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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

EPIDEMIOLOGY, CLINICAL FEATURES AND DIAGNOSIS OF CELIAC DISEASE AMONG PEDIATRIC POPULATION IN KAZAKHSTAN

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Abstract.

Background: Issues of epidemiology, clinical presentation and diagnostic approaches of celiac disease (CD) remain important for developing countries. At the moment, there are no objective data on the prevalence of CD/gluten sensitivity among children in Kazakhstan. Thus, this study was aimed at a retrospective evaluation of the prevalence of CD, as well as a prospective study of the clinical manifestations and diagnostic features of CD and gluten sensitivity among children in Kazakhstan.

Methods: Epidemiological data were collected by regions of Kazakhstan for 2019 and was based on the number of confirmed cases of CD among children. To study the clinical features and diagnostic approaches of CD among children a prospective study was conducted during the 2018-2022 in the cities of Astana and Almaty.

Results: The overall prevalence of confirmed cases of CD/gluten allergy among children in Kazakhstan was 5.66 per 100,000 population and showed a high difference between the results obtained with the global and predicted rates. Abdominal pain and nausea were more common in patients with CD. Extra-intestinal manifestations were seen more often in children with gluten allergy. The EMA titer test showed the highest value in CD diagnosis (AUC = 0.857). The IgA and IgG anti-tTG tests had the highest specificity. The sensitivity of genetic analysis in this study was 81.82%, and the specificity was 97.59% (AUC = 0.897). Moreover, the nausea, thirst, IgG anti-tTG test results were independent predictors of disease activity by MARSH.

Conclusions: The results of this study showed high implications for the health systems of developing countries. Thus, the differences between the available and actual epidemiological indicators may lead to large socio-economic consequences. Moreover, this study describes the clinical and diagnostic features of celiac disease and gluten sensitivity, which has a high clinical significance.

Key words. Celiac disease, gluten sensitivity, children, diagnosis, genetics, epidemiology, serologic tests.

Introduction.

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals [1,2]. The diagnosis of CD is guided by initial serologic test for circulating antibodies against tissue transglutaminase and endomysium, followed by confirmation with an upper endoscopy and small intestinal biopsy [3-5]. The pooled global seroprevalence of CD was 1.4%, at the same time prevalence of biopsy-confirmed CD was 0.7% with significantly greater prevalence among children than adults [6]. Moreover, diagnosis rates of CD are increasing, and this appears to be due to a true increase in incidence rather than increased awareness and detection [4].

The availability of serological tests showed that CD is common not only in Europe, but also in developing countries, where the staple food is wheat [7]. According the Savvateeva et al. (2017) CD prevalence among children in Kazakhstan was 0.38% [8], however, these data are disputed due to shortcomings in the diagnostic approach and study design, which could lead to a significant underestimation of the actual prevalence [9]. It was also found that carrier frequencies of HLA-DQB1*02 and HLA-DQB1*03:02 in Kazakhstani healthy blood donors were 38% and 12.5%, respectively. Given the high consumption of wheat products in Kazakhstan, it was previously suggested that the prevalence of CD could be comparable to that registered in Europe [9,10]. Moreover, the low level of awareness of physicians about CD in Kazakhstan was reported [11,12].

Early diagnosis and treatment can reduce and prevent serious complications, but diagnosis of CD can be challenging [13]. CD has a very wide spectrum of manifestations, from asymptomatic disease to severe diarrhea. In addition to typical gastroenterological symptoms (malabsorption syndrome, abdominal pain, distention, vomiting, anorexia and failure to thrive), CD is also characterized by extra-intestinal manifestations such as growth retardation, arthritis and osteopenia, hematological and neurological disorders [14]. If the effects of CD were taken into account, as other causes of death from diarrhea are declining, CD may become a proportionately growing problem among children [15]. CD also had a negative impact on life, including social isolation, recurring symptoms, reduced travel, constant anxiety, and economic burden leading to depression among Kazakhstani patients with CD [16]. Thus, CD remains an issue for pediatric practice and health care, especially in developing countries such as Kazakhstan. The purpose of this study was to investigate the prevalence, clinical and diagnostic features of celiac disease among children in Kazakhstan.

