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სარჩევი / CONTENT

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PULMONARY AND EXTRAPULMONARY POST COVID-19 CHRONIC COUGH

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რევაზ სეფიაშვილი [1], სოფიო გამყრელიძე [1,2,3], მანანა ჩიხლაძე [1,2], დარეჯან ხაჭაპურიძე [1,2], ნინო ჯოჯუა [2,3], დალი შონვაძე [2,3]

კოვიდ-19 პანდემიის შემდგომი პულმონარული და ექსტრაპულმონარული ქრონიკული ხველა

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რეზიუმე

ქრონიკული ხველა ერთ-ერთი ყველაზე მნიშვნელოვანი გამოწვევაა პოსტ კოვიდ-19 პანდემიის შემდგომი პერიოდისა, ხოლო მის მართვასთან დაკავშირებული სირთულეები კლინიკური მედიცინის ერთ–ერთი აქტუალური საკითხია. კვლევა მიზნად ისახავს პანდემიის შემდგომი ქრონიკული ხველის პულმონარული და ექსტრაპულმონარული მდგომარეობების იდენტიფიცირებასა და სკრინინგს დასავლეთ საქართველოს პოპულაციაში.

კვლევაში გაერთიანებულია 58 პაციენტი (18 დან 75 წლამდე ასაკის, 34 ქალი და 24 კაცი), პოსტ კოვიდ–19 რესპირაციული სიმპტომებით - გახანგრძლივებული, შემაწუხებელი ხველით და სუნთქვის უკმარისობით.

კვლევის დიზაინი: 1) ანამნეზის შეგროვება; 2) სასუნთქი სისტემის ჰიპერ-რეაქტიულობისა და ჰიპერმგრძნობელობის შეფასება კომპიუტერული სისტემის მქონე ხელსაწყო Spirolab 3–ის მეშვეობით; 3) ლაბორატორიული მარკერების კვლევა: C რეაქტიული ცილა, Helicobacter pylori; საერთო IgE, D ვიტამინი სისხლის შრატში.

მიღებული შედეგების ანალიზის საფუძველზე გამოიყო ორი ჯგუფი: I ჯგუფში გაერთიანდა 27 (46,5%) პაციენტი პოსტკოვიდური პულმონარული ქრონიკული ხველით, ხოლო II ჯგუფში შევიდა 31 (53,5%) ექსტრაპულმონარული ქრონიკული ხველის მქონე პაციენტი.

ფილტვში და ბრონქში სავარაუდოდ მიმდინარე ობსტრუქციის და/ან რესტრიქციის ხარისხის და შესაბამისად სუნთქვის უკმარისობის სიმძიმის დადგენის მიზნით ჩატარებული კომპიუტერული სპირომეტრიით I ჯგუფში, II ჯგუფისგან განსხვავებით მივიღეთ სპირომეტრული მაჩვენებლების (FEV1; FVC; FEV1/FVC) სარწმუნო ცვლილებები ($p>0,05$). აქედან 12 პაციენტს დაუდგინდა შექცევადი ხასიათის ბრონქოობსტრუქცია და მხოლოდ 6 პაციენტს შეუქცევადი ხასიათის. 10 პაციენტში აღინიშნა მსუბუქი და საშუალო სიმძიმის რესტრიქცია. II ჯგუფის სპირომეტრული მაჩვენებლები ნორმის ფარგლებში. სარწმუნო ცვლილებები გამოვლინდა ლაბორატორიული მარკერების მიხედვითაც, როგორიცაა: C რეაქტიული ცილა, Helicobacter pylori; საერთო IgE-სა და D ვიტამინი.

კვლევამ შესაძლებლობა მოგვცა სწორი აქცენტებით მოგვეხდინა პულმონარული და ექსტრაპულმონარული გენეზის ქრონიკული ხველის დიფერენცირება, რაც განსაზღვრავს საბოლოო კლინიკური დიაგნოზის სიზუსტეს და მიზანმიმართულ, ინდივიდუალობის პრინციპზე დაფუძნებულ მენეჯმენტს.

INTRODUCTION. Cough is one of the important post-pandemic challenge of 21 century and with them associated management difficulties are an active issue in clinical medicine. Post-pandemic chronic cough is globally prevalent across all age groups. This disorder is challenging to treat because many pulmonary and extra pulmonary conditions can present with chronic cough, and cough can also be present without any identifiable underlying cause or be refractory to therapies that improve associated conditions. Post-pandemic patients are just more aware of coughing. Lingering, nagging cough persists. For many, it's a six-to-eight-week cough. For others, it can last up to 100 days [1,2,3,10]. The airway reactivity

increased after recovery from COVID-19 in individuals who did not have severe illness [4,5,6]. The impact of COVID-19 on pulmonary function or airway reactivity is established. As cough reflex is determined by interaction of the nervous system with immune system, persistent dysregulation of one or both of these systems may lead to chronic cough hypersensitivity. This may explain the difficulties associated with post-pandemic cough. Various environmental and host factors, such as respiratory infection, air pollutants, occupational irritants, allergens, eosinophils or refluxate, can sensitize and trigger cough and are potential risk factors for chronic cough [4].

Infection with respiratory viruses (such as rhinovirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) is a common cause of acute cough and is usually self-limiting, but post-infectious cough may persist for months in some individuals. Common pulmonary causes of chronic cough in non-smokers with normal chest X-rays and spirometry are corticosteroid-responsive cough such as eosinophilic conditions, including cough variant asthma, non-asthmatic eosinophilic bronchitis and atopic cough [8,9]. Extrapulmonary conditions are also commonly associated with cough, including GERD and upper airway cough syndrome (previously called 'post-nasal drip syndrome') due to rhinitis or rhinosinusitis [10]. Indeed, cough variant asthma, eosinophilic bronchitis, upper airway cough syndrome and GERD account for 51–92% of cases of adult chronic cough globally [10].

The aforementioned has raised the need for studying the functional status of the respiratory system, conducting computer spirometry, as well as providing permanent monitoring of laboratory markers in clinical medicine among all the patients with persistent cough [3,5].

Based on the above, the presented study is aimed at screening and identifying some pulmonary and extrapulmonary conditions which are reason of post pandemic chronic cough in West Georgian population.

METHODS. 58 patients (18 to 75 years of age, 34 women and 24 men) who were reffered to the National Institute of Allergology, Asthma & Clinical Immunology with post-COVID-19 conditions, especially with respiratory complications – long-term, dry, lingering cough, shortness of breath, for further diagnosis and problem management, were involved in the study.

The research design included: 1) collection of anamnesis - via a specially designed questionnaire for collecting the medical history; 2) assessment of airway hyperreactivity and hypersensitivity performed by a modern, computerized spirometer - Spirolab 3; 3) studying and analysis of laboratory markers, such as: C-reactive protein, Helicobacter pylori, total IgE, Vitamin D3.

RESULTS. Based on the analysis of medical history, of airway hyperreactivity and hypersensitivity performed by a modern, computerized spirometer - Spirolab 3 and of specific laboratory markers the patients were divided into two groups: 27 (46,5%) patients with pulmonary chronic cough were involved in group I, and 31 (53,5%) patients with extrapulmonary chronic cough - in group II, respectively.

Reliable changes ($p>0.05$) in the spirometric parameters (FEV1; FVC; FEV1/FVC) were observed in the I group after computerized spirometry performed to determine the degree of possible obstruction and/or restriction in the lung and bronchus and, consequently, the severity of respiratory failure, compared to the II groups. PEF < 70% peak expiratory flow was reduced in 22 (81%) patients with pulmonary chronic cough, compared to the norm. Mild-moderate-severe obstruction were observed in 18 (66%) patients, 12 cases from this obstruction were reversible and only 6 irreversible. Mild-moderate restriction was observed in 11 (40%) of cases. In the II group patients, the spirometric indicators varied within the norm.

Since the main clinical symptoms of I group patients were a dry, lingering chronic cough and respiratory failure with difficulty in expiration and/or inspiration, allergological status was evaluated, and an increase in the level of the allergomarker total IgE was revealed (M±m=318.5 ±21.45 (norm < 100) in 13 (48%) of I group patients, while among the patients of II group it was fixed in 8 (25%).

Based on the analysis of laboratory markers the obtained results showed that C-reactive protein was increased in 23 (85%) cases of patients from I group and only in 11 (35%) patients from II group with extrapulmonary chronic cough.

In addition, detection of Helicobacter pylori showed an increase in the level of this marker in 19 (61%) patients from II group, while in the patients of the I group, changes in the above-mentioned marker were revealed only in 4 (14%) cases.

Vitamin D (such as marker of immunomodulation) monitoring revealed that in I group patient with pulmonary chronic cough, vitamin D insufficiency was detected in 8 (31%) patients, deficiency in 10 (35%) and normal level in only 9 (34%) patients, respectively, while in the II group, insufficiency of vitamin D was detected in 6 (19.3%), deficiency in 10 (32.2%), and norm in 15 (48.5%) patients, respectively (Table N1).

Cough monitoring tools have been useful to evaluate the efficacy of cough medicines. Owing to differences in the pathology, the organs involved and individual patient factors, treatment of chronic cough is progressing towards a personalized approach, and, in the future, novel ways to endotype patients with cough may prove valuable in management.

Table N1. **Analyzing the Laboratory Markers in Patients with Post-COVID chronic cough condition**

Indicators	* I Study Group n=27			II Control Group n= 31			P value (Confidence Interval)
	Abs.	%	(M±m)	Abs.	%	(M±m)	
C-reactive protein (CRP)	23	85	22±2,5	11	35	10±0.23	>0,05
Total IgE	13	48	370±4.56	8	25	125±2,45	<0,05
Vitamin D	18	66	19±2.35	16	51	25±1,65	>0,05
Helicobacter pylory	4	14	0,7±0,16	19	67	1,5±0.76	<0,05

* I Group – Patient with pulmonary chronic cough; II Group - Patient with extrapulmonary chronic cough

Screening for chronic cough is not carried out in clinical practice. How screening could be done and whether it would lead to clinical benefit is unclear. Screening patients with chronic respiratory disease may be beneficial as cough is often overlooked during clinical evaluation. Moreover, early identification may improve the quality of life (QOL) of patients and possibly avoid over-treatment by specifically targeting cough. One simple screening method is a numerical rating scale that assesses cough severity and ascertains the duration of cough [10].

CONCLUSION. Screening the general population could identify patients with respiratory disorders such as COPD, asthma, lung cancer and smoking-related chronic bronchitis at an earlier stage. The most important diagnosis is that of lung cancer, where development of a cough may be the first symptom, particularly in a smoker. Whether non-smoking-related chronic cough is preventable is unknown. A greater understanding of the mechanism of cough, particularly cough hypersensitivity, is needed.

