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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 ВИНТИ 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 ВИНТИ 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. Корректур авторам не высылаются, 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 computer-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 საყურადღებო!

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, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების 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 ფხიხლებში 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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CHRONIC URTICARIA AND LEAD EXPOSURE: EVALUATION OF IMMUNOLOGICAL MARKERS

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Abstract.

Background: Chronic urticaria (CU) is a mast-cell-driven disorder involving inflammatory and autoimmune mechanisms. Lead can affect immune function, but its relationship with CU has been little studied.

Objective: To examine the association of blood lead levels (BLLs) with CU, active wheals at blood sampling, and selected immunological markers.

Methods: This single-center case-control study included 303 participants from Western Georgia: 211 patients with CU and 92 healthy controls. BLLs were measured by inductively coupled plasma mass spectrometry. Eosinophils, total IgE, histamine, anti-IgE autoantibodies, and FcεRIα autoantibodies were assessed. BLL ≥10 µg/dL was used as the predefined analytical threshold for higher lead exposure. Associations were evaluated using group comparisons, Spearman correlation, and age-adjusted regression analyses.

Results: BLLs were higher in patients with CU than in healthy controls. BLL ≥10 µg/dL was present in 66.8% of patients and 33.7% of controls (OR 3.96; 95% CI 2.36–6.66; $p < 0.001$), and the association remained significant after adjustment for age (aOR 4.07; 95% CI 2.38–6.96; $p < 0.001$). Within the CU group, higher BLLs were associated with eosinophilia and higher histamine, anti-IgE, and FcεRIα autoantibody levels, but not with total IgE. BLL ≥10 µg/dL was also associated with active wheals at blood sampling after adjustment for age (aOR 3.36; 95% CI 1.75–6.45; $p < 0.001$). In an exploratory analysis, the dual-positive anti-IgE/FcεRIα group had the highest frequencies of BLL ≥10 µg/dL (83.3%) and active wheals (92.4%). Compared with patients in whom neither autoantibody was elevated, the dual-positive group had the strongest age-adjusted association with BLL ≥10 µg/dL (aOR 5.49; 95% CI 2.38–12.70; $p < 0.001$).

Conclusions: Patients with CU had higher BLLs than healthy controls. Within the CU group, higher BLLs were associated with eosinophilia, histamine, anti-IgE and FcεRIα autoantibodies, and active wheals, but not with total IgE. These associations require confirmation in prospective studies.

Key words. Chronic urticaria, lead exposure, blood lead level, anti-IgE autoantibodies, FcεRIα autoantibodies, histamine, eosinophils.

Introduction.

Chronic urticaria (CU) is characterized by recurrent wheals, angioedema, or both for more than six weeks and is a heterogeneous mast-cell-driven disorder [1-3]. Mast-cell and basophil activation are central to its pathogenesis, but the underlying mechanisms vary among patients. These include IgE-dependent autoallergic pathways, autoimmune mechanisms

involving antibodies against IgE or the high-affinity IgE receptor (FcεRI), and other inflammatory processes [4-8].

Lead is a widespread environmental toxicant with neurological, hematological, renal, and cardiovascular effects and can also alter immune function [9-15]. Experimental studies have reported effects on lymphocyte function, cytokine signaling, antigen-presenting cells, and Th1/Th2 balance [14-17]. Associations between heavy-metal exposure and allergic disease have also been investigated [18-20]. However, evidence specifically linking lead exposure with CU is limited, and little is known about the relationship between blood lead levels (BLLs) and immunological markers in these patients.

This question is relevant in Georgia, where population studies have documented substantial childhood lead exposure [21,22]. BLLs declined following public-health interventions, but subsequent surveillance has shown that lead exposure remains a concern [23,24]. Current public-health guidance does not define a safe level of lead exposure, particularly in children [9,25-27]. In this study, BLL ≥10 µg/dL was used only as an analytical threshold to identify participants with higher exposure and not as a safety threshold.

The aim of this study was to compare BLLs in patients with CU and healthy controls from Western Georgia and to examine the relationship between BLL and eosinophils, total IgE, histamine, anti-IgE autoantibodies, and FcεRIα autoantibodies. We also examined the presence of active wheals at blood sampling and, in an exploratory analysis, combined anti-IgE/FcεRIα autoantibody profiles.

Materials and Methods.

Study Design and Setting: This single-center observational case-control study was conducted at Medical Clinic “XXI SAUKUNE” in Kutaisi, Western Georgia, between April 2019 and April 2026. The study included 303 participants: 211 patients with chronic urticaria (CU) and 92 healthy controls. Participants were categorized as <18 or ≥18 years for age-stratified analyses.

Study Population:

The CU group included 83 participants aged <18 years and 128 aged ≥18 years. CU was defined as recurrent wheals, angioedema, or both for more than six weeks, in accordance with international urticaria guidelines [1].

The control group included 92 apparently healthy individuals from the same geographic region: 31 aged <18 years and 61 aged ≥18 years. Controls had no history of CU or systemic autoimmune disease.

Exclusion criteria were acute urticaria, urticarial vasculitis, mastocytosis, active parasitic or other clinically significant infection, malignancy, severe systemic autoimmune disease, and known occupational lead exposure.

Clinical Assessment and Sample Collection:

The presence of visible urticarial wheals was recorded at the time of blood sampling. Of the 211 patients with CU, 153 had active wheals and 58 had no visible wheals at sampling.

Blood samples were obtained after a 72-hour interruption of antihistamines and systemic corticosteroids. Venous blood was collected and processed according to the requirements of the respective laboratory assays.

Laboratory Measurements:

BLLs were measured in whole blood by inductively coupled plasma mass spectrometry (ICP-MS). Eosinophil percentage was determined using an automated hematology analyzer, with peripheral blood smear evaluation when required.

Total IgE and histamine were measured using standardized immunoassays. Anti-IgE autoantibodies and autoantibodies against the α -subunit of the high-affinity IgE receptor (Fc ϵ RI α) were measured by commercially available ELISA assays (Eagle Biosciences, USA). Analyses were performed according to the manufacturers' instructions with routine internal quality control.

Analytical Definitions:

BLL ≥ 10 $\mu\text{g/dL}$ was used as the analytical threshold for higher lead exposure. This threshold was selected to identify a more highly exposed subgroup in a population with substantial background lead exposure and was not considered a public-health safety threshold.

Categorical analyses used the following thresholds: eosinophilia $>5\%$, total IgE >200 IU/mL, histamine ≥ 1 ng/mL, anti-IgE autoantibodies ≥ 1 ng/mL, and Fc ϵ RI α autoantibodies >7.5 U/mL. Total IgE >200 IU/mL was used as a conservative common threshold for clearly elevated total IgE across age groups. Anti-IgE ≥ 1 ng/mL was used as the predefined analytical threshold based on the assay reporting characteristics, and Fc ϵ RI α >7.5 U/mL was based on the assay reference data.

Autoantibody-Defined Immunophenotypes:

Patients with measurements of both anti-IgE and Fc ϵ RI α autoantibodies were classified into four mutually exclusive profiles: neither autoantibody elevated, anti-IgE only, Fc ϵ RI α only, and both elevated. These profiles were used for exploratory comparisons of BLL, active wheals at blood sampling, and age and were not considered established mechanistic CU endotypes.

Statistical Analysis:

Statistical analyses were performed using Stata version 18. Continuous variables are presented as median and interquartile range (IQR) and were compared using the Mann–Whitney U test. Categorical variables are presented as n (%) and were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Associations between categorical variables were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Correlations between BLL and continuous immunological markers were assessed separately in the CU and control groups using Spearman's rank correlation coefficient (ρ).