Materials and Methods.

Study design: An epidemiological analysis of the prevalence of CD among the pediatric population of Kazakhstan included a retrospective analysis of registered cases in 2019. The assessment of clinical and diagnostic features for CD was prospective and based on data from an examination of children with suspected CD.

Procedure:

The study of clinical, laboratory and endoscopic manifestations of celiac disease was carried out during the 2018-2022 on the basis of city clinics in Astana and Almaty (Kazakhstan). A total of 2016 primary pediatric patients with suspected celiac disease were examined. Age limit for study participants: from 1 year

to 18 years. Patients at the initial stage underwent a physical examination and questionnaires for the presence of symptoms of CD. Immunological research methods included analysis for EMA (endomysium) IgA, Anti-tTG (tissue transglutaminase) IgA and IgG, Anti-DGP (deamidated gliadin peptides) IgA and IgG. Genetic testing of patients with celiac disease was aimed at determining characteristic alleles of HLA-DQ2 and HLA-DQ8. For pathomorphological diagnosis of biopsy specimens, the classification of the degrees of enteropathy according to Marsh was used.

Patient inclusion criteria are based on risk groups identified by the World Organization for Gastroenterology (OMGE) [17], which include people who are more likely to develop celiac disease. The disease occurs more often in the presence of certain diseases and factors: close relatives of a patient with celiac disease, down syndrome, autoimmune thyroiditis, type 1 diabetes mellitus - damage to the pancreas, leading to an increase in blood sugar levels, lymphocytic colitis - an inflammatory disease of the colon with an increased accumulation of specific immune cells - lymphocytes - in the intestinal wall, irritable bowel syndrome - a complex of functional (caused by dysfunction of the intestine in the absence of structural damage to its tissue) intestinal disorders, which is characterized by pain and/or discomfort in the abdomen, relieved after defecation (emptying the rectum), chronic active hepatitis – long-term (more than 6 months) inflammation of the liver, lesions of the skin and mucous membranes.

Statistical analysis:

Data analysis was conducted using Jamovi version 1.2.17. Percentages were computed for qualitative variables. We performed $\chi 2$-test to evaluate independent associations of the independent variables. ROC analysis was used to analyze the sensitivity and specificity of laboratory tests. A statistically significant difference was accepted at a p-value of less than 5%.

Ethics Approval:

The study was approved by the Local Ethics Committee of the NpJSC "Astana Medical University" (extract from protocol No. 4, held on 20.12.2018). All aspects of this study were carried out in accordance with the 1964 Helsinki Declaration on Ethical Standards. Parents and/or legal guardians were informed of the purposes of the study prior to its implementation and signed informed consent to participate in the study.

Results.

Data on the prevalence of celiac disease/gluten allergy among children were analyzed. Data were collected on the number of children with a confirmed diagnosis in the regions of Kazakhstan; the results are presented in Figure 1 and Table 1 of suppl. materials. As a result of frequency analysis, 4 levels of prevalence of the disease per 100,000 children were identified: < 1.9 – low, 1.9 - 4.22 – medium, 4.23 - 7.42 – high, and > 7.43 – very high. The overall prevalence of celiac disease and gluten allergy among children in Kazakhstan was 5.66 per 100,000 population.

Comparative frequency analysis revealed the following levels of prevalence of celiac disease and gluten allergy among the child population by regions: a low level in Kostanay, North

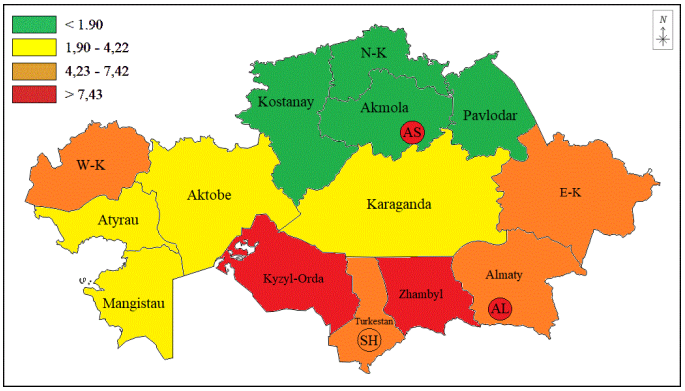

Figure 1. *Prevalence of celiac disease/gluten allergy per 100,000 children in Kazakhstan. Cities of republican significance: AS – Astana, AL – Almaty, SH – Shymkent. Regions: E-K – East Kazakhstan region, N-K – North Kazakhstan region, W-K – West Kazakhstan region.*