The obtained results will be of great value to prevent post-covid chronic cough, to establish causes of hyper reactivity and hypersensitivity of airway and active planning of disease management, especially to patients with post-covid conditions. In addition, the study results are also interesting and meaningful not just scientific sense but from clinical perspective as well. Consequently, researches are actively keep continuing in this direction worldwide.

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PULMONARY AND EXTRAPULMONARY POST COVID-19 CHRONIC COUGH

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SUMMARY

Chronic cough is one of important post Covid-19 challenge of 21 century and with them associated management difficulties are an active issue in clinical medicine. The presented study is aimed at screening and identifying some pulmonary and extrapulmonary conditions which are reason of post Covid-19 pandemic chronic cough in West Georgian population.

58 patients (18 to 75 years of age, 34 women and 24 men) were involved in the study. The research design included: 1) collection of anamnesis 2) assessment of airway hyperreactivity and hypersensitivity by a modern, computerized spirometer - Spirolab 3; 3) studying and analysis of laboratory markers, such as: C-reactive protein, Helicobacter pylori, total IgE, Vitamin D3. Based on the analysis of results patients were divided into two groups: 27 (46,5%) patients with pulmonary chronic cough were involved in group I, and 31 (53,5%) patients with extrapulmonary chronic cough - in group II, respectively. Reliable changes ($p>0.05$) in the spirometric parameters (FEV1; FVC; FEV1/FVC) were observed in the I group after computerized spirometry performed to determine the degree of possible obstruction and/or restriction in the lung and bronchus and, consequently, the severity of respiratory failure, compared to the II groups. In the II group patients, the spirometric indicators varied within the norm. With studying and analysis of laboratory markers, such as: C-reactive protein, Helicobacter pylori, total IgE, Vitamin D3 was found the statistically significant changes between the patients from both groups. In addition, the study results are also interesting and meaningful not just scientific sense but from clinical perspective as well. Consequently, researches are actively keep continuing in this direction worldwide.

Keywords: Spirometry, Post covid-19 pandemic, chronic cough, Helicobacter pylori

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UTILITY OF NON-INVASIVE HEMATOLOGICAL BIOMARKERS IN NEWLY DIAGNOSED RHEUMATOID ARTHRITIS PATIENTS

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არაინვაზიური ჰემატოლოგიური ბიომარკერები რევმატოიდული ართრიტის მქონე ახლადდიაგნოსტირებულ პაციენტებში

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რეზიუმე

შესავალი: რევმატოიდული ართრიტი ქრონიკული აუტოიმუნური დარღვევაა, რომელსაც სინოვიუმის ქრონიკული ანთება ახასიათებს და სახსრის დაზიანებისა და სისტემური გართულებისკენ მივყავართ. რევმატოიდული არტრიტის სამკურნალო პირველი რიგის წამალი იმუნოსუპრესიული პრეპარატი მეტოტრექსატია. თუმცა პაციენტთა საგრძნობი რაოდენობა მეტოტრექსატის მიმართ რეზისტენტულია. სისხლის საერთო ანალიზიდან გამოთვლილი ბიომარკერები, როგორიცაა სისხლის წითელი უჯრედების განაწილების ფართობი (RDW), ჰემოგლობინისა და თრომბოციტების შეფარდება (HPR) და ჰემოგლობინ მონოციტების შეფარდება (HMR) სხვადასხვა ანთებითი მდგომარეობების დროს დაავადებისა და თერაპიაზე პასუხის მარკერებად გვევლინება. თუმცა ჯერჯერობით დადგენილი არ არის რევმატოიდული ართრიტის მქონე ახლადდიაგნოსტირებულ პაციენტებში ამ ბიომარკერების მეტოტრექსატით მკურნალობის გამოსავლის პროგნოზული ღირებულება.

მიზანი: კვლევის მიზანია რევმატოიდული ართრიტის მქონე ახლადდიაგნოსტირებულ პაციენტებში, მათ ვინც მეტოტრექსატით მკურნალობა დაიწყეს, RDW, HPR და HMR პროგნოზული ბიომარკერების პოტენციალის განსაზღვრა და დაავადების აქტიურობის ქულასთან (DAS-28) მათი კორელაციის დადგენა.

მეთოდები: კვლევაში ჩართული იყო 64 პაციენტი, რომლებიც დაიყო მეტოტრექსატ-რეზისტენტულ და მეტოტრექსატ-მგრძნობიარე ჯგუფებად, და 28 ასაკითა და სქესით შესაბამისი ჯანმრთელი ინდივიდები. სტანდარტული t-ტესტი იყო გამოყენებული ჯგუფებს შორის სპეციფიკური ბიომარკერების შესადარებლად. ორივე ჯგუფში RDW, HPR, HMR და DAS28 შორის კორელაციების დასადგენად Pearson-ის კორელაციის ტესტი იქნა გამოყენებული. ბიომარკერების პროგნოზული მნიშვნელობის შესაფასებლად მიმღების ოპერაციული მახასიათებლის (ROC) მრუდის ანალიზი ჩატარდა.

შედეგები: მეტოტრექსატ-რეზისტენტულ და მეტოტრექსატ-მგრძნობიარე ჯგუფებს შორის RDW-SD სარწმუნოდ განსხვავდება. სარწმუნო პოზიტიური კორელაცია შესწავლილ ბიომარკერებსა და DAS-28 შორის არც ერთ ჯგუფში არ დადგენილა. ROC მრუდების ანალიზი გვიჩვენებს, რომ მათ პროგნოზული ღირებულება არ აქვთ.

დასკვნა: RDW-SD-ის მომატებული დონე მეტოტრექსატ-რეზისტენტობის ადრეულ ინდიკატორად შეიძლება ჩაითვალოს ახლად დიაგნოსტირებულ პაციენტებში. ჩვენი კვლევით დადგინდა, რომ დაავადების აქტივობის მონიტორინგისთვის RDW-SD, HPR და HMR DAS-28-ს რევმატოიდული ართრიტის მქონე პაციენტებში ვერ ჩაანაცვლებს.

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by joint inflammation, which can lead to irreversible joint damage and disability if left untreated [1]. The disease activity in RA is typically assessed using clinical and laboratory parameters, such as the Disease Activity

Score of 28 joints (DAS-28), which incorporates swollen and tender joint counts, acute-phase reactant levels, and patient-reported outcomes [2]. In recent years, there has been growing interest in identifying the role of different complete blood count-derived (CBC) biomarkers that can serve as cost-effective, non-invasive tools across various medical conditions. Among these biomarkers, red cell distribution width (RDW), hemoglobin platelet ratio (HPR), and hemoglobin monocyte ratio (HMR) derived from complete blood count (CBC) measurements have emerged as promising candidates. RDW, a measure of the variation in the size of circulating red blood cells, has been shown to be an accessible and economical parameter that, together with other characteristics of the presentation and evolution of patients with COVID-19, can help determine the prognosis [3]. Interestingly, another study has shown that a preoperatively elevated standard deviation of RDW (RDW-SD) predicts favorable survival in patients with intrahepatic cholangiocarcinoma after curative resection [4]. RDW, along with other CBC-derived biomarkers such as neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios, has demonstrated good predictive value for early-phase severe acute pancreatitis (SAP) prediction, exhibiting the highest discriminatory capacity among other biomarkers and consequently indicating its potential as a convenient and reliable indicator for predicting SAP [5]. Similarly, HPR and HMR have garnered attention for their ability to reflect alterations in hematopoietic and inflammatory processes associated with various medical conditions. HPR, calculated as the ratio of hemoglobin to platelet count, has been proposed as a marker of developing radiation-induced trismus (RIT) among locally advanced nasopharyngeal carcinoma patients undergoing concurrent chemoradiotherapy (CCRT) [6]. Another study suggests that HPR combined with carcinoembryonic antigen (CEA) can increase diagnostic efficacy and may be a useful diagnostic marker for patients with rectal cancer [7]. Despite the growing body of evidence supporting the potential utility of these biomarkers, their utility in RA remains unclear. The correlation with DAS-28 scores as well as their predictive capabilities for treatment outcomes in newly diagnosed RA patients have not been investigated yet. Therefore, the main aim of this study was to investigate the associations between RDW, HPR, and HMR levels and DAS-28 scores in RA patients, as well as their predictive value for treatment response in individuals initiating methotrexate therapy, which serves as the standard initial treatment for RA.

Materials and Methods. Study population: This retrospective study involved 64 newly diagnosed patients with rheumatoid arthritis from the V. Tsitlanadze Scientific-Practical Center of Rheumatology in Tbilisi, Georgia, along with 28 age- and sex-matched controls who did not have any type of cancer, acute or chronic infections, or autoimmune diseases. To be included in the study, patients had to meet the diagnostic criteria for rheumatoid arthritis as established by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR). We gathered demographic information and detailed medical histories from each patient. Clinical and laboratory evaluations included recording the number of swollen and tender joints (SJC and TJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-CCP antibodies, complete blood count, and disease activity assessment using the DAS28 score. The DAS28 score was calculated using SJC, TJC, and ESR parameters. Patients were required to exhibit high disease activity (DAS28 > 3.2).

Exclusion criteria: Patients with diabetes, hypertension, renal failure, coronary artery disease, pulmonary disease, malignancy, infection, pregnancy or postpartum, granulomatous disease, or any inflammatory disorder were excluded from the study.

All patients were initiated on methotrexate with starting doses ranging from 7.5 to 15 mg weekly. The maximum titration was up to 25 mg weekly, as per standard clinical protocols.

Data collection: Complete blood count (CBC) data were collected from all patients. CBC measurements included hemoglobin, MCV, monocyte, and platelet counts, which allowed the calculation of RDW-SD, HPR, and HMR ratios. RDW-SD was calculated by dividing the standard deviation (SD) of the mean corpuscular volume (MCV) by the MCV and multiplying by 100. HPR and HMR were calculated as follows: hemoglobin count divided by platelets and monocytes, respectively.

Response assessment: After three months of treatment with methotrexate, patients underwent a reassessment to determine their response to the treatment. Based on disease activity markers such as DAS-28, improvement in clinical symptoms, decrease in the number of tender and swollen joint counts,

reduction of acute phase reactants (ESR and CRP), and better performance in vocational and avocational activities, patients were categorized into two groups: responders or non-responders. Those in the responder group (MTXS) who achieved remission or a significant reduction in disease activity continued their methotrexate treatment. Those in the non-responder group (MTXR), who did not achieve remission or showed inadequate improvement in disease activity were switched to treatment with tocilizumab, an interleukin-6 receptor inhibitor.