Binary logistic regression was used to examine the association of BLL ≥ 10 $\mu\text{g/dL}$ with CU case status and, separately within the CU group, with active wheals at blood sampling. Both models were adjusted for age group (<18 vs ≥ 18 years), and adjusted odds ratios (aORs) with 95% CIs were reported.

For the exploratory immunophenotype analysis, multinomial logistic regression was performed with the group in which neither autoantibody was elevated as the reference category. The model included BLL category (≥ 10 vs <10 $\mu\text{g/dL}$) and age group (<18 vs ≥ 18 years).

Analyses were based on available measurements for each variable; denominators therefore varied for biomarkers with missing measurements. All tests were two-sided, with $p < 0.05$ considered statistically significant.

Ethical Considerations:

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Akaki Tsereteli State University (Approval No. 09/2019, April 15, 2019). Written informed consent was obtained from adult participants and from the parents or legal guardians of participants younger than 18 years.

Results.

Study Population and Blood Lead Levels:

A total of 303 participants were included: 211 patients with chronic urticaria (CU) and 92 healthy controls. BLL measurements were available for all participants.

BLLs were significantly higher in patients with CU than in healthy controls. Median BLL was 10.9 $\mu\text{g/dL}$ (IQR 8.85–12.8) in the CU group and 7.25 $\mu\text{g/dL}$ (IQR 5.58–10.43) in the control group ($p < 0.001$) (Table 1 and Figure 1).

BLL ≥ 10 $\mu\text{g/dL}$ was found in 141/211 (66.8%) patients with CU and 31/92 (33.7%) healthy controls ($p < 0.001$). Participants with BLL ≥ 10 $\mu\text{g/dL}$ had higher odds of CU than those with BLL <10 $\mu\text{g/dL}$ (OR 3.96; 95% CI 2.36–6.66; $p < 0.001$). The association remained significant after adjustment for age group (<18 vs ≥ 18 years) (aOR 4.07; 95% CI 2.38–6.96; $p < 0.001$). Age group was not independently associated with CU case status (aOR 1.11; 95% CI 0.64–1.94; $p = 0.707$).

Immunological Profile of Patients with Chronic Urticaria Compared with Healthy Controls.

Patients with chronic urticaria (CU) differed significantly from healthy controls across the immunological parameters examined (Table 2).

Median eosinophil percentage was 6.0% (IQR 3.0–9.0) in patients with CU and 3.0% (IQR 2.0–4.0) in healthy controls ($p < 0.001$). Eosinophilia ($>5\%$) was present in 110/211 (52.1%) patients with CU and 11/92 (12.0%) controls ($p < 0.001$).

Median total IgE was 288 IU/mL (IQR 210–376.5) in the CU group and 12 IU/mL (IQR 8–30.25) in controls ($p < 0.001$). Total IgE >200 IU/mL was found in 174/211 (82.5%) patients with CU and 2/92 (2.2%) controls ($p < 0.001$).

Histamine measurements were available for 204 patients with CU and all 92 controls. Median histamine was 1.6 ng/mL (IQR 1.0–1.9) and 0.6 ng/mL (IQR 0.4–0.7), respectively ($p < 0.001$). Histamine ≥ 1 ng/mL was present in 156/204 (76.5%) patients with CU and 6/92 (6.5%) controls ($p < 0.001$).

Anti-IgE autoantibodies were measured in 208 patients with CU and all 92 controls. Median anti-IgE concentration was 1.0 ng/mL (IQR 0–45.25) in the CU group and 0 ng/mL (IQR 0–0) in controls ($p < 0.001$). Using the predefined analytical threshold of ≥ 1 ng/mL, elevated anti-IgE was found in 106/208 (51.0%) patients with CU and 7/92 (7.6%) controls ($p < 0.001$).

FcεRIα autoantibodies were measured in 208 patients with CU and 75 controls. Median recorded concentrations were 0 U/mL (IQR 0–47.25) and 0 U/mL (IQR 0–0), respectively; despite identical medians, the distributions differed significantly ($p<0.001$). FcεRIα concentrations >7.5 U/mL were found in 93/208 (44.7%) patients with CU and 6/75 (8.0%) controls ($p<0.001$).

Association Between Blood Lead Levels and Immunological Markers Within the Chronic Urticaria Group.

Patients with chronic urticaria (CU) were stratified according to the predefined analytical threshold into a higher-BLL group ($\text{BLL} \geq 10 \mu\text{g/dL}$; $n=141$) and a lower-BLL group ($\text{BLL} < 10 \mu\text{g/dL}$; $n=70$). Immunological markers were compared between the two groups (Table 3).

Eosinophil percentages were significantly higher in patients with $\text{BLL} \geq 10 \mu\text{g/dL}$ than in those with $\text{BLL} < 10 \mu\text{g/dL}$ [median 7.0% (IQR 3.0–10.0) vs 4.0% (IQR 2.0–6.75); $p<0.001$]. Eosinophilia ($>5\%$) was present in 86/141 (61.0%) patients in the higher-BLL group and 24/70 (34.3%) in the lower-BLL group. $\text{BLL} \geq 10 \mu\text{g/dL}$ was associated with higher odds of eosinophilia (OR 3.00; 95% CI 1.65–5.45; $p<0.001$).

Total IgE did not differ significantly between BLL groups. Median total IgE was 299 IU/mL (IQR 206–389) in the higher-BLL group and 276 IU/mL (IQR 237–340) in the lower-BLL group ($p=0.160$). Total IgE >200 IU/mL was present in 113/141 (80.1%) and 61/70 (87.1%), respectively, and was not significantly associated with $\text{BLL} \geq 10 \mu\text{g/dL}$ (OR 0.60; 95% CI 0.26–1.34; $p=0.208$).

Histamine measurements were available for 134 patients in the higher-BLL group and all 70 patients in the lower-BLL group. Median histamine was 1.6 ng/mL (IQR 1.1–1.98) and 1.4 ng/mL (IQR 0.8–1.7), respectively ($p=0.007$). Histamine ≥ 1 ng/mL was present in 110/134 (82.1%) patients with $\text{BLL} \geq 10 \mu\text{g/dL}$ and 46/70 (65.7%) patients with $\text{BLL} < 10 \mu\text{g/dL}$ (OR 2.39; 95% CI 1.23–4.64; $p=0.009$).

Anti-IgE autoantibody measurements were available for 138 patients in the higher-BLL group and all 70 patients in the lower-BLL group. Median anti-IgE concentration was 5.2 ng/mL (IQR 0–62.25) and 0 ng/mL (IQR 0–2.75), respectively ($p<0.001$). Elevated anti-IgE (≥ 1 ng/mL) was present in 85/138 (61.6%) patients with $\text{BLL} \geq 10 \mu\text{g/dL}$ and 21/70 (30.0%) patients with $\text{BLL} < 10 \mu\text{g/dL}$ (OR 3.74; 95% CI 2.02–6.93; $p<0.001$).

FcεRIα autoantibody measurements were also available for 138 patients in the higher-BLL group and all 70 patients in the lower-BLL group. Median FcεRIα concentration was 8.0 U/mL (IQR 0–74.75) and 0 U/mL (IQR 0–12.75), respectively ($p<0.001$). FcεRIα >7.5 U/mL was present in 74/138 (53.6%) patients with $\text{BLL} \geq 10 \mu\text{g/dL}$ and 19/70 (27.1%) patients with $\text{BLL} < 10 \mu\text{g/dL}$ (OR 3.10; 95% CI 1.66–5.79; $p<0.001$).

