the quantitative data between the groups was performed using Student's *t* test in the normally distributed variables, and Mann Whitney *U* test in the non-normally distributed variables. Whereas qualitative data were compared using Chisquare test and P values ≤ 0.05 were considered statistically significant.

Results

The study included 89 patients (55 UC, 34 CD) from 3 centers. Mean age ± SD of the patients were 12.1 ± 3.9 years (range 2 months–18 years, median 11.5 years), and 9 (10.1%) patients were younger than 5 years old age. 50 (56.2%) Patients were female, and 12 (13.5%) were underweight and 4 (4.5%) were stunted. E3 + E4 disease in UC and ileocolonic disease for CD was found 29/55 (52.7%) and 16/34 (47%) of the patients, respectively. Penetrating disese was found in 8 (23.5%) of the 34 patients with CD. Patients were followed for 57.8 ± 33.3 months and 5 (5.6%) patients required surgical resection (Table 1).

LALT levels were found in 26 (29.2%) patients with IBD at initial diagnostic process (within the 3 months after first admission) (Table 2). LALT was more common in female patients (92.3 vs. 41.3%, $P < 0.001$) and patients with CD (57.7 vs. 30.2%, $P = 0.01$). 75% of the eight patients with penetrating CD had LALT ($P = 0.002$). No difference was found in patients with and without LALT when compared the disease extension (E3 + E4 disease for UC, and ileocolonic disease for CD) and nutritional status of the patients. Hemoglobin levels (10.4 ± 2.1 vs. 11.7 ± 1.9 g/dL, $P = 0.01$), folic acid levels (5.2 ± 3.3 vs. 8.6 ± 5.9 ng/mL, $P = 0.02$) and serum albumin levels (3.6 ± 0.8 vs. 4.7 ± 5 g/dL, $P = 0.002$) were significantly low in patients with LALT.

During the follow-up, LALT was seen in 16 (17.9%) patients with 14 ± 7.5 months after diagnosis. None of them had LALT at initial admission. LALT was associted with the disease relapse within 2 weeks in 12 of the 16 patients with LALT whereas it was seen in 16 of the 73 patients without LALT during the follow-up (75 vs. 21.9%, $P < 0.001$). Additionally, steroid dependency was more common in patients with LALT during the follow-up (62.5 vs. 12.3%, $P < 0.001$) (Table 3).

Discussion

In this study, we aimed to analyze the clinical significance of LALT in children with IBD, and we found that (1) LALT was found 47.1% of the patients (29.2% at initial admission, 17.9% during the follow-up), it was more common in female patients and (2) patients with CD and patients with

Table 1 Demographic and clinic characteristics of the patients with IBD

Variables	UC ($n=55$)	CD ($n=34$)	Total ($n=89$)
Age (y), mean ± SD	11.7 ± 4.1	12.7 ± 3.5	12.1 ± 3.9
0 to < 5, *n* (%)	7 (12.7)	2 (5.9)	9 (10.1)
≥ 5 to < 10, *n* (%)	6 (10.9)	4 (11.8)	10 (11.2)
≥ 10, *n* (%)	42 (76.4)	28 (82.4)	70 (78.7)
Gender (female), *n* (%)	29 (52.7)	21 (61.8)	50 (56.2)
Nutrition status, *n* (%)			
Underweight (< − 2*Z*-score)	4 (7.3)	8 (23.5)	12 (13.5)
Stunted (< − 2*Z*-score)	2 (3.6)	2 (5.9)	4 (4.5)
Paris endoscopic classification, *n* (%)			
L1 (terminal ileitis)	–	5 (14.7)	5 (5.6)
L2 (colonic)	–	4 (11.8)	4 (4.5)
L3 (ileocolonic)	–	16 (47.1)	16 (17.9)
L4 (isolated upper disease)	–	–	–
L3 + L4	–	9 (26.5)	9 (10.1)
E1 + L1	1 (1.8)	–	1 (1.1)
E3 + L1	2 (3.6)	–	2 (2.1)
E1 (proctitis)	9 (16.4)	–	9 (10.1)
E2 (left sided colitis)	14 (25.5)	–	14 (15.7)
E3 (extensive)	14 (25.5)	–	14 (15.7)
E4 (pancolitis)	15 (27.2)	–	15 (16.8)
B1 (non stricturing/penetrating)	55 (100)	24(70.6)	79 (87.8)
B2 (stricturing)	–	–	–
B3 (penetrating)	–	8 (23.5)	8 (8.9)
P (perianal disease)	–	2 (5.9)	2 (2.1)
Duration of follow-up (mon), mean ± SD	58.7 ± 32.1	56.9 ± 36.4	57.8 ± 33.3