Statistical analysis: Statistical analyses were performed using Prism 9 and IBM SPSS Statistics for Windows, Version 26 (released 2010; IBM Corp., Armonk, New York, United States). Descriptive statistics were used to summarize patient demographics and baseline characteristics. All quantitative data were expressed as mean +/- standard deviation. Unpaired t-tests were used for group comparisons where appropriate. The statistical significance between groups for categorical variables was calculated using the chi-squared test. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values for RDW-SD, HPR, and HMR in predicting treatment response. Pearson's correlation test was used for the correlation study. All tests were two-tailed. Differences below 0.05 were considered statistically significant.

Ethical considerations: The study protocol was approved by the Tbilisi State Medical University Biomedical Research Ethics Committee (approval number N1-2022/94). All participants provided informed consent before enrollment.

Table 1. Comparison between the study populations' baseline clinical and serological characteristics

	MTXS group n=37	MTXR group n =27	Control n=28	p^1	p^2	p^3
Age (years), (mean ± SD)	52.24±15.03	51.81±12.71	48.29±15.68	0.7380	0.5356	0.1821
Female, n (%)	33 (89.19%)	24 (88.89%)	20 (71.42%)	0.2217	0.1705	0.0655
DAS28	5.76±0.64	5.75±0.69		0.9625		
ANA positive (>1:80), n(%)	1 (2.7%)	5 (18.52%)	0 (0 %)	0.0164	0.0031	<0.0001
RF, n (%)	16 (43.24%)	27 (100%)	0 (0 %)	<0.0001	<0.0001	0.0001
Anti CCP, n (%)	27 (72.97%)	66 (96.30%)	0 (0 %)	0.0732	0.0035	0.0109
CRP (mg/L), (mean ± SD)	30.28±20.37	19.71±21.45		0.0493		
ESR (mm/h) (mean ± SD)	30.59±17.73	42.29±14.63		0.0130		
Neutrophils (10^3 cells/mL)	5.91±1.84	5.02±1.56	3.65±0.93	0.0455	<0.0001	<0.0001
Lymphocytes (10^3 cells/mL)	2.57±0.93	2.01±0.60	2.05±0.40	0.0084	0.0025	0.0905
Monocytes (10^3 cells/mL)	0.63±0.32	0.44±0.16	0.51±0.12	0.0053	0.0040	0.4022
Platelets (10^9 cells /mL)	313.22±92.67	326.1±69.04	248.93±43.93	0.5432	0.0003	<0.0001
RDW-SD	5.39±0.30	7.89±0.65	3.21±0.35	<0.0001	<0.0001	<0.0001
HPR	0.43±0.10	0.41±0.14	0.06±0.01	0.4364	<0.0001	<0.0001
HMR	258.68±176.51	329.93±166.11	28.30±5.10	0.1072	<0.0001	<0.0001

SD - Standard deviation, **DAS28** – Disease activity score for 28 joints, **ANA** - Antinuclear antibody, **Anti-CCP** – Anti-cycling citrullinated peptide antibody, **RF** – Rheumatoid factor, **CRP** – C reactive protein, **ESR** – Erythrocyte sedimentation rate, **RDW-SD – red cell distribution width** – standard deviation**, HPR** – Hemoglobin-platelet ratio**, HMR –** Hemoglobin-monocyte ratio. **p^1** – MTXS group vs. MTXR group**, p^2** – MTXR group vs. Control group**, p^3 –** MTXS vs. Control group.

Results. Table 1 summarizes the demographic, clinical, and laboratory data of studied subjects. Out of 64 enrolled patients, 57 were female and 7 were male. A total of 37 patients were included in the MTXS group, 27 patients in the MTXR group, and 28 age- and sex-matched individuals in the control group. The average age and gender distribution of the patients in the MTXS, MTXR, and control groups did not differ significantly. Statistically significant differences have been observed between the MTXR and MTXS groups regarding RDW-SD, ESR, CRP, neutrophils, lymphocytes, and monocytes ($p<0.0001$, $p=0.0130$,

0.0493, 0.0455, 0.0084, and 0.0053 respectively). RDW-SD, along with ESR was substantially elevated in the MTXR group. Conversely, higher levels of CRP have been observed in the MTXS group. However, there was no statistically significant difference found between the groups in terms of DAS-28, HGR, and HMR (p=0.9625, 0.4364, and 0.1072 respectively). The correlation between RDW-SD, HPR, HMR, and DAS-28 was also studied, but no significant positive correlations were identified in either the MTXR or MTXS groups. The prognostic potential of studied CBC-derived biomarkers in predicting treatment outcomes among RA patients initiating methotrexate was assessed using Receiver Operating Characteristic (ROC) curve analysis. The ROC curve analysis demonstrated that the area under the curve (AUC) for each biomarker did not surpass the threshold indicative of predictive capability (Figure 1, Figure 2).

Figure 1. ROC curve analyzes the prognostic value of the Hemoglobin-Monocyte Ratio (HMR) in RA patients under MTX treatment

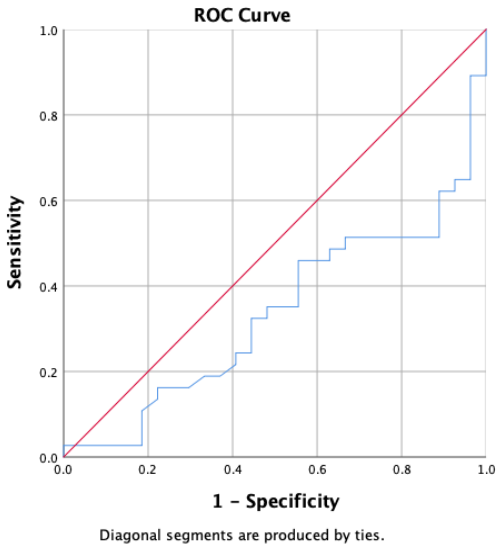


Figure 2. ROC curve analyzes the prognostic value of the Hemoglobin-Platelet Ratio (HPR) in RA patients under MTX treatment

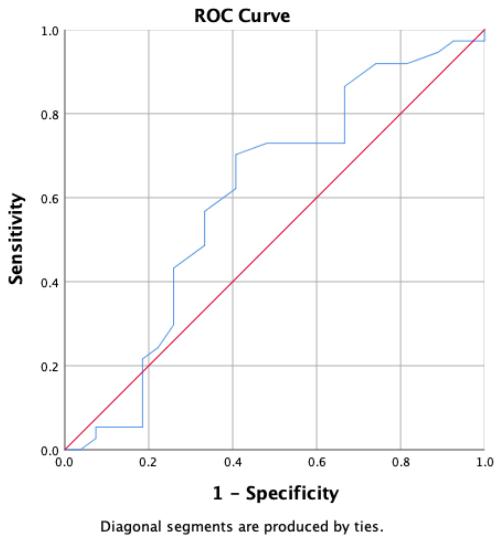
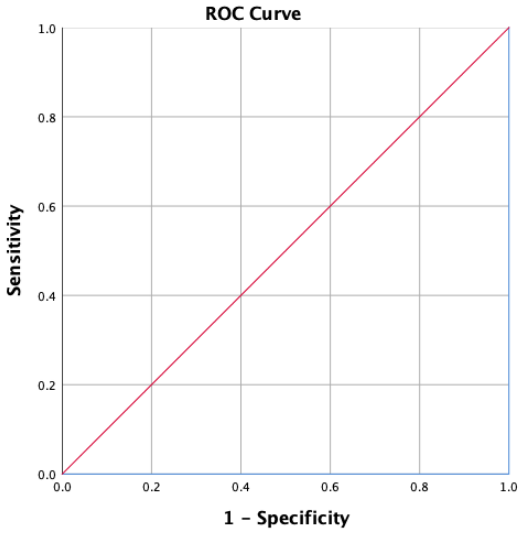


Figure 3. ROC curve analyzes the prognostic value of the red cell distribution (RDW) in RA patients under MTX treatment



Discussion: Rheumatoid arthritis represents a significant burden on global healthcare systems, with its chronic inflammatory nature often leading to joint damage and functional impairment if not effectively managed. In pursuit of improved treatment strategies and prognostic indicators, researchers have turned their attention to hematological biomarkers derived from routine CBC measurements. Among these biomarkers, RDW, HPR, and HMR have garnered interest for their potential utility in assessing disease activity and predicting treatment outcomes across various diseases. However, the specific relevance of these biomarkers in the context of RA has remained largely unexplored. Our study's primary and potentially pioneering finding is the identification of a statistically significant difference in RDW-SD between MTXR and MTXS groups. In the MTXR group, we observed a higher RDW-SD compared to the MTXS group ($p < 0.0001$) The observed difference in RDW-SD between the two groups may suggest a potential association between red blood cell morphology variability and methotrexate response in RA patients. Methotrexate, a cornerstone therapy in RA management, exerts its therapeutic effects through the inhibition of dihydrofolate reductase, thereby disrupting folate metabolism and ultimately suppressing immune-mediated inflammation. It is credible that variations in red blood cell morphology, as reflected by RDW-SD, could influence the efficacy of methotrexate therapy through as-yet-unknown mechanisms. One possible explanation for the observed difference in RDW-SD between MTXR and MTXS groups could be related to differences in systemic inflammation levels. RA is characterized by dysregulated immune responses and chronic inflammation, which can lead to alterations in red blood cell parameters, including RDW. Methotrexate resistance may be associated with heightened inflammatory activity, resulting in increased red blood cell variability as reflected by RDW-SD. Conversely, MTXS patients may exhibit lower levels of inflammation, leading to more stable red blood cell parameters and lower RDW-SD values. A similar finding has been demonstrated in a study of gastric cancer, where higher RDW-SD levels were associated with poor outcomes [8]. Additionally, genetic factors may play a role in mediating the relationship between RDW-SD and methotrexate response in RA patients. Genetic polymorphisms involved in folate metabolism and inflammation could potentially influence both RDW-SD values and individual responses to methotrexate therapy. Future studies incorporating genetic analyses may help elucidate the underlying genetic determinants of RDW-SD and its association with methotrexate resistance in RA. Furthermore, we investigated and found no significant correlation between RDW, HPR, and HMR levels and the DAS-28 in either group. This suggests that any of the biomarkers of interest cannot replace the DAS-28 to monitor disease activity and progression. Another study demonstrated a positive relationship between RDW, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and cardiac troponin I (cTnI) in acute myocardial infarction [9] and this underscores the need for further research in the direction of RA. Also, we have assessed the predictive capabilities of RDW-SD, HPR, and HMR for treatment outcomes in newly diagnosed RA patients initiating methotrexate therapy. Our findings

revealed that none of the examined CBC-derived biomarkers demonstrated predictive capability for treatment response. The AUC values for these biomarkers remained near or below the threshold of 0.5, indicative of outcomes no better than chance. These results, once again, highlight the limitations of RDW, HPR, and HMR as biomarkers in managing RA. The lack of predictive capability for treatment outcomes further underscores the complexity of RA pathogenesis and the need for multifaceted approaches to disease management. Although there is emerging data highlighting the predictive ability of those biomarkers in other medical settings [10], RA has its distinct inflammatory environment and underlying mechanisms, which may not be accurately represented by biomarkers that have demonstrated effectiveness in other diseases. Furthermore, variables such as age, gender, serological markers, concomitant medications, disease severity at the beginning of treatment, and lifestyle factors may interact with RDW, HPR, and HMR levels, impacting treatment response and complicating the interpretation of the study results.