Correlation Between Blood Lead Levels and Immunological Markers.

To assess relationships with BLL independently of the 10 $\mu\text{g/dL}$ threshold, BLL was analyzed as a continuous variable using Spearman's rank correlation. Analyses were performed separately in patients with chronic urticaria (CU) and healthy controls (Table 4 and Figure 2).

In the CU group, BLL correlated positively with eosinophil percentage ($\rho=0.229$; $p<0.001$), histamine concentration ($\rho=0.158$; $p=0.024$), anti-IgE autoantibody concentration ($\rho=0.217$; $p=0.002$), and FcεRIα autoantibody concentration ($\rho=0.167$; $p=0.016$). These correlations were modest in magnitude. Total IgE was not significantly correlated with BLL ($\rho=0.103$; $p=0.137$).

No significant correlations between BLL and the investigated immunological markers were observed in healthy controls (Table 4).

Blood Lead Levels and Immunological Markers According to the Presence of Active Wheals at Blood Sampling.

At the time of blood sampling, 153 of 211 patients with chronic urticaria (72.5%) had visible active wheals, whereas 58 patients (27.5%) had no active wheals.

$\text{BLL} \geq 10 \mu\text{g/dL}$ was present in 113/153 (73.9%) patients with active wheals and 28/58 (48.3%) patients without active wheals (Table 5). $\text{BLL} \geq 10 \mu\text{g/dL}$ was associated with higher odds of active wheals at blood sampling (OR 3.03; 95% CI 1.61–5.68; $p<0.001$). Median BLL was also higher in patients with active wheals than in those without active wheals [11.2 $\mu\text{g/dL}$ (IQR 9.8–13.8) vs 9.85 $\mu\text{g/dL}$ (IQR 5.43–12.33); $p<0.001$].

Patients with active wheals had higher eosinophil percentages [median 7.0% (IQR 3.0–9.0) vs 3.0% (IQR 2.0–6.75); $p<0.001$] and higher histamine concentrations [1.7 ng/mL (IQR 1.5–2.1) vs 0.8 ng/mL (IQR 0.6–0.9); $p<0.001$] than patients without active wheals.

Anti-IgE and FcεRIα autoantibody concentrations were also higher in patients with active wheals. Median anti-IgE concentration was 2.2 ng/mL (IQR 0–64.5) compared with 0 ng/mL (IQR 0–9.5) in patients without active wheals ($p=0.001$). Median FcεRIα concentration was 11.0 U/mL (IQR 0–89) compared with 0 U/mL (IQR 0–0) ($p<0.001$).

Total IgE did not differ significantly between the groups [median 289 IU/mL (IQR 233–378) vs 277 IU/mL (IQR 209–360); $p=0.343$].

In the age-adjusted logistic regression model, $\text{BLL} \geq 10 \mu\text{g/dL}$ remained associated with active wheals at blood sampling (aOR 3.36; 95% CI 1.75–6.45; $p<0.001$). Age group was not significantly associated with active wheals in this model ($p=0.104$).

Age-Specific Patterns of Blood Lead Exposure and Immunological Markers.

Age-stratified analyses compared participants aged <18 years with those aged ≥ 18 years. The CU group included 83 participants aged <18 years and 128 aged ≥ 18 years; the control group included 31 and 61 participants, respectively (Table 6).

Within the CU group, BLLs were higher in participants aged <18 years than in adults. Median BLL was 11.8 $\mu\text{g/dL}$ (IQR 10.05–13.95) in the younger group and 10.6 $\mu\text{g/dL}$ (IQR 6.95–12.50) in adults ($p<0.001$). $\text{BLL} \geq 10 \mu\text{g/dL}$ was present in 63/83 (75.9%) younger patients and 78/128 (60.9%) adults ($p=0.024$).

Median total IgE was also higher in younger patients [342 IU/mL (IQR 265–435) vs 276 IU/mL (IQR 205.75–345); $p<0.001$]. However, the proportion with total IgE >200 IU/mL did not differ significantly between age groups [70/83 (84.3%) vs 104/128 (81.3%); $p=0.565$].

Table 1. Blood Lead Levels in Patients with Chronic Urticaria and Healthy Controls.

Parameter	CU patients (n=211)	Healthy controls (n=92)	p-value
BLL, µg/dL, median (IQR)	10.9 (8.85–12.8)	7.25 (5.58–10.43)	<0.001
BLL ≥10 µg/dL, n (%)	141 (66.8)	31 (33.7)	<0.001

Note: Data are presented as median (IQR) or n (%). BLL, blood lead level; CU, chronic urticaria; IQR, interquartile range. Continuous BLL values were compared using the Mann–Whitney U test and categorical distributions using Pearson's χ^2 test.

Table 2. Immunological Characteristics of Patients with Chronic Urticaria and Healthy Controls.

Parameter	CU patients	Healthy controls	p-value
Eosinophils, %, median (IQR)	6.0 (3.0–9.0)	3.0 (2.0–4.0)	<0.001
Eosinophilia >5%, n/N (%)	110/211 (52.1)	11/92 (12.0)	<0.001
Total IgE, IU/mL, median (IQR)	288 (210–376.5)	12 (8–30.25)	<0.001
Total IgE >200 IU/mL, n/N (%)	174/211 (82.5)	2/92 (2.2)	<0.001
Histamine, ng/mL, median (IQR)	1.6 (1.0–1.9)	0.6 (0.4–0.7)	<0.001
Histamine ≥1 ng/mL, n/N (%)	156/204 (76.5)	6/92 (6.5)	<0.001
Anti-IgE autoantibodies, ng/mL, median (IQR)	1.0 (0–45.25)	0 (0–0)	<0.001
Elevated anti-IgE ≥1 ng/mL, n/N (%)	106/208 (51.0)	7/92 (7.6)	<0.001
FcεRIα autoantibodies, U/mL, median (IQR)	0 (0–47.25)	0 (0–0)	<0.001
Elevated FcεRIα >7.5 U/mL, n/N (%)	93/208 (44.7)	6/75 (8.0)	<0.001

Note: Data are presented as median (IQR) or n/N (%). CU, chronic urticaria; IgE, immunoglobulin E; FcεRIα, α-subunit of the high-affinity IgE receptor; IQR, interquartile range. Continuous variables were compared using the Mann–Whitney U test and categorical variables using Pearson's χ^2 test or Fisher's exact test, as appropriate. Values recorded as 0 for anti-IgE represented concentrations <1 ng/mL; values recorded as 0 for FcεRIα represented concentrations below the assay limit of quantification (LoQ, 0.694 U/mL). FcεRIα >7.5 U/mL was used as the assay-based cut-off for categorical analysis.

Table 3. Immunological Markers According to Blood Lead Level Within the Chronic Urticaria Group.

