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Short communication

Incidence of β-lactoglobulin intolerance among lactose intolerance suspected population and diagnostic approach

Boban Dobrevski[1*], Tanja Petreska Ivanovska[2], Zoran Zhivikj[2], Olgica Sibinovska[1],Olivija Efinska Mladenovska[1], Teodora Brnjarchevska Blazevska[1], Meri Kirijas[1]

[1]*Ss. Cyril and Methodius University in Skopje, Faculty of Medicine, Institute of Immunobiology and Human Genetics, 50 Divizija 6, 1000 Skopje, Republic of North Macedonia*
[2]*Ss. Cyril and Methodius University of Skopje, Faculty of Pharmacy, Institute of Applied Biochemistry, Majka Tereza 47, 1000 Skopje, Republic of North Macedonia*

Introduction

Milk and dairy products have high nutritional value due to its protein, vitamin, mineral and fatty acid content (FAO, 2013). However, regular usage of these products in some individuals may result in manifestation of adverse reactions, such as lactose intolerance (LI) and cow`s milk protein intolerance (CMPI). LI is a syndrome with primarily gastrointestinal symptoms as a result of lactase deficiency in the intestinal mucosa and lactose malabsorption. It can be genetically driven, known as primary LI, where homozygous *LCT*-13910C and *LCT*-22018G variants are coding low lactase activity, or secondary LI due to damaged mucosa. CMPI is an immune mediated reaction to milk`s proteins causing abdominal pain, diarrhea, vomitus, nausea etc. Since LI is highly prevalent in the population, while clinical features of LI and CMPI are similar, the last is often misdiagnosed. Treatment of both conditions is mainly based on food restrictions excluding lactose or cow`s milk proteins, so relevant diagnosis is important in successful disease management (Di Constanzo et al., 2019).

The aim of this study was to determine the incidence of β-lactoglobulin intolerance (the most frequent form of CMPI) in LI suspected population and to identify diagnostic tools that can help to differentiate CMPI and LI.

Materials and methods

The study included 71 patients suspect of LI after medical examination and routine analysis. DNA and sera samples were used to test *LCT* polymorphisms (Sugar Intolerance StripAssay® kit, ViennaLab Diagnostics, Austria) as well as the presence of anti-β-lactoglobulin antibodies (BlueDot Milk Intolerance IgG kit, D-tek, Belgium). Most of the participants, upon entering the study, fulfilled a questionnaire concerning their medical condition, including symptoms, time of their development and type of food that triggered those symptoms. Statistical analysis was done using IBM SPSS Statistic software - Version 23, while p value was calculated using a Chi-square test.

Results and discussion

LCT genotype testing revealed that out of 71 patients suspected to have LI, 41 had the homozygous *LCT*-13910CC/*LCT*-22018GG genotype defining primary LI. Twenty-six patients had the heterozygous, while 4 had the homozygous *LCT*-13910TT/*LCT*-22018AA, both of which coding sufficient lactase activity. No association was found between the sex and the age with the genotype of symptomatic patients suspected to have LI.

Analyzing the presence of anti-β-lactoglobulin antibodies, 8 patients tested positive and 63 patients were detected negative. Sex was not found to be significant, while age had implication on the presence of these

*boban.dobrevski@medf.ukim.edu.mk

antibodies in patients having symptoms χ^2 (2, N=71) =34.58, p<0.00001. Intolerance of β-lactoglobulin was more frequent in childhood (7/8 patients) than in puberty and adolescence (0/8) and in adults (1/8).

Correlation analysis between *LCT* genotype and presence of anti-β-lactoglobulin antibodies in patients suspected to have LI was done and statistical significance was confirmed χ^2 (2, N=71), p=0.22. Seven out of 8 patients with detected antibodies had a *LCT* genotype that is not defining LI. The correct diagnosis in these patients was CMPI instead LI as previously suspected, and cow`s milk proteins should be excluded from their nutrition. Forty patients had the homozygous *LCT*-13910CC/*LCT*-22018GG genotype and were negative for the presence of anti-β-lactoglobulin antibodies. In this group LI was confirmed and total lactose exclusion until retraction of symptoms is usually recommended. However, LI individuals can tolerate different amount of lactose (Di Constanzo et al., 2019), so defining the lactose tolerance range could be beneficial in these patients. Twenty-three patients did not have anti-β-lactoglobulin antibodies or LI defining genotype. These patients could have secondary LI or some other condition and additional tests like Hydrogen Breath Test before excluding lactose from food should be done. Only one patient had anti-β-lactoglobulin antibodies and LI defining genotype and, in this case, both lactose and cow`s milk proteins should be restricted.

Forty-one patients fulfilled a questionnaire concerning their medical condition. To identify possible differential tools in diagnosis establishment, patients were divided in 3 groups, according to the laboratory testing results. Group 1 (G1) included 24 patients with primary LI (who had homozygous LI defining genotype and did not have anti-β-lactoglobulin antibodies present), Group 2 (G2) consisted of 11 patients with presumed secondary LI (who had heterozygous LI non-defining genotype and did not have anti-β-lactoglobulin antibodies present) and Group 3 (G3) covered 6 patients with CMPI (who had heterozygous LI non-defining genotype and had anti-β-lactoglobulin antibodies detected in their sera).

Correlation analysis between type of symptoms and presumed diagnosis was done. Data analysis emerged abdominal pain (G1:20/24; G2:8/11; G3:2/6) χ^2 (2, N=41)=6.1142, p=0.047 and bloating (G1:20/24; G2:7/11; G3:1/6) χ^2(2, N=41)=10.0025, p=0.006 as more frequent symptoms in LI group, while others like nausea (G1:17/24; G2:5/11; G3:2/6), diarrhea (G1:14/24; G2:6/11; G3:2/6) and flatulence (G1:19/24; G2:8/11; G3:2/6) were almost equally present in all groups. Even though statistical significance was not found, eczema was present in 50% of CMPI patients, and only in 25% of patients with primary LI (G1:6/24; G2:6/11; G3:3/6). Literature evidence also pointed to this symptom as more frequent in CMPI (Oranje at al., 2002).

Our analysis found statistical significance between time of symptom appearance and presumed diagnosis χ^2 (4, N=41), p=0.028. Problematic foods triggered symptoms within 2 h of ingestion in most of the LI patients (G1), while CMPI patients experienced symptoms constantly (G3) (occurrence in less than 2h: G1:18/24; G2:5/11; G3:1/6. Symptoms occurred in more than 2 h: G1:4/24; G2:2/11; G3:1/6 and were persistent: G1:2/24; G2:4/11; G3:4/6). This finding is in correlation with the literature (Heine et al., 2017).

Regarding the food that triggers symptoms i.e. milk all participants experienced unpleasant symptoms (G1:24/24; G2:11/11; G3:6/6) due to lactose and proteins. All CMPI patients could not tolerate dairy products compared to 56.16% of LI patients (G1:13/24; G2:6/11; G3:6/6). This difference is due to the fact that lactose in a majority of dairy products is either fermented or extracted. Moreover, LI patients can tolerate small to moderate amount of lactose. All patients tolerated well fruits, vegetables, meat and its products and most of them can digest bread and pasta.

Conclusion

Our analysis revealed that 11.27% of LI suspected patients have β-lactoglobulin intolerance. LI can be developed at any age, while CMPI is more likely to occur during childhood. Even though the clinical manifestation of LI and CMPI is very similar, there are some indicators that can help differentiating these conditions one from another. Time of symptom appearance and type of food that triggers those symptoms seems to be relevant.

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