When interpreting the results, it's important to consider the limitations of this study. These limitations include the relatively small sample size, data collection at a single medical center, and the retrospective nature of the study. It's important to note that these findings may not apply to patients who are receiving different treatment regimens or those at more advanced disease stages, as the study only looked at the use of methotrexate as the sole conventional disease-modifying antirheumatic drug (DMARD), along with short-term non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, for newly diagnosed patients.

Conclusion: We propose that there may be a relationship between an elevated RDW-SD and resistance to methotrexate in RA patients, suggesting that RDW-SD could be a novel, cost-effective, and easily measured parameter for predicting RA treatment outcomes at the start of treatment. We do not recommend using RDW-SD, HPR, and HMR as substitutes for DAS-28 for monitoring disease severity and activity. Our study emphasizes the need for ongoing research to identify reliable biomarkers to guide clinical decision-making and enhance outcomes for RA patients.

Conflict of interest: The authors of this article declare no conflicts of interest.

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UTILITY OF NON-INVASIVE HEMATOLOGICAL BIOMARKERS IN NEWLY DIAGNOSED RHEUMATOID ARTHRITIS PATIENTS

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SUMMARY

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation of the synovium, leading to joint damage and systemic complications. Methotrexate (MTX) is commonly used as a first-line treatment for RA due to its immunosuppressive properties. However, a significant proportion of patients exhibit resistance to MTX therapy. Lately, certain complete blood count (CBC) derived biomarkers such as red cell distribution width (RDW), hemoglobin platelet ratio (HPR), and hemoglobin-monocyte ratio (HMR) have emerged as promising indicators in various inflammatory conditions, providing insights into disease prognosis and therapeutic response. However, there is currently limited data available on the effectiveness of the abovementioned biomarkers as prognostic ones to predict treatment outcomes in newly diagnosed RA patients who are initiating MTX treatment.

Objective: This study aimed to determine the potential of RDW, HPR, and HMR as prognostic biomarkers in newly diagnosed RA patients commencing MTX therapy. Additionally, to investigate their possible correlation with the Disease Activity Score of 28 joints (DAS-28).

Methods: We conducted a comprehensive analysis involving 64 RA patients categorized into Methotrexate-resistant (MTXR) and Methotrexate-sensitive (MTXS) groups and 28 age- and sex-matched healthy individuals. Standard T-tests were used to compare specific biomarkers between MTXR, MTXS, and control groups. For the comparison of categorical variables between the groups Chi-square test was employed. We examined correlations with Pearson's correlation test between RDW, HPR, HMR, and DAS28 in both groups. To determine the predictive capabilities of these biomarkers, Receiver Operating Characteristic (ROC) curve analysis was performed.

Results: We identified statistically significant different RDW-SD values in MTXR and MTXS groups, according to an unpaired t-test. The RDW-SD was higher in the MTXR group compared to the MTXS. No significant positive correlations were identified between hematological biomarkers of interest and DAS-28 in either the MTXR or MTXS group. Additionally, The ROC curve analysis showed that their predictive capability was insignificant.

Conclusion: Elevated RDW-SD levels can be an early indicator of MTX resistance at the beginning of therapy in newly diagnosed RA patients. Additionally, based on our study cohort RDW-SD, HPR, and HMR cannot replace DAS-28 for assessing and monitoring disease activity in RA patients.

Keywords: Rheumatoid arthritis, RDW, HPR, HMR, Biomarkers

KETEVAN LOMIDZE, MARINA GORDELADZE, NINO KIKODZE, TINATIN CHIKOVANI

CASE OF INDUCED GRAVE'S DISEASE BY NIVOLUMAB TREATMENT

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ქეთევან ლომიძე, მარინა გორდელაძე, ნინო ქიქოძე, თინათინ ჩიქოვანი

ნივოლუმაბით ინდუცირებული გრეივსის დაავადების შემთხვევა

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი

რეზიუმე

იმუნური მაკონტროლებელი მოლეკულების ინჰიბიტორები (იმმი) სიახლეა კიბოს მკურნალობაში. მიუხედავად იმუნოთერაპიის წარმატებული შედეგებისა ონკოლოგიაში, გარდამავალი თირეოტოქსიკოზი და ჰიპოთირეოზი წარმოადგენს ფარისებრი ჯირკვლის დისფუნქციით მიმდინარე, იმუნური გვერდითი მოვლენების ყველაზე ხშირ ენდოკრინულ გამოვლინებას. თუმცა, ლიტერატურა ასევე აღწერს იმმი-ით გამოწვეული გრეივსის დაავადების რამდენიმე შემთხვევას. ჩვენ წარმოგიდგენთ, გრეივსის დაავადებას, რომელიც განვითარდა ანტი-PD-1 თერაპიის შედეგად. მეტასტაზური მელანომის მქონე, 63 წლის მამაკაცს ნივოლუმაბის მეექვსე ინფუზიის შემდეგ განუვითარდა - ტაქიკარდია, პალპიტაცია, გადაჭარბებული ოფლიანობა და ნეგატიური სიზმრები. მისი ფარისებრი ჯირკვლის ფუნქციური ტესტი (ფჯფ) იყო დარღვეული და მას მკურნალობა ჩაუტარდა მეთიმაზოლით და პროპრანოლოლით. მეთიმაზოლის დაწყებიდან ათი კვირის შემდეგ, ფჯფ-ი დაუბრუნდა ნორმას და სიმპტომებიც ალაგდა. მიუხედავად იმისა, რომ გრეივსის დაავადება წარმოადგენს იმუნოთერაპიის იშვიათ გართულებას, სასიცოცხლოდ მნიშვნელოვანია მისი განვითარების გათვალისწინება, რათა მოხდეს დაავადების სწრაფი დიაგნოსტირება და მკურნალობა, რაც უზრუნველყოფს ონკოპაციენტებში სიცოცხლის მაღალ ხარისხს და გადარჩენას.

Introduction. More than twelve decades ago, William Coley made the initial connection between immunology and oncology to find effective cancer-targeting techniques [1]. At the end of the 20th century, James Allison discovered the immune checkpoints, which led to the development of novel immunotherapy against tumors and awarded him with the Nobel Prize. Immune checkpoint inhibitors (ICIs) are powerful new drugs for the treatment of cancer. These monoclonal antibodies trigger the immune system against cancer cells, blocking inhibitory signals of T-cells, namely cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Programmed death 1(PD-1), and Programmed death ligand 1 (PD-L1) [2]. Immune checkpoint inhibitors markedly increased cancer patients' progression-free survival, but they also brought on a wide range of adverse events that are referred to as immune-related adverse events (irAEs). While immunotherapy affects nearly every organ, the skin, gastrointestinal, and endocrine systems are particularly affected. Among immune-related endocrinopathies, thyroid dysfunction is the most common. The majority of immune-related thyroid dysfunctions are caused by transient thyrotoxicosis and hypothyroidism [3], only several cases of ICI-induced Grave's disease are described in the literature. We report a case of Grave's disease acquired after anti-PD-1 therapy.

Case Presentation. A 63-year-old male was sent to our endocrinological department with complaints of tachycardia, palpitations, excessive perspiration, and vivid horrific dreams after the sixth infusion of anti-PD-1 monoclonal antibody - Nivolumab (240mg IVq 2 weeks) for metastatic melanoma. He had nightmares even after the third injection, but he ignored them until now. A thyroid ultrasound and thyroid function tests (TFTs) were performed before the beginning of Nivolumab treatment. TFTs were normal, and thyroid ultrasonography revealed no alterations. He and his family have no previous history of thyroid illness. On physical examination, he showed tachycardia at 122 beats per minute, occasional irregular rhythm, T/A at 145/95mmHg, dewy skin, and no symptoms of ocular problems. ECOG was 2.

Thyroid function tests were indicative of Grave's disease: TSH- < 0.008 μIU/ml (NR: 0.4-4.2), FT4-38.96pmol/L (NR: 12-22), FT3- 13.11 pmol/L (NR: 3.1-6.8), thyrotropin receptor antibodies (TRAb) - 14,2

IU/L (NR< 1.0), TPO antibodies and Tg antibodies were negative. The ultrasound was also suggestive of Grave's disease, with the thyroid gland enlarged to 23mL, hyperechoic, and hypervascularity in the parenchyma on Doppler imaging. ^{99m}Tc-pertechnetate scintigraphy was not done because of the patient's unwillingness. Thus, we recognized his thyrotoxicosis as a new-onset Graves' disease after Nivolumab therapy based on TFTs and ultrasound and initiated treatment with methimazole 25mg/day and propranolol.

At the next follow-up, 2 weeks later, the symptoms of thyrotoxicosis subsided, but the TFT was still abnormal. The patient came for a check-up every fortnight. 10 weeks after the initiation of methimazole, TFTs were normalized, and all the symptoms disappeared (Table 1). The patient was relieved to return to sleep without nightmares. Consequently, methimazole was reduced to 5mg/day while keeping euthyroidism stable. The patient has resumed his immunotherapy treatment, and he has completed the 7th dose infusion.

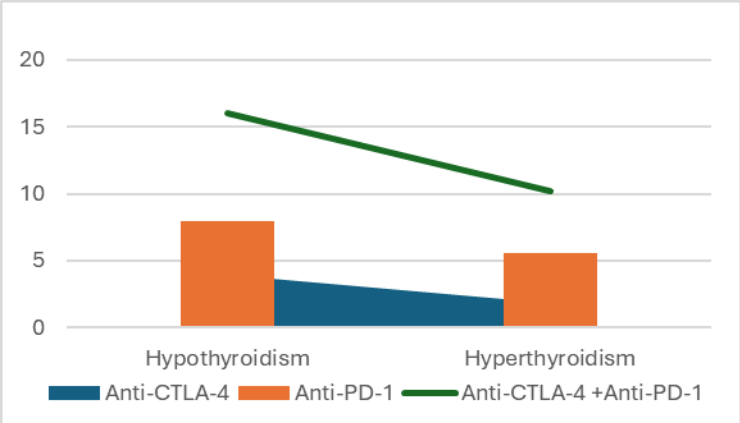
Table 1. Thyroid tests and symptoms examined before methimazole medication, after weeks 6 and 10

TFTs & Symptoms	Week 0	Week 6	Week 10
TSH (NR: 0.4-4.2 μIU/ml)	0.008	0.15	0.96
Free T4 (NR: 12-22 pmol/L)	38.96	24.66	18.53
Free T3 (NR: 3.1-6.8 pmol/L)	13.11	8.34	4.1
TRAb (NR< 1.0 IU/L)	14.2	5.42	0.71
ECOG	2	1	0
Tachycardia/Palpitation	Present	Absent	Absent
Perspiration	Present	Present	Absent
Horrific dreams	Present	Present	Absent

Discussion. Main mechanism of ICI therapy is removing the brakes of immune system, thus facilitating destruction of cancer cells by activated tumor-specific T cells. This can cause adverse effects which affect the whole organism through autoimmunity. Thyroid dysfunction has been noted as a common side effect of ICI medication and can occur during the treatment with any type of ICI (Figure 1) [1,4].