Parameter	BLL <10 µg/dL (n=70)	BLL ≥10 µg/dL (n=141)	OR (95% CI)†	p-value
Eosinophils, %, median (IQR)	4.0 (2.0–6.75)	7.0 (3.0–10.0)	—	<0.001
Eosinophilia >5%, n/N (%)	24/70 (34.3)	86/141 (61.0)	3.00 (1.65–5.45)	<0.001
Total IgE, IU/mL, median (IQR)	276 (237–340)	299 (206–389)	—	0.160
Total IgE >200 IU/mL, n/N (%)	61/70 (87.1)	113/141 (80.1)	0.60 (0.26–1.34)	0.208
Histamine, ng/mL, median (IQR)	1.4 (0.8–1.7)	1.6 (1.1–1.98)	—	0.007
Histamine ≥1 ng/mL, n/N (%)	46/70 (65.7)	110/134 (82.1)	2.39 (1.23–4.64)	0.009
Anti-IgE autoantibodies, ng/mL, median (IQR)	0 (0–2.75)	5.2 (0–62.25)	—	<0.001
Elevated anti-IgE ≥1 ng/mL, n/N (%)	21/70 (30.0)	85/138 (61.6)	3.74 (2.02–6.93)	<0.001
FcεRIα autoantibodies, U/mL, median (IQR)	0 (0–12.75)	8.0 (0–74.75)	—	<0.001
Elevated FcεRIα >7.5 U/mL, n/N (%)	19/70 (27.1)	74/138 (53.6)	3.10 (1.66–5.79)	<0.001

Note: Data are presented as median (IQR) or n/N (%). BLL, blood lead level; CU, chronic urticaria; IgE, immunoglobulin E; FcεRIα, α-subunit of the high-affinity IgE receptor; IQR, interquartile range; OR, odds ratio; CI, confidence interval. Continuous variables were compared using the Mann–Whitney U test and categorical variables using Pearson's χ^2 test or Fisher's exact test, as appropriate. †ORs represent the odds of the indicated elevated immunological marker in patients with BLL ≥10 µg/dL relative to those with BLL <10 µg/dL. Total IgE >200 IU/mL was used as a conservative common threshold across age groups. Anti-IgE ≥1 ng/mL and FcεRIα >7.5 U/mL were based on the respective assay reference data. Values recorded as 0 for anti-IgE represented concentrations <1 ng/mL; values recorded as 0 for FcεRIα represented concentrations below the assay limit of quantification (LoQ, 0.694 U/mL). Histamine measurements were available for 134/141 patients and anti-IgE and FcεRIα measurements for 138/141 patients in the BLL ≥10 µg/dL group.

Table 4. Spearman Correlations Between Blood Lead Levels and Immunological Markers in Patients with Chronic Urticaria and Healthy Controls.

Immunological marker	CU patients, n	p	p-value	Healthy controls, n	p	p-value
Eosinophils (%)	211	0.229	<0.001	92	0.185	0.078
Total IgE (IU/mL)	211	0.103	0.137	92	−0.028	0.791
Histamine (ng/mL)	204	0.158	0.024	92	0.079	0.454
Anti-IgE autoantibodies (ng/mL)	208	0.217	0.002	92	0.012	0.911
FcεRIα autoantibodies (U/mL)	208	0.167	0.016	75	−0.081	0.490

Note: p, Spearman's rank correlation coefficient; CU, chronic urticaria; BLL, blood lead level; IgE, immunoglobulin E; FcεRIα, α-subunit of the high-affinity IgE receptor. Correlations were calculated between continuous BLL values and each immunological marker. Statistical significance was defined as p<0.05.

Table 5. Blood Lead Levels and Immunological Markers According to the Presence of Active Wheals at Blood Sampling in Patients with Chronic Urticaria.

Parameter	Active wheals present (n=153)	No active wheals (n=58)	p-value
BLL, µg/dL, median (IQR)	11.2 (9.8–13.8)	9.85 (5.43–12.33)	<0.001
BLL ≥10 µg/dL, n/N (%)	113/153 (73.9)	28/58 (48.3)	<0.001
Eosinophils, %, median (IQR)	7.0 (3.0–9.0)	3.0 (2.0–6.75)	<0.001
Total IgE, IU/mL, median (IQR)	289 (233–378)	277 (209–360)	0.343
Histamine, ng/mL, median (IQR)	1.7 (1.5–2.1)	0.8 (0.6–0.9)	<0.001
Anti-IgE autoantibodies, ng/mL, median (IQR)	2.2 (0–64.5)	0 (0–9.5)	0.001
FcεRIα autoantibodies, U/mL, median (IQR)	11.0 (0–89)	0 (0–0)	<0.001

Note: Data are presented as median (IQR) or n/N (%), as indicated. CU, chronic urticaria; BLL, blood lead level; IgE, immunoglobulin E; FcεRIα, α-subunit of the high-affinity IgE receptor; IQR, interquartile range. Active wheals were defined as visible urticarial wheals present at the time of blood sampling. Histamine, anti-IgE, and FcεRIα measurements were available for 150 of 153 patients with active wheals and for all 58 patients without active wheals. Continuous variables were compared using the Mann–Whitney U test; categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate.

Table 6. Age-Specific Distribution of Blood Lead Levels and Immunological Markers in Patients with Chronic Urticaria and Healthy Controls.

Parameter	CU <18 years (n=83)	CU ≥18 years (n=128)	p-value	Controls <18 years (n=31)	Controls ≥18 years (n=61)	p-value
BLL, µg/dL, median (IQR)	11.8 (10.05–13.95)	10.6 (6.95–12.50)	<0.001	10.4 (7.95–11.55)	6.2 (5.20–8.00)	<0.001
BLL ≥10 µg/dL, n/N (%)	63/83 (75.9)	78/128 (60.9)	0.024	19/31 (61.3)	12/61 (19.7)	<0.001
Eosinophils, %, median (IQR)	5.0 (3.0–9.0)	6.0 (3.0–9.0)	0.678	3.0 (2.0–5.0)	2.0 (2.0–3.0)	0.023
Eosinophilia >5%, n/N (%)	41/83 (49.4)	69/128 (53.9)	0.522	6/31 (19.4)	5/61 (8.2)	0.119
Total IgE, IU/mL, median (IQR)	342 (265–435)	276 (205.75–345)	<0.001	10 (8–38.5)	16 (8–24)	0.747
Total IgE >200 IU/mL, n/N (%)	70/83 (84.3)	104/128 (81.3)	0.565	1/31 (3.2)	1/61 (1.6)	1.000
Histamine, ng/mL, median (IQR)	1.6 (1.0–2.1)	1.5 (1.1–1.75)	0.074	0.6 (0.4–0.7)	0.6 (0.4–0.7)	0.937
Histamine ≥1 ng/mL, n/N (%)	62/81 (76.5)	94/123 (76.4)	0.984	3/31 (9.7)	3/61 (4.9)	0.401
Anti-IgE autoantibodies, ng/mL, median (IQR)	17 (1–55)	0 (0–23)	<0.001	0 (0–0)	0 (0–0)	0.774
Anti-IgE ≥1 ng/mL, n/N (%)	66/83 (79.5)	40/125 (32.0)	<0.001	2/31 (6.5)	5/61 (8.2)	1.000
FcεRIα autoantibodies, U/mL, median (IQR)	8 (0–89)	0 (0–21)	0.018	0 (0–0)	0 (0–0)	0.255
FcεRIα >7.5 U/mL, n/N (%)	43/83 (51.8)	50/125 (40.0)	0.094	1/30 (3.3)	5/45 (11.1)	0.392

Note: Data are presented as median (IQR) or n/N (%). CU, chronic urticaria; BLL, blood lead level; IgE, immunoglobulin E; FcεRIα, α-subunit of the high-affinity IgE receptor; IQR, interquartile range. Participants were stratified as <18 years and ≥18 years. Total IgE >200 IU/mL was used as a conservative common threshold across age groups. Anti-IgE ≥1 ng/mL and FcεRIα >7.5 U/mL were based on the respective assay reference data. Continuous variables were compared using the Mann–Whitney U test and categorical variables using Pearson's χ^2 test or Fisher's exact test, as appropriate. Denominators vary where individual biomarker measurements were unavailable.