Kazakhstan, Akmola and Pavlodar regions (< 1.9 per 100,000 children), an average level in Atyrau, Karaganda, Aktobe and Mangystau regions (1.9 - 4.22 per 100,000 child population), a high level in Shymkent, West Kazakhstan, East Kazakhstan, Turkestan and Almaty regions (4.23 - 7.42 per 100,000 child population) and a very high level in Almaty and Astana cities and Kyzyl-Orda region (> 7.43 per 100,000 child population).

In this study, we provide screening data for 2016 children with suspected celiac disease or gluten allergy. Positive serological markers confirming the diagnosis of celiac disease were obtained in 121 (6%) pediatric patients. Thus, 121 pediatric patients took part in the study, among them 53 (43.8%) were males and 68 (56.2%) females. A comprehensive diagnostic examination of the sample made it possible to verify the following final diagnoses: celiac disease – 28 (23.15%), gluten allergy – 80 (66.1%), other pathology – 13 (10.75%).

Among the studied patients, gastrointestinal symptoms were noted in 109 (90.1%) children. The distribution of individual gastrointestinal symptoms relative to the final diagnosis is presented in Table 1.

Comparing individual symptoms of the gastrointestinal tract in 3 study groups, significant differences were determined by the following symptoms: abdominal pain ($p < 0.001$), fecal smearing and nausea ($p < 0.05$). Abdominal pain was more common among individuals diagnosed with celiac disease, and to a lesser extent among patients with gluten allergy. Fecal smearing was found in only one healthy patient. Nausea was more frequently identified among individuals diagnosed with celiac disease, and to a lesser extent among patients with other pathology.

Extra-intestinal manifestations were noted in 105 (86.8%) of the studied patients. The most common extraintestinal manifestations occurred among individuals with gluten allergy (95.0%), to a lesser extent among patients diagnosed with celiac disease (71.4%), and among participants with other pathology (69.2%), $p < 0.001$. The most common extraintestinal manifestations of celiac/gluten allergy were signs of anemia, skin rashes, and immunosuppression.

The EMA titer was studied in 65 (53.7%) patients, including 5 (38.5%) among children with other pathology, 35 (43.75%) among children with gluten allergy, and 25 (89.3%) among

Table 1. *Distribution of gastrointestinal symptoms (N=121).*

Gastrointestinal symptoms	Confirmed diagnosis			p
	Other pathology n=13	Gluten allergy n=80	Celiac disease n=28	
Gastrointestinal symptoms (n, %)	11 (84,6)	71 (88,8)	27 (96,4)	0,395
Irregular stool (n, %)	3 (23,1)	21 (26,3)	12 (42,9)	0,218
Unstable stool (n, %)	1 (7,7)	19 (23,8)	3 (10,7)	0,174
Painful defecation (n, %)	0	0	1 (3,6)	0,187
Loss of appetite (n, %)	3 (23,1)	18 (22,5)	1 (3,6)	0,083
Belching (n, %)	1 (7,7)	14 (17,5)	6 (21,4)	0,557
Nausea (n, %)	1 (7,7)	9 (11,3)	9 (32,1)	0,023*
Abdominal pain (n, %)	8 (61,5)	27 (33,8)	21 (75.0)	< 0,001**
Pungent odor from the mouth (n, %)	1 (7,7)	3 (3,8)	1 (3,6)	0,792
Vomiting (n, %)	1 (7,7)	8 (10,0)	4 (14,3)	0,764
Poor weight gain (n, %)	4 (30,8)	33 (41,3)	12 (42,9)	0,743
Bloating (n, %)	3 (23,1)	20 (25,0)	6 (21,4)	0,927
Fecal smearing (n, %)	1 (7,7)	0	0	0,015*
Thirst (n, %)	0	1 (1,3)	1 (3,6)	0,627
Streaks of blood in the stool	1 (7,7)	2 (2,5)	3 (10,7)	0,202
Strong odor of stool (n, %)	0	4 (5,0)	0	0,346
White coating on the tongue (n, %)	1 (7,7)	0	1 (3,6)	0,086
Fecal incontinence (n, %)	0	1 (1,3)	0	0,772
Diarrhea (n, %)	0	6 (7,5)	1 (3,6)	0,447