At this time, the exact mechanisms of thyroid irAEs induction by each of the ICIs is not fully understood. Many theories have emerged, and the most accepted current theory involves an interplay between genetic factors, cellular autoimmunity and humoral immunity, supported by T-cells cross-reactivity, increased levels of interferon gamma-inducible chemokines (which attract T-cells), the contribution of ADCC and the HLA-DR allele which is involved in autoimmunity.

Figure 1. The prevalence (%) of immune checkpoint inhibitor-induced hypothyroidism and hyperthyroidism with monotherapy vs combination treatment



Anti-PD-1 antibody treatment induces transient thyrotoxicosis. It seems to be primarily a T-cell mediated process, supported by the presence of $CD8^+$ T-cells in the thyroid, and $CD4^-CD8^-$ T-cells in the thyroid and blood of the patients [5,6]. For example, it is reported that PD-1 is not expressed on T-cells from pembrolizumab-induced thyroiditis, which supports a T-cell mediated mechanism, rather than a B-cell mediated one [7]. Th1/Th2 balance has been reported in favor of Th1, with increased levels of IL-2 (which might stimulate autoreactive lymphocytes), IL-1β, GM-CSF and decrease of Il-8, G-CSF and MCP-1 [8,9]. Thyrotoxicosis is usually followed by persistent hypothyroidism, which is mediated by – Th1 and Th17 cells. Decreased Th2 cell activity during thyrotoxicosis [8,9] can explain less possibility of development of hyperthyroidism – Graves' disease which is mediated by autoantibodies.

Graves' disease is a thyroid autoimmune condition that is triggered by TRAbs. Production of autoantibodies is responsibility of Th2 activity (mainly mediated through L-4). The lymphocytes in Graves' thyroid tissue are responsible for producing these antibodies [10]. TRAbs may exhibit either stimulatory, inhibitory, or neutral effects as antibodies. Stimulating thyroid-stimulating hormone receptor antibodies (also known as TSIg) enhance the production and function of sodium-iodide symporter and G proteins. As a result, there is an elevation in the absorption of iodine, the production of thyroid hormones, and their release, along with an increase in the growth and survival of thyroid cells, which leads to the manifestation of hyperthyroidism symptoms [11,12]. Patients with blocking TRAbs occasionally have clinical manifestation of hypothyroidism caused by inhibiting TSH activity. Neutral antibodies bind to the TSH receptor's hinge region without influencing TSH function. Although they have been linked to thyroid cell stress and apoptosis, their clinical importance remains unclear [13].

The patient we discussed manifested overt hyperthyroidism. In this particular instance, the criteria that enable the doctor to discriminate between autoimmune hyperthyroidism and thyrotoxicosis caused by destructive thyroiditis are the existence of TRAbs and the vascular pattern during color Doppler imaging. The limitations of this case study include the lack of scintigram and the absence of a baseline (pre-immunotherapy) test for TRAb assay. On the other hand, the fact that both the restoration and maintenance of euthyroidism by anti-thyroid drug - methimazole in this individual were successful is indicative of an accurate diagnosis and therapy.

In conclusion, even though Grave's disease is a relatively uncommon consequence of ICI therapy, it is very necessary to always keep it in mind to ensure that cancer patients get prompt diagnosis and treatment to maintain a good quality of life and overall survival.

Ethics Statements. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration. The study protocol was approved by the Tbilisi State Medical University Ethical Committee on Human Research. Informed consent was obtained from a patient included in the study.

Disclosure Statement. The authors have no conflict of interest.

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CASE OF INDUCED GRAVE'S DISEASE BY NIVOLUMAB TREATMENT

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SUMMARY

Immune checkpoint inhibitors (ICIs) are powerful new drugs for the treatment of cancer. Immune-related adverse events (irAEs), despite their successful use in oncology, resulted in a wide range of adverse effects. Transient thyrotoxicosis and hypothyroidism cause the majority of immune-related thyroid dysfunctions, but there are also reported a few cases of ICI-induced hyperthyroidism. We present a case of Graves' disease resulted from anti-PD-1 therapy. A 63-year-old male developed tachycardia, palpitations, excessive perspiration, and vivid, horrific dreams after the sixth infusion of Nivolumab for metastatic melanoma. His thyroid function test (TFT) was abnormal, and he was treated with methimazole and propranolol. Ten weeks after starting methimazole, the TFT returned to normal, and the symptoms subsided. In a nutshell, even though Grave's disease is a rare complication of immunotherapy, it is very important always keep it in mind to ensure quick access to prompt diagnosis and treatment to maintain a good quality of life and overall survival.

Keywords: Grave's disease, Nivolumab, hyperthyroidism, TRAb

ნინო კუკულაძე, ალექსანდრე ბახუტაშვილი

კუჭნაწლავის მიკრობიომის სტრუქტურა და დინამიკა ადამიანსა და ექსპერიმენტულ ცხოველებში

ვლ. ბახუტაშვილის სახ. სამედიცინო ბიოტექნოლოგიის ინსტიტუტი,
თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისი, საქართველო

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GUT MICROBIOME STRUCTURE AND DYNAMICS IN HUMAN AND EXPERIMENTAL ANIMALS

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SUMMARY

The human microbiome, comprising trillions of bacteria, fungi, and viruses, profoundly influences both our organism and the surrounding environment. Emerging research highlights the symbiotic relationship between human and microbial organisms, suggesting their co-evolution into superorganisms. Throughout life, the gut microbiome undergoes significant shifts, impacting immune, nervous, and cardiovascular system homeostasis. Understanding these dynamics offers insights into personalized medicine and therapeutic interventions targeting microbial dysbiosis.

Keywords: gut, microbiome, human, experimental animals

მიკრობიომი წარმოადგენს იმ უნიკალური, ტრილიონობით ბაქტერიის, სოკოსა და ვირუსის ერთობლიობას, რომლისგანაც შედგება ჩვენი ორგანიზმი - ცხვირისა და პირის ღრუ, კანი და ყველაზე დიდი რაოდენობით კუჭ-ნაწლავის ფლორა [1,2]. მიკრობიომი ჩვენი ორგანიზმისა და გარე სამყაროს ურთიერთკავშირის შედეგად ყალიბდება და ერთ-ერთ ყველაზე კომპლექსურ ეკოსისტემას წარმოადგენს [3]. მართალია, მიკრობიომის ჩამოყალიბება ჩვენი ცხოვრების ადრეულ წლებში ხდება, თუმცა, ის კვების რაციონის, მედიკამენტოზური მკურნალობისა და გარემო ფაქტორების გავლენით, დროთა განმავლობაში ცვლილებას განიცდის [4]. ზოგი მკვლევარი თვლის, რომ მიკრობიომის მიკროორგანიზმები და ადამიანის უჯრედები ჯამში წარმოადგენენ ერთ სუპერორგანიზმს [5,6]. ეს კონცეფცია ხაზს უსვამს რთულ ურთიერთობას ადამიანებსა და მიკროორგანიზმებს შორის, რომელიც ხშირ შემთხვევაში მნიშვნელოვან გავლენას ახდენს ორივეს ფუნქციაზე და სტრუქტურაზე. უკანასკნელი წლების განმავლობაში, სულ უფრო მეტი კვლევა ტარდება ადამიანის მიკრობიომის - კუჭ-ნაწლავის ფლორის შესასწავლად, რადგან აღმოჩნდა, რომ ის მნიშვნელოვნად არის დაკავშირებული ჩვენი იმუნური სისტემის [5], ნერვული სისტემისა [6] და გულ-სისხლძარღვთა სისტემის [7] ჩამოყალიბებასა და გამართულ ფუნქციონირებასთან. კუჭ-ნაწლავის მიკრობიომი შედგება ‘კეთილი’ და პოტენციურად ‘მავნე’ მიკრო ორგანიზმებისაგან, რომლებიც, საუკეთესო შემთხვევაში, მშვიდად თანაარსებობენ და ჩვენი ორგანიზმის კეთილდღეობას ემსახურებიან. თუმცა, მიკრო ფლორის დარღვევის შემთხვევაში, შესაძლოა ავტოიმუნური, მეტაბოლური ან სხვა სახის დაავადებები განვითარდეს, როგორიცაა: ჭარბწონიანობა [8], დიაბეტი [9], ალერგია [10], კარდიო-ვასკულარული [11], ნევროლოგიური [12], მენტალური ჯანმრთელობის პრობლემები [13] (როგორიც არის შფოთვა, დეპრესია).

კუჭ-ნაწლავის ტრაქტი თითქოს დერეფანს წარმოადგენს პირის ღრუდან მსხვილ ნაწლავამდე. ძირითადად, დიდი რაოდენობა მიკროორგანიზმებისა გვხვდება პირის ღრუში [14] და შემდეგ მსხვილ ნაწლავში [15], მაგალითად, ისეთი სპეციფიური ბაქტერიაც კი, როგორიც helicobacter-იაა, რომლის სახლად კუჭი ითვლება, ზოგჯერ მსხვილ ნაწლავში ხვდება [16]. გაცილებით ნაკლებია ბექტერიების კონცენტრაცია წვრილ ნაწლავში [17], მსხვილ ნაწლავთან ახლოს უკვე მათი რაოდენობა გაცილებით მეტია, დაახლოებით 10 ტრილიონზე მეტ ორგანიზმამდე აღწევს. ესენი ერთად დაახლოებით 3,3 მილიონი განსხვავებული უნიკალური გენის ექსპრესიას ახდენენ [18]. თუ გავითვალისწინებთ, რომ ადამიანის ცილის მაკოდირებელი გენების რაოდენობა დაახლოებით 19500 ცალს წარმოადგენს [19], შეგვიძლია

დავასკვნათ, რომ კუჭ-ნაწლავის მეტაბოლიზმის უდიდესი ნაწილი უცხო (მიკრობული) გენებით არის განპირობებული.