Table 7. Autoantibody-Defined Immunophenotypes and Their Association with Blood Lead Levels, Active Wheals, and Age in Patients with Chronic Urticaria.

Characteristic	Neither autoantibody elevated (n=75)	Anti-IgE only (n=40)	FcεRIα only (n=27)	Both elevated (n=66)	p-value
Immunophenotype distribution, n (%)	75 (36.1)	40 (19.2)	27 (13.0)	66 (31.7)	—
BLL ≥10 µg/dL, n/N (%)	34/75 (45.3)	30/40 (75.0)	19/27 (70.4)	55/66 (83.3)	<0.001
Active wheals at blood sampling, n/N (%)	43/75 (57.3)	23/40 (57.5)	23/27 (85.2)	61/66 (92.4)	<0.001
Age <18 years, n/N (%)	14/75 (18.7)	26/40 (65.0)	3/27 (11.1)	40/66 (60.6)	<0.001

Note: The analysis included 208 patients with CU with measurements of both anti-IgE and FcεRIα autoantibodies. Immunophenotypes were defined using anti-IgE ≥1 ng/mL and FcεRIα >7.5 U/mL. Active wheals refer to visible urticarial wheals present at blood sampling. BLL, blood lead level; CU, chronic urticaria; IgE, immunoglobulin E; FcεRIα, α-subunit of the high-affinity IgE receptor. Comparisons were performed using Pearson's χ^2 test or Fisher's exact test, as appropriate. These immunophenotypes were defined for exploratory analysis and do not represent established mechanistic CU endotypes.

Table 8. Age-Adjusted Association of BLL ≥ 10 $\mu\text{g/dL}$ with Autoantibody-Defined Immunophenotype Membership in Patients with Chronic Urticaria.

Autoantibody-defined immunophenotype	Age-adjusted OR (BLL ≥ 10 vs < 10 $\mu\text{g/dL}$)	95% CI	p-value
Neither autoantibody elevated	1.00 (reference)	—	—
Anti-IgE only	3.26	1.32–8.05	0.011
Fc ϵ RI α only	2.92	1.13–7.51	0.026
Both autoantibodies elevated	5.49	2.38–12.70	< 0.001

Note: Multinomial logistic regression was performed among 208 patients with CU. The group with neither autoantibody elevated was the reference outcome category. The model included BLL category (≥ 10 vs < 10 $\mu\text{g/dL}$) and age group (< 18 vs ≥ 18 years). Adjusted ORs represent the association of BLL ≥ 10 $\mu\text{g/dL}$ with membership in each autoantibody-positive immunophenotype relative to the reference group. OR, odds ratio; CI, confidence interval; BLL, blood lead level; IgE, immunoglobulin E; Fc ϵ RI α , α -subunit of the high-affinity IgE receptor.

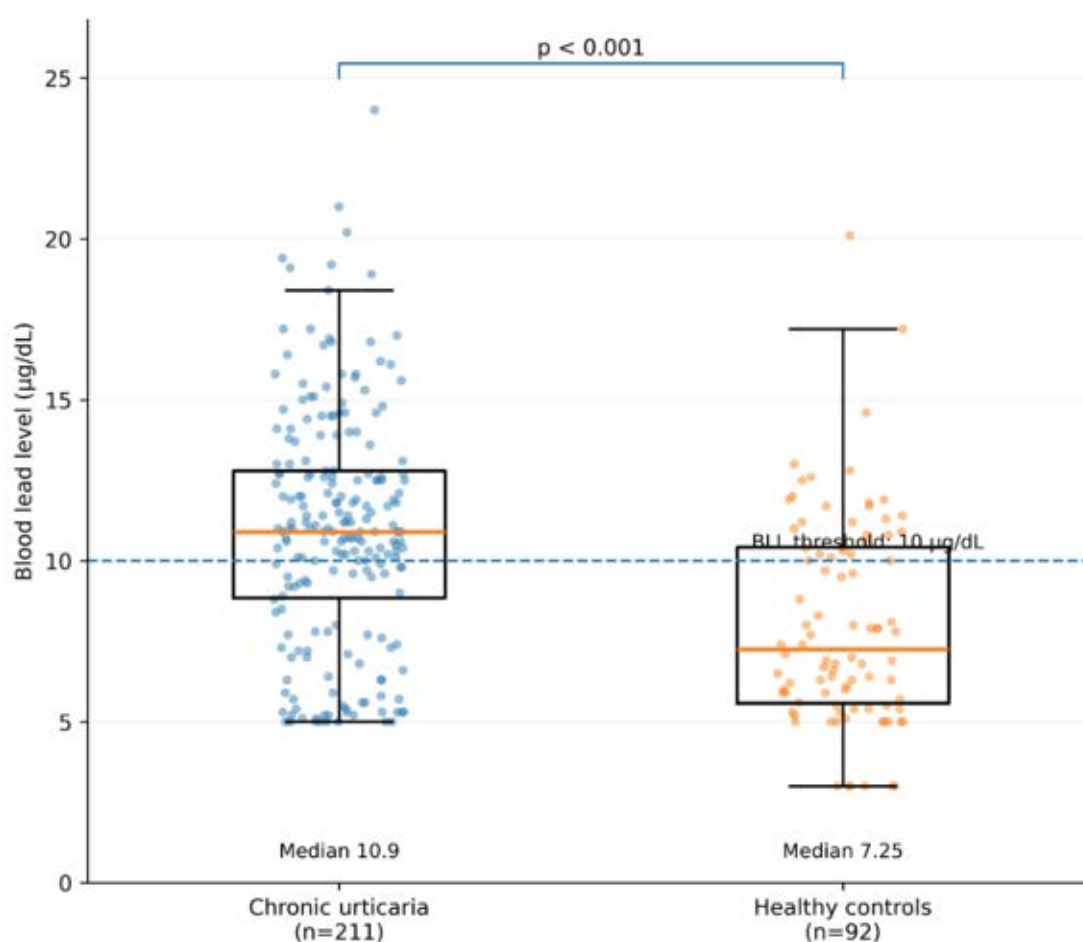


Figure 1. Distribution of BLLs in patients with chronic urticaria and healthy controls. Individual observations are shown with box-and-whisker summaries. The dashed horizontal line indicates the analytical threshold of BLL ≥ 10 $\mu\text{g/dL}$.