* p < 0,05
** p < 0,001
Other pathology: other functional disorders of the gastrointestinal tract

Table 2. *Results of serological tests among children.*

Serological tests	Confirmed diagnosis			p	Se	Sp	AUC
	Other pathology	Gluten allergy	Celiac disease				
EMA titer positive (%), N=65	0 (of 5)	14.3% (of 35)	84.0% (of 25)	< 0.001	84.5%	87.5%	0.857
Anti-tTG IgA positive (%), N=118	0 (of 10)	8.8% (of 80)	57.1% (of 28)	< 0.001	57.1%	92.2%	0.747
Anti-DGP IgA positive (%), N=117	0 (of 10)	11.3% (of 80)	37.0% (of 27)	0.002	37.0%	90%	0.635
Anti-tTG IgG positive (%), N=118	0 (of 10)	5.0% (of 80)	57.1% (of 28)	< 0.001	57.1%	95.6%	0.763
Anti-DGP IgG positive (%), N=114	0 (of 10)	89.6% (of 77)	77.8% (of 27)	< 0.001	77.8%	20.7%	0.492

Se – sensitivity, Sp – specificity
Other pathology: other functional disorders of the gastrointestinal tract

patients diagnosed with celiac disease. The results of the EMA titer analysis depending on the diagnosis are presented in Table 2. A positive EMA titer was determined in 84% of children with celiac disease, and 14.3% of patients with gluten allergy. According to the results of the ROC analysis, the sensitivity of the EMA titer test for diagnosing celiac disease in children in this study was 84%, the specificity was 87.5% (AUC = 0.857).

IgA anti-tTG and anti-DGP antibodies were tested in 118 and 117 patients, respectively. Among healthy children, anti-tTG IgA and anti-DGP IgA were tested in 10 (76.9%) patients. Anti-tTG IgA and anti-DGP IgA test results were obtained from all children with gluten allergy. Among patients diagnosed with celiac disease, the results of anti-tTG IgA were in all the subjects, while anti-DGP IgA in 27 (96.4%) of the subjects. Differences in the results of anti-tTG IgA and anti-DGP IgA in the three study groups were significant ($p<0.001$ and $p<0.05$, respectively). The sensitivity of the analysis for the determination of IgA anti-tTG had a sensitivity of 57.15%, a specificity of 92.22% (AUC=0.747). Similar parameters of the test for anti-DGP IgA were as follows: sensitivity – 37.04%, specificity – 90% (AUC=0.635).

The total amount of IgA antibodies was studied in 35 patients, including 1 patient with other pathology, 22 children with gluten allergy, and 12 among patients diagnosed with celiac disease. This analysis, due to the small sample size, did not reveal significant differences among the three comparison groups ($p>0.05$).

Anti-tTG and anti-DGP IgG antibodies were tested in 118 and 114 (94.2%) patients, respectively. Among children with other patology, anti-tTG IgG and anti-DGP IgG were tested in 10

patients. Among children with gluten allergy, anti-tTG IgG and anti-DGP IgG were tested in 80 and 77 patients, respectively. Among patients diagnosed with celiac disease, the results of anti-tTG IgG were in all the subjects, at the same time, anti-DGP IgG in 27 of the subjects. Anti-tTG IgG was positive in 5% of the patients with gluten allergy and 57% of patients diagnosed with celiac disease ($p < 0.001$). At the same time, the analysis for anti-DGP IgG showed a positive result in 90% of patients with gluten allergy, and 78% of those with celiac disease ($p < 0.001$). ROC analysis of the test for IgG anti-tTG showed a sensitivity of 57.14%, a specificity of 95.56% (AUC = 0.763). At the same time, the ROC analysis of the anti-DGP IgG test for celiac disease had a sensitivity of 77.78%, a specificity of 20.69%, with an AUC value of 0.492. A significant positive correlation was found between IgG anti-tTG test result and MARSH disease activity ($r=0.447$, $p<0.001$). To a lesser extent, the result of the Anti-DGP IgG test correlated with disease activity ($r=0.295$, $p<0.05$).