IBD inflammatory bowel disease, *UC* ulcerative colitis, *CD* Crohn's disease, *SD* standard deviation, – none

penetrating disease, (3) associated with low hemoglobin, folic acid and albumin levels and (4) LALT during the follow-up was associated with disease relapse and steroid dependency.

Low ALT levels were found approximately half of our patients with IBD. Due to lack of study in pediatric population, we could not able compare our results. Only Vadstrup [11] studied subnormal ALT levels (< 9 U/L) in adult patients with colitis, and found that 49 of 50 patients with CD, one of the 67 patients with UC, and five of the six patients with indeterminate colitis had subnormal ALT. None of the eight patients with microscopic colitis had subnormal ALT levels [11]. Similar to our study, subnormal ALT was more common in CD patients. The author concluded that pyridoxine deficiency and hyperoxalemia in patients with CD may cause subnormal ALT, and subnormal ALT levels in CD may be used as a laboratory parameter for differentiating from other types of colitis [11].

Pyridoxine deficiency and associated hyperhomocysteinemia are commonly seen especially in the active phase of IBD patients due to jejunal malabsorption or inadequate oral intake [12]. Both of these conditions are associated with LALT levels on hemodialysis patients with chronic kidney disease. Although we did not study the homocysteine and pyridoxine levels in our study due to retrospective nature, similar mechanisms may be involved IBD patients. Pyridoxine is converted to pyridoxal-5 phosphate that is cofactor for the transamination in the hepatocytes. Supplementation with pyridoxine increases the transaminase levels in pyridoxine deficient patients or in certain group of patients who are at risk for pyridoxine deficiency such as patients on hemodialysis, acholic patients, or using some type of drugs. As in pyridoxine deficiency, folic acid deficiency may also lead the hyperhomocysteinemia that may suppress the transamination. Low levels of folic acid in LALT group supports the effects of hyperhomocysteinemia in our patient group. Additionally, low albumin levels may also decrease the pyridoxal-5 phosphate levels, associated with LALT [13].

Higher frequency of LALT in female patients may be related differences in muscle mass in females compared to males. Additionally, it was shown that sex hormones especially estradiols have negative effect on transaminase levels [14]. The differences of transaminase levels within the genders were shown in population-based studies [15].

Table 2 Demographic and laboratory findings of the patients with and without LALTs at initial admission

Parameters	LALT (+) ($n=26$)	LALT (−) ($n=63$)	P
Age (y), mean ± SD	12.6 ± 3.4	11.9 ± 4.1	0.38
Gender (female), *n* (%)	24 (92.3)	26 (41.3)	**< 0.001**
Type of IBD, *n* (%)			
CD	15 (57.7)	19 (30.2)	**0.01**
UC	12 (46.2)	43 (68.3)	0.05
Disease extension, *n* (%)			
UC (E3 + E4)	9 (34.6)	22 (34.9)	0.90
CD (ileocolonic)	9 (34.6)	16 (25.4)	0.40
Disease behavior for CD			
B3 disease, *n* (%)	6 (23.1)	2 (3.2)	**0.002**
Nutritional status, *n* (%)			
Underweight	3 (11.6)	9 (14.3)	0.73
Stunted	1 (3.9)	3 (4.8)	0.84
Hemoglobin (g/dL), mean ± SD	10.4 ± 2.1	11.7 ± 1.9	**0.01**
Platelet ($\times 10^3$/μL), mean ± SD	482.6 ± 196.9	427.1 ± 196.2	0.20
CRP (mg/L), mean ± SD	4.1 ± 5.5	4.2 ± 5.2	0.90
ESR (mm/h), mean ± SD	31.5 ± 21.8	32 ± 26.5	0.70
Vitamin B12 (pg/mL), mean ± SD	340.1 ± 209	323.9 ± 188.5	0.62
Folic acid (ng/mL), mean ± SD	5.2 ± 3.3	8.6 ± 5.9	**0.02**
Ferritin (mg/L), mean ± SD	48.2 ± 86.9	53.2 ± 90.9	0.60
Albumin (g/dL), mean ± SD	3.6 ± 0.8	4.7 ± 5.0	**0.002**