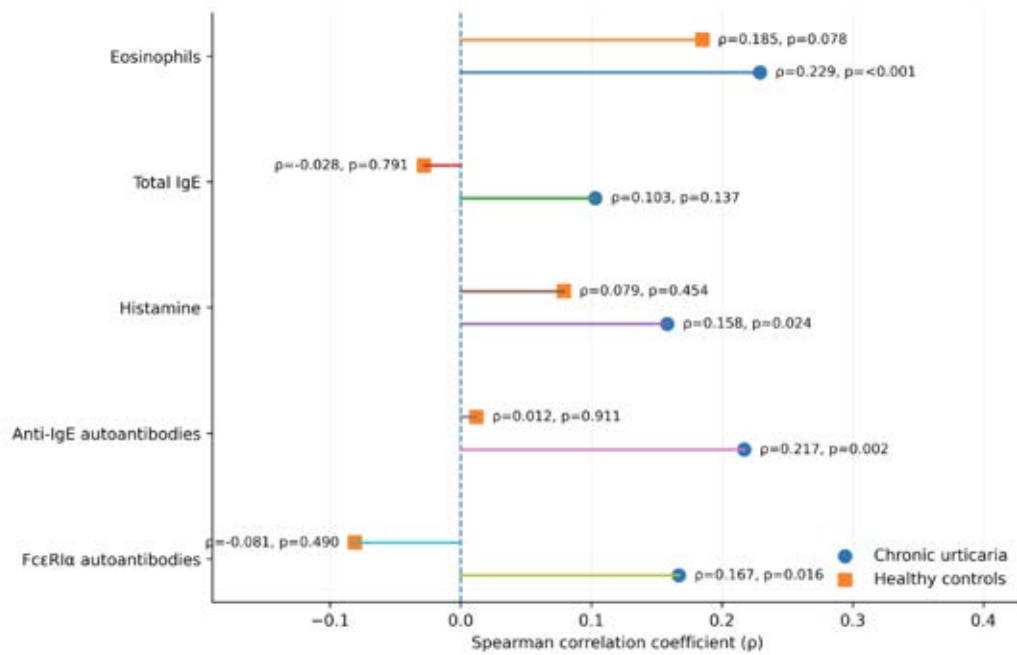


Figure 2. Spearman correlation coefficients (ρ) between BLL and eosinophils, total IgE, histamine, anti-IgE autoantibodies, and FcεRIα autoantibodies in patients with CU and healthy controls. Positive and negative values indicate the direction of the correlation.

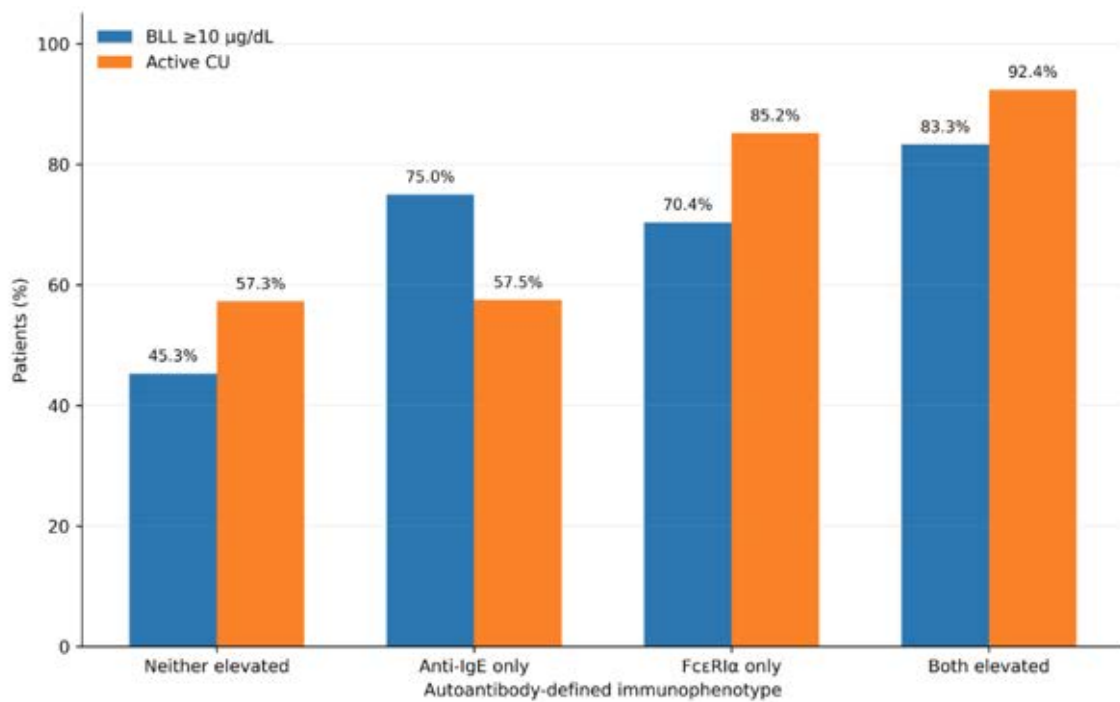


Figure 3. Proportions of patients with BLL ≥ 10 $\mu\text{g/dL}$ and active wheals at blood sampling across the four autoantibody-defined immunophenotypes. Differences across groups were significant for both BLL ≥ 10 $\mu\text{g/dL}$ and active wheals (both $p < 0.001$).

The largest age-related difference was observed for anti-IgE autoantibodies. Median anti-IgE concentration was 17 ng/mL (IQR 1–55) in patients aged <18 years and 0 ng/mL (IQR 0–23) in adults ($p<0.001$). Elevated anti-IgE (≥ 1 ng/mL) was present in 66/83 (79.5%) younger patients and 40/125 (32.0%) adults ($p<0.001$).

Median FcεRIα autoantibody concentration was also higher in younger patients [8 U/mL (IQR 0–89) vs 0 U/mL (IQR 0–21); $p=0.018$]. In contrast, the proportion with FcεRIα >7.5 U/mL did not differ significantly [43/83 (51.8%) vs 50/125 (40.0%); $p=0.094$].

No significant age-related differences were observed within the CU group for eosinophil percentage, eosinophilia $>5\%$, histamine concentration, or histamine ≥ 1 ng/mL (Table 6).

Among healthy controls, younger participants also had higher BLLs. Median BLL was 10.4 μg/dL (IQR 7.95–11.55) in controls aged <18 years and 6.2 μg/dL (IQR 5.20–8.00) in adults ($p<0.001$). BLL ≥ 10 μg/dL was present in 19/31 (61.3%) younger controls and 12/61 (19.7%) adult controls ($p<0.001$). Eosinophil percentage was modestly higher in younger controls ($p=0.023$), whereas no significant age-related differences were observed for total IgE, histamine, anti-IgE, or FcεRIα autoantibodies.

Autoantibody-Defined Immunophenotypes and Their Association with Blood Lead Levels and Active Wheals.

An exploratory analysis was performed in 208 patients with CU who had measurements of both anti-IgE and FcεRIα autoantibodies. Four mutually exclusive immunophenotypes were defined using anti-IgE ≥ 1 ng/mL and FcεRIα >7.5 U/mL: neither autoantibody elevated, anti-IgE only, FcεRIα only, and both autoantibodies elevated.

Of the 208 patients, 75 (36.1%) had neither autoantibody elevated, 40 (19.2%) had elevated anti-IgE only, 27 (13.0%) had elevated FcεRIα only, and 66 (31.7%) had elevations of both autoantibodies (Table 7).

The frequency of BLL ≥ 10 μg/dL differed across the four groups ($p<0.001$): 34/75 (45.3%) in the group with neither autoantibody elevated, 30/40 (75.0%) in the anti-IgE-only group, 19/27 (70.4%) in the FcεRIα-only group, and 55/66 (83.3%) in the dual-positive group.

Active wheals at blood sampling also differed across immunophenotypes ($p<0.001$). They were present in 43/75 (57.3%) patients with neither autoantibody elevated, 23/40 (57.5%) in the anti-IgE-only group, 23/27 (85.2%) in the FcεRIα-only group, and 61/66 (92.4%) in the dual-positive group (Figure 3).

Age distribution differed significantly across the four groups ($p<0.001$). Participants aged <18 years accounted for 14/75 (18.7%) of the group with neither autoantibody elevated, 26/40 (65.0%) of the anti-IgE-only group, 3/27 (11.1%) of the FcεRIα-only group, and 40/66 (60.6%) of the dual-positive group.