ნაწლავის მიკრობიომი ან ნაწლავის ფლორა არის მიკროორგანიზმები, მათ შორის ბაქტერიები, არქეები, სოკოები და ვირუსები, რომლებიც ცხოვრობენ საჭმლის მონელების ტრაქტში. ნაწლავი არის ადამიანის მიკრობიომის მთავარი ადგილი. ადამიანებში ნაწლავის ფლორა ყალიბდება დაბადებიდან ერთიდან ორ წელიწადში [20]. ამ დროისთვის ნაწლავის ეპითელიუმი და ნაწლავის ლორწოვანი ბარიერი თანაბრად განვითარებულია ისე, რომ წარმოადგენს ბარიერს პათოგენური ორგანიზმებისთვის.

მიკრობიომის შესწავლის მეთოდები შეიძლება 4 ბლოკად დაიყოს:

1. ნაწლავის ბაქტერიების ტრადიციული იდენტიფიკაცია ფენოტიპური მახასიათებლების საფუძველზე ზოგადად არ არის ზუსტი, 16S rRNA გენის თანმიმდევრობის ანალიზს შეუძლია უკეთესად გამოავლინოს ცუდად აღწერილი, იშვიათად იზოლირებული ან ფენოტიპურად აბერანტული შტამები [21]. კომპლექსურ თემებში ცალკეული ბაქტერიების სახეობების ვიზუალიზაციის ერთ-ერთ მეთოდს ეწოდება რიბოსომური რნმ-ის ფლუორესცენცია in situ ჰიბრიდიზაცია (FISH) [22].

2. რნმ-ის ანალიზი ნაწლავის მიკრობიომში გულისხმობს მაღალი წარმადობის ექსპერიმენტული ტექნოლოგიების გამოყენებას, როგორიცაა რნმ-ის თანმიმდევრობა (RNA-seq) ნაწლავის მიკრობების და მიკრობული მეტაბოლიტების გენის ექსპრესიის პროფილების შესასწავლად [23]. ეს ანალიზი მოგვცემს ინფორმაციას იმ ფერმენტების შესახებ, რომლებიც სინთეზირებულია ნაწლავის ბაქტერიების მიერ.

3. პროტეომიკა, განსაკუთრებით მეტაპროტეომიკა, არის ძლიერი მეთოდი, რომელიც გამოიყენება ნაწლავის მიკრობიომის ცილის შემადგენლობისა და ფუნქციური აქტივობის შესასწავლად. მეტაპროტეომიკა იძლევა ცილების იდენტიფიკაციისა და რაოდენობრივი განსაზღვრის საშუალებას ფართო დინამიური დიაპაზონის ფარგლებში, რაც საშუალებას აძლევს ნაწლავის მიკრობიომის გამოკვლევას ფუნქციურ დონეზე [24].

4. მეტაბოლომიკა არის მძლავრი მეთოდი, რომელიც გამოიყენება ადამიანის ნაწლავის მიკრობიომის მიერ წარმოქმნილი მეტაბოლიტების შესასწავლად, რაც გვაწვდის ინფორმაციას მასპინძელ-მიკრობული ურთიერთობის ფუნქციურ სტატუსზე [25]. მეტაბოლომიკა ფოკუსირებულია მასპინძელსა და ნაწლავის მიკრობებს შორის მეტაბოლური ურთიერთქმედების განსაზღვრაზე, გვთავაზობს უნიკალურ პერსპექტივას იმის შესახებ, თუ როგორ მოქმედებს ცხოვრების წესი, დიეტური ჩვევები და დაავადების პირობები ადამიანის ჯანმრთელობაზე.

ნაწლავის მიკრობიოტას მიკრობული შემადგენლობა განსხვავდება საჭმლის მომნელებელი ტრაქტის სხვადასხვა რეგიონში, მსხვილი ნაწლავი არის ნაწლავის მიკრობიომის მთავარი ადგილი. გასათვალისწინებელია, რომ ნაწლავის მიკრობიოტასა და

ადამიანს შორის ურთიერთობა არ არის მხოლოდ ნეიტრალური თანაარსებობა, არამედ ეს არის ურთიერთდამოკიდებულება [26,27] პირდაპირი კონტაქტით მის უჯრედებთან, ასევე ბიოაქტიური ნივთიერებების ლოკალური და სისტემური მოქმედებით [28]. მაგალითად, ბაქტერიები მასპინძლის საკვების გადამუშავების შედეგად გამოიმუშავებენ მოკლე ჯაჭვის ცხიმოვან მჟავეებს (SCFAs), როგორიცაა ძმარმჟავა, ბუტირის მჟავა და სხვა. ისინი შემდგომ გამოყოფენ SCFAs ნაწლავის სანათურში და წარმოადგენენ მსხვილი ნაწლავის ეპითელიური უჯრედების ძირითად ენერგიის წყაროს [29,30]. შეიძლება ითქვას, რომ ბაქტერიები კვებავენ ადამიანის ნაწლავის ეპითელიალურ უჯრედებს. ნაწლავის მიკრობიოტა მნიშვნელოვან როლს ასრულებს ვიტამინების წარმოებასა და უტილიზაციაში, მათ შორის B ვიტამინებისა და K ვიტამინის [31,32].

ნაწლავის მიკრობიოტა ასევე პირდაპირ ურთიერთქმედებს ნაწლავის ნერვულ სისტემასთან (ENS) [33], რომელიც არის ადამიანის ავტონომიური ნერვული სისტემის ნაწილი და პასუხისმგებელია ნაწლავის ფიზიოლოგიური აქტივობის სხვა ორგანოებთან და სისტემებთან ჰარმონიულ მუშაობაზე [34]. ნაწლავებსა და ტვინს შორის კომუნიკაციის ყველაზე პირდაპირი გზა არის ვაგუს ნერვი, რომელიც არის ავტონომიური ნერვული სისტემის მნიშვნელოვანი კომპონენტი. ვაგუსის „წარმომადგენელი“ ნაწლავის სანათურში არის ნეიროპოდი, სპეციალიზებული ენტეროენდოკრინული უჯრედი (სენსორული ეპითელური უჯრედები) ნაწლავში, რომლებსაც შეუძლიათ კავშირი მოახდინონ აფერენტულ ნერვებთან [35]. ნეიროპოდები უშუალოდ ეკონტაქტებიან ნაწლავის მიკროორგანიზმებს და ამის შედეგად გავლენას ახდენენ ნეიროტრანსმიტერების სინთეზზე და ნერვულ სასიგნალო გზებზე [36]. ნაწლავის ბაქტერიები სავარაუდოდ აყალიბებენ სინაფსურ კავშირებს ნეიროპოდებთან ლორწოვან გარსში და პირდაპირ ურთიერთქმედებენ ადამიანის ნერვულ სისტემასთან [37,38].

ნაწლავის მიკრობიოტას მიკრობული შემადგენლობა განსხვავდება საჭმლის მომნელებელ ტრაქტის სხვადასხვა უბანზე [39], კუჭსა და წვრილ ნაწლავში შედარებით მცირე რაოდენობით გვხვდება და ყველაზე დიდი რაოდენობით მიკროორგანიზმები მსხვილ ნაწლავშია.

წვრილ ნაწლავში გვხვდება **მიკრონაკეცი უჯრედები** ან M უჯრედები [40]. მიკრონაკეცი უჯრედები გვხვდება წვრილ ნაწლავში პეიერის ფოლაქების ნაწლავთან ასოცირებულ ლიმფოიდურ ქსოვილში (GALT), მეზობელი უჯრედებისგან განსხვავებით, M უჯრედებს უნიკალური უნარით, ტრანსციტოზის გზით გადასცემენ ანტიგენებს (Ag) ნაწლავის სანათურიდან ნაწლავთან ასოცირებულ ლიმფოიდურ ქსოვილში და წარუდგენენ მათ სხვადასხვა თანდაყოლილ და ადაპტირებულ იმუნურ უჯრედებს [41]. მიკროორგანიზმების ანტიგენები მიეწოდება ანტიგენის წარმომადგენელ უჯრედებს, როგორიცაა დენდრიტული უჯრედები და B ლიმფოციტები [42]. M უჯრედებს არ აქვთ მიკროვილი, მაგრამ ისევე როგორც სხვა ეპითელურ უჯრედებს, მათ ახასიათებთ ძლიერი უჯრედული შეერთებები, რასაც ასევე უჯრედშორის ხიდებს უწოდებენ [43]. გარდა ამისა, მათი ბაზალური პლაზმური მემბრანა ღრმად არის ინვაგინირებული, რათა შეიქმნას დიდი ტომრის მსგავსი სტრუქტურა, ე. წ. "M-უჯრედების ჯიბე", სადაც დენდრიტული უჯრედები და ლიმფოციტები არიან მოთავსებულები M-უჯრედისგან ანტიგენების მისაღებად [44].

მიკროორგანიზმები, რომლებისგანაც შედგება მიკრობიოტა, ძალიან მნიშვნელოვანი ნაწილია ორგანიზმის შემდგომი განვითარებისთვის. მაგ: გნოტობიონტები - სტერილური ლაბორატორიული ორგანიზმები, რომლებიც არ შეიცავენ მიკროორგანიზმებს ნაწლავის ღრუში [45]. მათი ნაწლავის სტრუქტურა განუვითარებელია [46], ასევე იმუნური სისტემაც [47]. ეს ერთმნიშვნელოვნად მიგვითითებს ნაწლავური მიკროორგანიზმების როლზე როგორც ბავშვის ჯანმრთელი ნაწლავის, ასევე სრულფასოვნად მოქმედი იმუნური სისტემის ჩამოყალიბებაში.

კვლევების უმეტესი ნაწილი მიუთითებს, რომ ბაქტერიები ისახება ბავშვის ორგანიზმში დაბადებისთანავე [48]. საშვილოსნოში ნაყოფი თითქმის სტერილურ პირობებშია, დაბადებისთანავე ის სწრაფად ითვისებს მიკროორგანიზმებს დედისგან და გარემოდან, 2-4 წლისათვის მიკრობიომის მრავალფეროვნების სტაბილიზაცია ხდება და იღებს ზრდასრული ადამიანის მახასიათებლებს [49]. ამ დროისთვის ნაწლავში კოლონიზდება და დომინირდება

შემდეგი ბაქტერიის ტიპები: Bacteroides, Clostridium, Faecalibacterium, Eubacterium, Ruminococcus, Peptococcus და Peptostreptococcus [50]. სტაბილური მიკრობიომი ადამიანს მთელი ცხოვრება თან ახლავს. სიბერისათვის ის, როგორც მასპინძელიც, ბერდება და კარგავს თავის მრავალფეროვნებას და ფუნქციურ აქტივობას [51]. საინტერესოა, რომ ახალგაზრდა თაგვების ნაწლავური მიკრობიომის გადანერგვა მოხუცებულ თაგვებში აახალგაზრდავებს ნაწლავის, თვალის და ტვინის ქსოვილებს [52]. გარდა ამისა, კვლევებმა აჩვენა, რომ ფეკალური მიკრობიოტას გადატანას ახალგაზრდა თაგვებში შეუძლია ნაწლავის მიკრობიომის სტიმულირება, ნაწლავის იმუნური სისტემის გაცოცხლება და ფიზიკური ვარჯიშის განახლება [53]. ეს ექსპერიმენტები პერსპექტიულ მიმართულებას წარმოადგენენ გერონტოლოგიაში და საერთო ჯანმრთელობის მართვაში.