Biopsies were obtained in 33 (27.3%) of the study subjects, including 13 (16.25%) children with gluten allergy and 21 (75.0%) children diagnosed with celiac disease. Biopsy results in children with gluten allergy and celiac disease are presented in Table 3. Among patients with gluten allergy, 12 (92.3%) had MARSH 0, this patient was also positive for EMA titer (1:20) and anti-DGP IgG, however, the result of the genetic study was negative. Among those studied with a diagnosis of celiac disease, the biopsy result was as follows: MARSH 1 in 8, MARSH 2 in 11, and MARSH 3 in 2 patients.

Genetic analysis was determined in 94 patients, including 8 (61.5%) children with other pathology, 75 (93.75%) children with gluten allergy, and 11 (39.3%) patients with celiac disease. A positive genetic analysis was found in 1 (12.5%) patient with other pathology, 1 (1.33%) patient with gluten allergy, and 9 (81.8%) children with celiac disease ($\chi2 = 60.1$, $p<0.001$), the sensitivity of genetic analysis in this study was 81.82%, and the specificity was 97.59%, ROC analysis showed a significant result (AUC = 0.897). Variants in the DQ2.5 gene of HLA class II were found in 5 (45.4%) examined children, DQ8 in 4 (36.4%) examined children, and variants in the DQ2 gene were detected in 2 (18.2%) study participants. The positive genetic analysis found in two study participants appeared to be variants in the DQ8 gene in the patient with gluten allergy, and in the DQ2.5 gene in the participant with other pathology.

Table 3. *Biopsy results in children (N=34).*

Biopsy results	**Confirmed diagnosis**	
	Gluten allergy (n=13)	**Celiac disease (n=21)**
MARSH 0	12 (92.3%)	0
MARSH 1	0	8 (38.1%)
MARSH 2	1 (7.7%)	11 (52.4%)
MARSH 3	0	2 (9.5%)

Discussion.

This study was devoted to the investigation of the clinical features of celiac disease in children, including the study of the prevalence and diagnostic approach of this disease in Kazakhstan. The prevalence of confirmed cases of celiac disease/gluten allergy among children in Kazakhstan was 5.66 per 100,000 population, which corresponds to 0.0057%. However, these results were inconsistent with the overall global prevalence of CD [6] and the assumptions of previously published results for Kazakhstan [8-10]. Such results are of high risk for health system planning in Kazakhstan, as in other developing countries, since there are no valid data on the prevalence of CD and the expected high number of undiagnosed cases, which may lead to severe long-term consequences of the disease. The reason for such misleading data may be due to an imperfect diagnostic system and lack of awareness of the population and healthcare providers about CD [11]. Given the heavy socio-economic and psychological burden of this disease, both for patients and for the healthcare system, timely and accurate diagnosis of celiac disease remains an urgent problem in Kazakhstan.

The study noted different levels of CD prevalence in different cities/regions of Kazakhstan. The difference in prevalence across the regions of Kazakhstan may be associated with the peculiarities of the culture and the level of organization of healthcare system; however, further epidemiological studies are needed to study the spread of CD in Kazakhstan.