Because both BLL and immunophenotype distribution differed by age, multinomial logistic regression was performed with adjustment for age group (<18 vs ≥ 18 years). The group with neither autoantibody elevated was used as the reference outcome category. BLL ≥ 10 μg/dL was associated with membership in the anti-IgE-only phenotype (aOR 3.26; 95%

CI 1.32–8.05; $p=0.011$), the FcεRIα-only phenotype (aOR 2.92; 95% CI 1.13–7.51; $p=0.026$), and the dual-positive phenotype (aOR 5.49; 95% CI 2.38–12.70; $p<0.001$) (Table 8). The largest age-adjusted association was observed for the dual-positive phenotype.

Discussion.

Patients with chronic urticaria (CU) had higher blood lead levels (BLLs) than healthy controls, and BLL ≥ 10 μg/dL was more frequent among patients with CU. The association remained significant after adjustment for age. Within the CU group, higher BLL was associated with eosinophilia, histamine, and anti-IgE and FcεRIα autoantibodies, but not with total IgE. Higher BLL was also associated with the presence of active wheals at blood sampling. These findings indicate that the relationship between lead exposure and CU in this cohort was linked to selected inflammatory and autoreactive immune features rather than to generalized elevation of circulating IgE.

Lead has recognized immunomodulatory effects in addition to its neurological, hematological, renal, and cardiovascular toxicity. Experimental studies have shown effects on lymphocyte function, cytokine regulation, antigen-presenting cells, and Th1/Th2 balance [14–17]. Lead exposure has also been examined in relation to allergic disease [18–20]. CU, however, is a heterogeneous mast-cell-driven disorder in which autoallergic, autoimmune, and other inflammatory mechanisms may coexist [1,3,5,8]. Evidence directly examining lead exposure in CU is limited. The present findings therefore identify an association that requires confirmation rather than establishing lead exposure as a cause of CU.

The relationships observed with eosinophils and histamine are relevant to the inflammatory characteristics of CU. Eosinophils participate in the inflammatory network of chronic spontaneous urticaria [28], while histamine released from activated mast cells and basophils is a major mediator of wheals and pruritus [1,3,4]. In our patients, both eosinophil percentage and histamine concentration were associated with BLL and were higher in those with active wheals. BLL was also higher in patients with active wheals, and the association between BLL ≥ 10 μg/dL and active wheals persisted after adjustment for age. Because activity was defined by the presence of wheals at blood sampling rather than by a longitudinal measure such as UAS7 [1,29], these findings describe activity at the time of sampling and not overall disease severity.

An important finding was the absence of a significant relationship between BLL and total IgE. Although lead exposure has previously been linked to changes in IgE regulation and Th2-related responses [14–18], total IgE in our cohort was associated neither with BLL nor with the presence of active wheals. In contrast, anti-IgE and FcεRIα autoantibodies were more frequent at higher BLLs, and their concentrations showed positive correlations with BLL. Thus, total IgE alone did not reflect the immunological pattern associated with higher lead exposure in these patients.

Autoantibodies against IgE and FcεRI have been implicated in autoimmune mechanisms in subsets of chronic spontaneous urticaria [20,29–31]. Their presence in our study should not, however, be considered diagnostic of type IIb autoimmune CSU,

which requires additional diagnostic and functional evidence [5,7,8]. Similarly, the anti-IgE antibodies measured in this study are distinct from IgE autoantibodies directed against specific self-antigens, which are associated with a different autoreactive mechanism [30–32]. These distinctions are important when interpreting the autoantibody findings.

Combined analysis of anti-IgE and FcεRIα autoantibodies showed additional heterogeneity within the CU group. BLL ≥10 μg/dL was most frequent in patients with both autoantibodies elevated, and this group also had the highest frequency of active wheals. Age was relevant because younger patients had higher BLLs and were more frequently represented in anti-IgE-positive profiles. Nevertheless, after adjustment for age, BLL ≥10 μg/dL remained associated with each autoantibody-positive immunophenotype, with the strongest association for the dual-positive group (aOR 5.49; 95% CI 2.38–12.70). These profiles were defined for exploratory analysis and should not be interpreted as established CU endotypes. Functional mast-cell or basophil assays would be needed to determine the biological relevance of the detected autoantibodies.

Age-related differences in lead exposure should be considered in the environmental context of Georgia. Younger participants had higher BLLs in both the CU and control groups, consistent with previous reports of substantial childhood lead exposure in the country [21–24]. Higher BLL among younger participants was therefore not specific to CU. However, the association between BLL ≥10 μg/dL and CU remained significant after adjustment for age. The pronounced age difference in anti-IgE positivity was observed within the CU group but not among healthy controls. Although adjustment for age addressed an important potential confounder, residual confounding by environmental, demographic, and clinical factors cannot be excluded.

The BLL ≥10 μg/dL cut-off used in this study was selected to identify a more highly exposed subgroup within a population with substantial background lead exposure. It should not be interpreted as a biological or public-health safety threshold. Current public-health guidance recognizes adverse effects at lower BLLs, particularly in children, and does not define a level of lead exposure that can be considered without risk [9,25–27].

The study has several strengths. BLL and multiple immunological markers were assessed in patients and geographically comparable controls, biomarkers were analyzed as both continuous and categorical variables, and the main associations were examined with adjustment for age. The analysis of combined autoantibody profiles provided an additional approach to the immunological heterogeneity of CU.

Several limitations should also be considered. The single-center, observational design does not establish temporality or causality. BLL was measured at one-time point and therefore does not represent cumulative exposure. Some biomarker measurements were unavailable for a small number of participants. Regression models were adjusted primarily for age; individual-level sex data were not available for inclusion in these models, and potentially relevant factors such as atopic background, residential and environmental exposures, socioeconomic characteristics, and exposure to other toxicants were not comprehensively assessed.

Clinical activity was determined from the presence of wheals at blood sampling rather than a validated longitudinal activity score, and functional testing of the detected autoantibodies was not performed.

The present findings warrant further investigation of lead exposure as a possible modifier of inflammatory and autoreactive immune activity in CU, particularly in populations with substantial environmental exposure. They do not establish lead as a cause of CU, justify routine lead screening solely because a patient has CU, or demonstrate that reducing lead exposure would improve urticaria. Prospective studies should include repeated assessment of lead exposure, validated longitudinal measures of CU activity, broader control of potential confounders, and functional evaluation of autoreactive pathways. Replication of the association between higher BLL and the dual-positive anti-IgE/FcεRIα profile in independent populations would be particularly informative.

Conclusion.

Patients with chronic urticaria had higher blood lead levels than healthy controls, and this association remained significant after adjustment for age. Within the CU group, higher BLLs were associated with eosinophilia, histamine, anti-IgE autoantibodies, FcεRIα autoantibodies, and the presence of active wheals at blood sampling, but not with total IgE.

In the exploratory autoantibody analysis, BLL ≥10 μg/dL showed the strongest age-adjusted association with the dual-positive anti-IgE/FcεRIα phenotype. These findings support a relationship between higher lead exposure and selected inflammatory and autoreactive features of CU.

Because the study was observational, causality cannot be established. Prospective studies with repeated BLL measurements, longitudinal assessment of CU activity, broader adjustment for confounders, and functional evaluation of autoantibodies are needed to confirm these associations.

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ქრონიკული ურტიკარია და ტყვიის ექსპოზიცია: იმუნოლოგიური მარკერების შეფასება

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აბსტრაქტი.