მიკრობიომის შემადგენლობა განაწილებულია ადამიანის გეოგრაფიულ ადგილმდებარეობისა და ცხოვრების წესის მიხედვით [54]. მალავიაში, ამერიკელი ინდიელებისა და აშშ-ს მოსახლეობის ოპერატიული ტაქსონომიური ერთეული (OTU) განაწილებულია ცხოვრების წესის და ასაკის მიხედვით. ამ ქვეყნებში მცხოვრები ადამიანის მიკრობიომის ანალიზი აჩვენებს, რომ მალავიასა და ინდიელებს მსგავსი მიკრობიომი აქვს [55]. ადაპტირებული ძირითადად მცენარეული საკვების მოსანელებლად, მათი ნაწლავის მიკრობიომი მაღალი ბაქტერიული მრავალფეროვნებით გამოირჩევა. ამის მიზეზად ასევე შესაძლებელია ჰიგიენური პირობები ჩაითვალოს. აშშ-ს მაცხოვრებლების მიკრობიომი ბაქტერიების მრავალფეროვნება შემცირებულია. შემადგენლობა ადაპტირებულია დასავლეთის დიეტის მოსანელებლად.

ადამიანის მიკრობიომის შესწავლა სულ უფრო აქტუალური თემა ხდება მედიცინისთვის. კვლევების შედეგები აჩვენებს, რომ ნაწლავის მიკრობიომი მგრძნობიარეა ნებისმიერი დაავადების დროს ორგანოებისა თუ სისტემების პათოლოგიური ცვლილებების მიმართ. მიკრობიომის დარღვევა შესაძლებელია ასოცირებული იყოს შემდეგ დაავადებებთან: დეპრესია, ფილტვების ქრონიკული ობსტრუქციული დაავადებები, პნევმონია, ასთმა, დიაბეტი, ჭარბი წონა, დერმატიული დაავადებები, ალერგია, აუტიზმის სპექტრის დაავადება, სისხლ-ძარღვთა სისტემის დაავადებები, კოლიტი, გაღიზიანებული ნაწლავის სინდრომი IBD, კიბო [56,57]. ძალიან მნიშვნელოვანი ხდება მოდულირება მოხდეს მიკრობიოტის შემადგენელი ბაქტერიების სხვადასხვა თერაპიული მიზნებისთვის. ჯანსაღი მიკრობიოტა რომ შევინარჩუნოთ შეგვიძლია მივმართოთ დიეტას, პრობიოტიკებს და ასევე განსაკუთრებულ შემთხვევებში ანტიბიოტიკებს პრობიოტიკებთან კომბინაციაში. ანტიბიოტიკების გამოყენება წინააღმდეგობებს ხვდება, მაგრამ არის ზოგირთი კვლევა, სადაც ნაჩვენებია, რომ ზოგიერთი გენეზის დიარეების, ასევე ნაწლავური ანთებების დროს მისი მკურნალობაში ჩართვა დადებით ეფექტს იძლევა [58]. ასევე, გენური ინჟინერიის საშუალებით [59] შეიქმნა სპეციფიკური თვისებებით აღჭურვილი მიკროორგანიზმები, სინთეზირებული, მაგალითად, ბაქტერიოციდულ პეპტიდებთან, ან ცხიმოვან უჯრედებთან, რათა გამოიწვიონ ნაწლავის ენტეროციტების გააქტიურება. შესაძლებელია ასევე შეიქმნას ბაქტერიოფაგები, არასასურველი მიკროორგანიზმების გასანადგურებლად.

კვლევების შედეგები გვაჩვენებს, რომ მომავალში მიკრობიოტას მოდიფიკაცია მნიშვნელოვან მეთოდად მოგვევლინება ადამიანის ფართო სპექტრის დაავადებათა სამკურნალოდ. ჩვენის აზრით, ადამიანის ნაწლავის მიკრობიომი მიუხედავად იმისა, რომ მრავალი წელიწადი იკვლევა, ეხლა განიცდის რენესანსს და მოითხოვს მედიცინის პროფესიონალების ყურადღებას და კვლევების პროგრამების ჩართვას.

მადლობას ვუხდით პროფესორ გ. კვიტაიშვილს ამ ნარკვევის კრიტიკული განხილვისთვის.

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ნინო კუკულაძე, ალექსანდრე ბახუტაშვილი

კუჭნაწლავის მიკრობიომის სტრუქტურა და დინამიკა ადამიანსა და ექსპერიმენტულ ცხოველებში

ვლ. ბახუტაშვილის სახ. სამედიცინო ბიოტექნოლოგიის ინსტიტუტი, თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისი, საქართველო

რეზიუმე

ადამიანის მიკრობიომი ტრილიონობით ბაქტერიას, სოკოსა და ვირუსს მოიცავს. ის მნიშვნელოვან გავლენას ახდენს ჩვენს ორგანიზმსა და გარემოზეც. წარმოდგენილ კვლევაში აქცენტია ადამიანისა და მიკრობების სიმბიოზზე, რამაც მათი თანაევოლუცია გამოიწვია სუპერორგანიზმად. სიცოცხლის განმავლობაში საჭმლის მომნელებელი ტრაქტის მიკრობიომი გავლენას ახდენს იმუნური, ნერვული და კარდიოვასკულური სისტემის ჰომეოსტაზზე. მიკრობიომის დინამიკის ცოდნა პერსონალიზებული მედიცინისა და მიკრობული დისბიოზის თერაპიული ინტერვენციების კვლევაში დაგვეხმარება.

NINO JOJUA, NINO ADAMIA, DAVID TOPHURIA, MANANA CHIKHLADZE, DAREJAN KHACHAPURIDZE, MAIA MATOSHVILI, DALI SHOVNADZE, TAMAR VALISHVILI, SOPHIO GAMKRELIDZE, DIMITRI ABELASHVILI, ELENE KHURTSIDZE

IMMUNE CHANGES IN THE PATHOLOGY OF FORMATION ALLERGIC DISEASE CHARACTERISTICS, AT A TIME OF BRAIN AND ISCHEMIC STROKE

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ნინო ჯოჯუა, ნინო ადამია, დავით თოფურია, მანანა ჩიხლაძე, დარეჯან ხაჭაპურიძე, მაია მათოშვილი, დალი შოვნაძე, თამარ ვალიშვილი, სოფიო გამყრელიძე, დიმიტრი აბელაშვილი, ელენე ხურციძე

იმუნური ძვრები ალერგიული დაავადების ფორმირების პათოლოგიაში, თავის ტვინისა და იშემიური ინსულტის დროს

ა. წერეთლის სახელმწიფო უნივერსიტეტი, თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

რეზიუმე

ჩვენი კვლევის მიზანი იყო ისეთი სპეციფიკური მონაცემების მოპოვება, რომელიც დააზუსტებდა ცერებრალური ქსოვილის პროცესში (როგორც იშემიურ ფოკუსში, ასევე პენუმბრაში) ფოკალური დარტყმის ფორმირების პროცესს: 1. ადგილობრივი სისხლის მიმოქცევა და ჟანგბადის ნაწილობრივი წნევის ცვლილებები და აზოტის ოქსიდის დონე სხვადასხვა დროის ინტერვალებით; 2. სისხლის რეოლოგიური თვისებების და თავისუფალი რადიკალების ცვლილების როლი ორივე, გეომეტრიული განზომილებებისა და სისხლის მიმოქცევის დონის განსაზღვრაში პენუმბრაში; 3. ფოკალური იშემიის ცენტრისა და პენუმბრას ქსოვილებში მორფოლოგიური ცვლილებების ანალიზის შედეგები.

Introduction: In cases of brain focal strokes, optimal use of so called “therapeutic window” is of critical significance, with respect of the treatment outcome. First of all, this deals with maintenance of penumbral area of infarction developed in the neural tissue and its saving from involvement into the ischemic process and, certainly, relieving of the processes developed in the ischemic focus, through minimization of the volume of necrotic tissue [4,8,9]. For the purpose of obtaining of this extremely significant information, first of all, for the research, supposedly, we should select the experimental model that is as close as possible with the pattern of ischemic stroke development, where the relevant processes develop in the organism, without external impact (whether medial or traumatic nature). [1,2,3]. And, certainly, we should study the processes developed in the course of the external intervention, where such intervention is necessary for the patient and is directly related to the possibility of formation of the ischemic stroke in the brain. Regarding the literary materials and own experience, as such models, we have selected non-invasive photochemical method for development of the focal ischemia in the brain and local hyperthermia exposition that is used for treatment of the cancer tissues, together with radio- or chemotherapy. In both cases, the status of blood rheological properties actively influences formation of the ischemic stroke, as well as free radicals bound with oxygen and nitrogen oxide [5,6,7,10].

Research goals and objectives: regarding all above, the main goal of our research was obtaining of such specific data that would specify the following, in the process of cerebral tissue (both, in ischemic focus and penumbra) in the process of formation of focal strike and upon its completion: 1. Dynamics of local blood circulation and oxygen partial pressure changes and level of nitrogen oxide at different time intervals; 2. Role of change of blood rheological properties and free radicals in determination of both, geometrical dimensions and blood circulation level in penumbra; 3. Results of analysis of the morphological changes in focal ischemia center and penumbra area tissues.

Scientific novelty of the obtained results: in the brain, in both processes of ischemic stroke development processes that we have used, the most significant complications are caused by thrombosing of the cerebral vessels, in development of which the rheological properties of blood are of primary

significance. In case of increased viscosity of the blood, the injury induced in the cerebral tissue is more prominent. By using of antioxidants and such powerful scavenger of free radicals as DMSO and/or by changing of the concentration balance of nitrogen oxide and oxygen radicals (in favor of nitrogen oxide), reduction of the scale and severity of injury induced by the focal infarction (by relevant morphological changes) is possible. Cerebral tissue is characterized with extremely high sensitivity to hyperthermia impact developed in the tissue itself, rather than in the environment.

Statistical analysis of the obtained results was provided by the software package of variation statistics (ANOVA), implementation of which was provided by means of Excel program. Statistical reliability of the differences was checked by Student-t criterion.