The first step in CD diagnosing is to study its complaints and symptoms. In this connection, in order to improve diagnostic approaches, the clinical manifestation of celiac disease in children was studied and compared with those who were diagnosed with gluten allergy or the absence of celiac disease and gluten allergy. A thorough knowledge of the differences and overlaps in the clinical manifestations of celiac disease, gluten allergy, and other gastrointestinal disorders will assist clinicians in the differential diagnosis process [18-20]. In the current study, the various gastrointestinal manifestation of CD was noted in 90% of children, however, their overall prevalence among children with other pathology, children diagnosed with gluten allergy and CD did not have statistically significant differences. Also, the following intestinal manifestations did not have significant differences between the comparison groups: irregular and unstable stool, painful defecation, loss of appetite, frequent belching, pungent odor from the mouth, vomiting, poor weight gain, bloating, thirst, streaks of blood in the stool, sharp stool odor, yellow coating on the tongue, fecal incontinence and diarrhoea ($p>0.05$). This was due to the fact that these manifestations are not pathognomic for certain symptoms and are only a manifestation of a general violation of the digestive tract. At the same time, it was found that abdominal pain ($p<0.001$) and nausea ($p<0.05$) were more common in patients with CD compared with patients from other groups. Moreover, the presence of nausea and thirst were independent predictors of disease activity according to MARSH ($p<0.05$). Extra-intestinal manifestations were seen more often in children with gluten allergy, to a lesser extent among patients with CD ($p<0.001$).

The use of various serological methods for diagnosing CD in children showed different diagnostic value. Since the tests used were negative in children with other pathology, they were comparatively evaluated in patients with gluten allergy and CD. A positive titer of EMA, Anti-tTG IgA, Anti-DGP IgA, Anti-tTG IgG was significantly more common in children diagnosed

with CD compared to patients with gluten allergy ($p<0.05$). In turn, a positive test result for the determination of Anti-DGP IgG was among patients with gluten allergy. In the ROC analysis, the EMA titer test (AUC = 0.857) showed the highest value with a sensitivity of 84% and a specificity of 87.5%. The IgA and IgG anti-tTG tests had the highest specificity: 92.22% and 95.56%, respectively. The sensitivity of genetic analysis in this study was 81.82%, and the specificity was 97.59% (AUC = 0.897). A significant positive correlation was also found between IgG anti-tTG test result and MARSH disease activity ($p<0.001$). To a lesser extent, the result of the Anti-DGP IgG test correlated with disease activity ($r=0.295$, $p<0.05$). Thus, the high specificity of the IgG anti-tTG test and genetic analysis was of value in clinical practice for diagnosing CD in children, and the level of IgG anti-tTG can be a predictor of disease activity. In other studies, the tTG-IgA antibody was showed as the diagnostic tool of choice to detect CD [3,21]. High sensitivity and specificity of the EMA titer test allows considering this analysis as a screening method for diagnosing CD, which is also emphasized in a study evaluating the cost-effectiveness of this test in adult population [22]. Although EMA may serve as an acceptable first-line screening tool in low-risk populations, higher cost and user-dependent accuracy make tTG-IgA the preferred choice in most pediatric populations [3,23,24].

Study limitations.

This study had a number of limitations related to data collection and prospective study design. First, the data obtained on the prevalence of celiac disease among the pediatric population was most likely not reliable. However, the disconcerting results obtained should form the basis for improving the health care system in Kazakhstan and other developing countries. Secondly, not all participants in the screening study underwent diagnostic examinations to the same extent due to various organizational and economic issues, which could affect the assessment of the diagnostic value of certain serological / genetic tests. Moreover, the patient cohort was small. In this connection, a more extensive study with a clear design is recommended.

Conclusion.

Thus, this study examined the prevalence of celiac disease in the pediatric population of Kazakhstan and showed a high difference between the results obtained with the global and predicted rates. These findings should form the basis for further epidemiological studies in Kazakhstan and other developing countries. This study also described the clinical manifestations of celiac disease and gluten allergy in children, which is of value in clinical practice to improve knowledge in the differential diagnosis of these conditions. Moreover, the diagnostic value of various serological and genetic tests was described in terms of the level of awareness of medical personnel in a developing country. These results may further contribute to the development of cost-effective diagnostic approaches for celiac disease in children.

Declarations.

Conflict of interest statement: The authors declare that they have no conflict of interest.

Ethics approval: The study was approved by the Local Ethics Committee of the NpJSC "Astana Medical University" (extract from protocol No. 4, held on 20.12.2018).

Consent for publication: Not applicable

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