Bold values indicate that P values are significant ($P < 0.05$). *LALT* low alanine aminotransaminase, *IBD* inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *SD* standard deviation

Table 3 Comparison of final clinical characteristics of the patients with and without LALT during the follow-up

Parameters	LALT (+) ($n=16$)	LALT (−) ($n=73$)	P
Gender (female), *n* (%)	9 (56.3)	41 (56.1)	0.90
Type of IBD, *n* (%)			
CD	4 (25.0)	30 (41.1)	0.23
UC	12 (75.0)	43 (58.9)	0.23
Relapse of disease, *n* (%)	12 (75.0)	16 (21.9)	**0.001**
Outcome, *n* (%)			
Surgery requirement	2 (12.5)	3 (4.1)	0.18
Steroid dependency	10 (62.5)	9 (12.3)	**0.001**
TNF-α usage	3 (18.8)	11 (15)	0.70
Only with 5-ASA	3 (18.8)	18 (24.7)	0.60
Final nutritional status, *n* (%)			
Underweight	2 (12.5)	10 (13.7)	0.90
Stunted	1 (6.3)	3 (4.1)	0.70

Bold values indicate that P values are significant ($P < 0.05$). *LALT* low alanine aminotransaminase, *IBD* inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *TNF* tumor necrosis factor, *5-ASA* 5-aminosalicylic acid

Many biochemical markers such as C-reactive protein and fecal calprotectin were studied for predicting the relapse in patients with IBD. C-reactive protein higher than 20 mL/L and/or fecal calprotectin above 250 μg/g were associated with increased risk of relapse especially in patients with UC [16]. Additionally fecal S100A12 and lactoferrin were also shown reliable marker of relapse in adult patients with IBD [17]. In this study, we found that LALT may be a predictor of relapse. Additionally, we also found that it may be used as a marker of steroid dependency. It is an exaggerated claim

to predict the steroid dependency with only one biochemical analysis. In previous study thrombocytosis at diagnosis predicted cortico steroid-dependency in IBD. Stricturing phenotype of CD and the presence of anemia in UC predicted subsequent course of corticosteroid refractoriness [18].

We analyze the clinical significance of LALT in children with IBD for the first time in this study but we have some limitations: due to retrospective nature of the study, (1) we did not able to analyze the vitamin B6 and homocysteine levels in our patient group, and (2) prospective evaluation of the patients will give more reliable information about the role of LALT in predicting the relapse and steroid dependency.

In conclusion, LALT is common in children with IBD especially in CD and associated with low albumin and folic acid levels. Further prospective studies with additional laboratory parameters (vitamin B6, homocysteine) is needed for the usefulness of LALT in prediction of complicated disease.

Author contributions MC participated in the design of the study and drafted the manuscript and carried out the statistical analysis. ES participated in the design of the study and drafted the manuscript and collected the clinical data. GD collected the clinical data and helped to draft the manuscript. FU collected the clinical data and participated in the design of the study and critical revision of the article for the important content. EK collected the clinical data and participated in the design of the study and critical revision of the article for the important content. All authors had read and approved the final manuscript.

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Compliance with ethical standards

Ethical approval The study was approved by the Karadeniz Technical University, Faculty of Medicine, Scientific Research Ethic Committee, Reference Number 2018/270.

Conflict of interest The author(s) declare that they have no competing interests.

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