შესავალი: ქრონიკული ურტიკარია (CU) არის მასტოციტებით განპირობებული დაავადება, რომლის პათოგენეზში მონაწილეობს ანთებითი და აუტოიმუნური მექანიზმები. ტყვიას შეუძლია იმუნურ სისტემაზე ზემოქმედება, თუმცა მისი კავშირი ქრონიკულ ურტიკარიასთან ნაკლებად არის შესწავლილი.

მიზანი: სისხლში ტყვიის დონის (BLL) კავშირის შეფასება ქრონიკულ ურტიკარიასთან, სისხლის აღების მომენტში აქტიური ურტიკარიული ელემენტების არსებობასთან და შერჩეულ იმუნოლოგიურ მაჩვენებლებთან.

მეთოდები: ერთცენტრიან case-control კვლევაში მონაწილეობდა დასავლეთ საქართველოს 303 პირი: ქრონიკული ურტიკარიის მქონე 211 პაციენტი და 92 ჯანმრთელი საკონტროლო პირი. სისხლში ტყვიის დონე განისაზღვრა ინდუქციურად შეწყვილებული პლაზმის მას-სპექტრომეტრიით. შეფასდა ეოზინოფილები, საერთო IgE, ჰისტამინი, anti-IgE და FcεRIα აუტოანტისხეულები. BLL ≥10 µg/dL გამოყენებული იყო ტყვიის უფრო მაღალი ექსპოზიციის წინასწარ განსაზღვრულ ანალიზურ ზღვრად. ასოციაციები შეფასდა ჯგუფთაშორისი შედარებებით, სპირმენის კორელაციითა და ასაკზე კორექტირებული რეგრესიული ანალიზით.

შედეგები: BLL ქრონიკული ურტიკარიის მქონე პაციენტებში უფრო მაღალი იყო, ვიდრე ჯანმრთელ კონტროლებში. $BLL \geq 10 \mu\text{g/dL}$ გამოვლინდა პაციენტების 66.8%-სა და კონტროლების 33.7%-ში (OR 3.96; 95% CI 2.36–6.66; $p < 0.001$); კავშირი მნიშვნელოვანი დარჩა ასაკზე კორექტირების შემდეგ (aOR 4.07; 95% CI 2.38–6.96; $p < 0.001$). CU ჯგუფში უფრო მაღალი BLL დაკავშირებული იყო ეოზინოფილიასთან და ჰისტამინის, anti-IgE და FcεRIα აუტოანტისხეულების უფრო მაღალ მაჩვენებლებთან, მაგრამ არა საერთო IgE-სთან. $BLL \geq 10 \mu\text{g/dL}$ ასევე დაკავშირებული იყო სისხლის აღების მომენტში აქტიური ურტიკარიული ელემენტების არსებობასთან ასაკზე კორექტირების შემდეგ (aOR 3.36; 95% CI 1.75–6.45; $p < 0.001$). სამივე ანალიზში anti-IgE/FcεRIα ორმაგად დადებით ჯგუფში ყველაზე მაღალი იყო როგორც $BLL \geq 10 \mu\text{g/dL}$ -ის (83.3%), ისე აქტიური ურტიკარიული ელემენტების (92.4%) სიხშირე. იმ პაციენტებთან შედარებით, რომლებშიც არც ერთი აუტოანტისხეული არ იყო მომატებული, ორმაგად დადებით ჯგუფს $BLL \geq 10 \mu\text{g/dL}$ -თან ყველაზე ძლიერი ასაკზე კორექტირებული კავშირი ჰქონდა (aOR 5.49; 95% CI 2.38–12.70; $p < 0.001$).

დასკვნა: ქრონიკული ურტიკარიის მქონე პაციენტებში BLL ჯანმრთელ კონტროლებთან შედარებით უფრო მაღალი იყო. CU ჯგუფში უფრო მაღალი BLL დაკავშირებული იყო ეოზინოფილიასთან, ჰისტამინთან, anti-IgE და FcεRIα აუტოანტისხეულებთან და აქტიურ ურტიკარიულ ელემენტებთან, მაგრამ არა საერთო IgE-სთან. აღნიშნული ასოციაციები საჭიროებს დადასტურებას პროსპექტულ კვლევებში.

საკვანძო სიტყვები: ქრონიკული ურტიკარია, ტყვიის ექსპოზიცია, სისხლში ტყვიის დონე, anti-IgE აუტოანტისხეულები, FcεRIα აუტოანტისხეულები, ჰისტამინი, ეოზინოფილები.

Хроническая крапивница и воздействие свинца: оценка иммунологических маркеров

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Аннотация.

Введение: Хроническая крапивница (ХК) представляет собой заболевание, опосредованное тучными клетками,

в патогенезе которого участвуют воспалительные и аутоиммунные механизмы. Свинец способен влиять на иммунную систему, однако его связь с хронической крапивницей изучена недостаточно.

Цель: Оценить связь уровня свинца в крови (BLL) с хронической крапивницей, наличием активных уртикарных элементов на момент взятия крови и выбранными иммунологическими показателями.

Методы: В одноцентровое исследование типа «случай–контроль» были включены 303 участника из Западной Грузии: 211 пациентов с хронической крапивницей и 92 здоровых лица контрольной группы. BLL определяли методом масс-спектрометрии с индуктивно связанной плазмой. Оценивали эозинофилы, общий IgE, гистамин, аутоантитела anti-IgE и FcεRIα. $BLL \geq 10 \text{ мкг/дл}$ использовали как заранее установленный аналитический порог более высокой экспозиции свинца. Ассоциации оценивали с помощью межгрупповых сравнений, корреляции Спирмена и регрессионного анализа с поправкой на возраст.

Результаты: BLL был выше у пациентов с хронической крапивницей, чем у здоровых лиц контрольной группы. $BLL \geq 10 \text{ мкг/дл}$ выявлен у 66,8% пациентов и 33,7% контрольных лиц (OR 3,96; 95% CI 2,36–6,66; $p < 0,001$); связь сохранялась после поправки на возраст (aOR 4,07; 95% CI 2,38–6,96; $p < 0,001$). В группе ХК более высокий BLL был связан с эозинофилией и более высокими уровнями гистамина, аутоантител anti-IgE и FcεRIα, но не общего IgE. $BLL \geq 10 \text{ мкг/дл}$ также был связан с наличием активных уртикарных элементов на момент взятия крови после поправки на возраст (aOR 3,36; 95% CI 1,75–6,45; $p < 0,001$). В поисковом анализе группа с одновременным повышением anti-IgE и FcεRIα имела наиболее высокую частоту $BLL \geq 10 \text{ мкг/дл}$ (83,3%) и активных уртикарных элементов (92,4%). По сравнению с пациентами без повышения обоих аутоантител эта группа имела наиболее сильную скорректированную по возрасту связь с $BLL \geq 10 \text{ мкг/дл}$ (aOR 5,49; 95% CI 2,38–12,70; $p < 0,001$).

Заключение: У пациентов с хронической крапивницей BLL был выше, чем у здоровых лиц контрольной группы. В группе ХК более высокий BLL был связан с эозинофилией, гистамином, аутоантителами anti-IgE и FcεRIα и наличием активных уртикарных элементов, но не с общим IgE. Эти ассоциации требуют подтверждения в проспективных исследованиях. Ключевые слова: хроническая крапивница, экспозиция свинца, уровень свинца в крови, аутоантитела anti-IgE, аутоантитела FcεRIα, гистамин, эозинофилы.