Obtained results: as evidenced by the provided data, increase of temperature to 41 degrees cause growth of local blood flow and its level, in 20-30 minutes, achieve 150 percent of the initial level. Further increase of temperature to 43 degrees initially cause drastic growth, actually doubling of local blood flow, compared with the initial level but after 20-30 minutes its level falls dramatically, to 60 percent of the initial level. As for high temperature hyperthermia, where there was used heating of the cerebral cortex surface to 45 degrees, local blood flow falls significantly and in 20-30 minutes its measurement became impossible.

Prior administration of Dextran provided significant difference (compared with the normal rats) at 43 degrees, in 20-30 minutes from beginning of hyperthermia, local blood flow in cerebral cortex reduced significantly and approached to 40 percent of initial level. With further increase of temperature, blood flow could not be measured and this means that it has stopped.

Administration of such powerful scavenger of free radicals as dimethyl sulfoxide (DMSO) has dramatically changed the picture, in 20-30 minutes after beginning of 43-degree hyperthermia, local blood flow actually returned to the initial level and, unlike the dextran-treated group, at 45 degrees, initially, the local blood flow was measurable (for 5-10 minutes of hyperthermia) and in 20-30 minutes, blood flow in this group of the animals became unmeasurable as well.

Thus, administration of scavenger of free radicals, dimethyl sulfoxide provides practical opportunity to reduce, at least partially, the scale of brain injury caused by hyperthermia.

Conclusion: immediately upon beginning of illumination (i.e. ischemisation) of cerebral cortex great quantities of active forms of oxygen and nitrogen oxide form; emergence of the complexes of NO and hemic iron takes place as well. In the process of ischemia, nitrosylation of the proteins containing mitochondria iron-sulfur centers takes place and due to this, suppression of electrons transport and oxidizing phosphorylating. It was established that similar processes develop in penumbra area of cerebral infarction as well, though, with certain delay and lower intensity. And this allows prevention of cytotoxic effect of nitrogen oxide in the therapeutic window. For this, it is necessary to suspend reduction of nitrogen oxide quantity in penumbra and break concentration balance between nitrogen oxide and oxygen radicals, in favor of the former. Thus, nitrogen oxide acquires the function of antioxidant and protects the cells from destructive action of the oxygen radicals. Extremely high sensitivity of the tissues of central nervous system to local hyperthermia exposition is established even at $41^{O}C$, necessitating urgent preventive measures, if in normal cerebral (non-cancer) tissue the temperature achieves $41^{O}C$ limit that would inevitably cause formation of ischemic stroke. In the conditions of local hyperthermia, one of the most significant causes of central nervous system tissues injury is emergence of micro thrombi in the cerebral vessels. Stopping of blood flow, together with the other outcomes, worsens thermal clearance, where the tissue maintains high temperature. This amplifies destructive action of hyperthermia and contributes to formation of ischemic stroke. Growth of blood viscosity decelerates blood flow and create favorable conditions for thrombus formation, especially in the venous system. Worsening of blood rheological properties causes intensification and increase of dimensions of cerebral tissue injury induced by both, photochemical method and local hyperthermia. For the purpose of prevention and stopping of such development of the processes, permanent control of the rheological properties of the blood flowing from the cerebral system is necessary. Administration of the free radicals scavenger DMSO (dimethyl sulfoxide) significantly delays development of the ischemic stroke induced in the cerebral tissue and also

significantly improve functional condition of penumbra area, thus reducing its size and contributing to increase of so called therapeutic window.

Theoretical and practical significance. We regard that the results of this work would, primarily, contribute to more exact specification of general principles of hyperthermia therapy and at a time of its use at oncological clinics, the limit of thermal tolerance of the central nervous system tissues and the roles of blood rheological properties and free radicals in prevention of possible injury induced by hyperthermia of the normal (non-cancer) tissue will be duly taken into consideration.

Within the therapeutic window, in penumbra area of focal cerebral infarction, cytotoxic effect of nitrogen oxide should be avoided and for this, reduction of the quantities of nitrogen oxide in penumbra area must be stopped (as demonstrated in our experiments) and break the concentration balance between nitrogen oxide and oxygen radicals, in favor of the former. In this way, nitrogen oxide acquires the antioxidant function and protects the cells from destructive effect of the oxygen radicals.

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IMMUNE CHANGES IN THE PATHOLOGY OF FORMATION ALLERGIC DISEASE CHARACTERISTICS, AT A TIME OF BRAIN AND ISCHEMIC STROKE

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SUMMARY

The main goal of our research was obtaining of such specific data that would specify the following, in the process of cerebral tissue (both, in ischemic focus and penumbra) in the process of formation of focal strike and upon its completion: 1. Dynamics of local blood circulation and oxygen partial pressure changes and level of nitrogen oxide at different time intervals; 2. Role of change of blood rheological properties and free radicals in determination of both, geometrical dimensions and blood circulation level in penumbra; 3. Results of analysis of the morphological changes in focal ischemia center and penumbra area tissues.

Keywords: allergic disease, immune changes, brain, ischemic stroke

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SARS-COV2 VIRUS AND THYROID GLAND DISORDERS; A REVIEW

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ნანული ნინაშვილი [1,2], ირაკლი მჭედლიშვილი [1], ხათუნა ჭაავა [1,3], მარინა გიორგობიანი [1], ლევან გიორგობიანი [1], ნინო გეგეშიძე [1,3]

SARS-COV2 ვირუსი და ფარისებრი ჯირკვლის დაავადებები

[1]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისი, საქართველო; [2]დაავადებათა კონტროლისა და საზოგადოებრივი ჯანმრთელობის ეროვნული ცენტრი, თბილისი, საქართველო; [3]კლინიკა „რედი", თბილისი, საქართველო

რეზიუმე

კვლევა მიზნად ისახავდა SARS-COV2 ვირუსის გავლენის შესწავლას ფარისებრ ჯირკვალზე. მიუხედავად კონტრასტული შედეგებისა, მზარდი მტკიცებულებების მიხედვით, SARS-COV2 ვირუსი ფარისებრი ჯირკვლის ფუნქციის დარღვევებს იწვევს, რაც, ძირითადად, ქვემწვავე თირეოიდიტის, არაფარისებრი ჯირკვლის დაავადების სინდრომისა და ჰიპოთირეოზის სახით ვლინდება. თავის მხრივ, ფარისებრი ჯირკვლის დარღვევები გავლენას ახდენენ SARS-COV2 ვირუსით გამოწვეული ინფექციური დაავადების COVID-19-ის მიმდინარეობის სიმძიმესა და გამოსავალზე. ეს ურთიერთქმედება კომპლექსურ ხასიათს ატარებს. ქვემწვავე თირეოიდიტი ფარისებრი ჯირკვლის ყველაზე გავრცელებული დარღვევაა და, შესაძლოა, COVID-19-ის პოტენციურ გრძელვადიან გართულებად ჩამოყალიბდეს.

Background: The recent respiratory infection pandemics showed that they are a great public health problem worldwide and a serious disease and economic burden to all populations. A newly emerged disease – COVID-19, caused by SARS-CoV2 virus, rapidly acquired pandemic patterns in 2020. Viral infections are frequently cited as a major environmental factor implicated in subacute thyroiditis and autoimmune thyroid diseases [1,8]. Clusters of the disease have been reported during outbreaks of viral infection. Onset of the disease are observed between June and September and this seasonal distribution is almost identical to that of established infections due to some enteroviruses (Echovirus, Coxsackievirus A and B), suggesting that enterovirus infections might be responsible for a large proportion of cases [2,3]. Subacute thyroiditis has occurred in epidemic form: patients with subacute thyroiditis diagnosed during a mumps epidemic were found to have circulating anti-mumps antibodies even without clinical evidence of mumps [4]. Patients with subacute thyroiditis, who had no clinical evidence of viral disease, demonstrated increases by at least four times in viral antibodies. These viral antibodies included antibodies to mumps virus, but also coxsackie, adenovirus and influenzae. Coxsackie viral antibodies were the most commonly found, and the changes in their titers most closely approximated the course of the disease [5]. Thyroid disorders in patients with congenital rubella were first reported in 1975 [6]. A substantial number of patients with SARS have shown abnormalities in thyroid function. As SARS is a disease known to cause multiple organ injury, it has been supposed that SARS could have a harmful effect on the thyroid gland [7]. However, low serum triiodothyronine and thyroxine levels associated with decreased TSH concentration are in favor of central hypothyroidism assumed to be of viral origin [8]. In a recent study Weider T. et al. investigated the presence of enteroviruses, parvovirus B19, HHV-6, EBV, CMV and HCV in addition to five gastroenteric viruses (adenovirus, astrovirus, norovirus, rotavirus and sapovirus) in thyroid tissue from AITD (autoimmune thyroid disease) patients and controls and concluded that viruses may represent environmental triggers of thyroid autoimmunity. Actually, the findings may add evidence to this possibility proving that multiple viral agents are capable of producing unapparent infection of the gland [9].

Aim: The study aimed to identify whether COVID-19 infection impact on thyroid gland function based on the literature review.

Methods: Thyroid gland disorders were selected in accordance with ICD-10: E00-E04 – Subclinical iodine deficiency hypothyreosis and other forms of hypothyreosis, E06 – Thyroiditis, presented by: EO6.0Acute thyroiditis, E06.1Subacute thyroiditis, EO6.2Chronic thyroiditis with transient thyrotoxicosis and E06.3Autoimmune thyroiditis, E0-05 – Thyrotoxicosis, C73 – Thyroid cancer. References were searched in PubMed and ResearchGate for articles published during COVID-19 pandemic. Preference was given to studies, published in 2021and 2022. The MeSH terms were based on the thyroid gland pathology in accordance with ICD-10.

Results: Studies showed that the prevalence of thyroid dysfunction in patients positive for COVID-19 virus varied widely between 13-64% [10] and SARS-CoV2 can contribute to increased rates and severity of thyroid dysfunction in COVID-19 patients. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to multiorgan dysfunction through pulmonary and systemic inflammation. Infection also affects the thyroid gland directly via cytopathological effects of the virus or indirectly through cytokines, complement systems and coagulation mechanisms. The direct cytopathological damage of host cells and the dysregulated immune response caused by the severe acute respiratory syndrome coronavirus 2 is assumed to be the primary underlying mechanisms of COVID-19 [11]. Though cases of subacute thyroiditis developing secondarily to SARS-CoV-2 virus infection has been described in literature during the pandemic induced by hypophysitis or by hypothalamic dysfunction [7], growing evidences suggest that subacute thyroiditis is a prevalent disease during COVID-19 epidemic years [12-15]. Furthermore, independent of any other underlying causes, patients with hyperthyroidism are likely to be at risk for poor outcomes, such as long hospital stay and mortality, as well as higher risks of severe and fatal COVID-19 disease [16]. Given that thyroid abnormalities have been linked to disorders such as diabetes, obesity, kidney dysfunction and liver disease, and that patients with these conditions are more likely to contract COVID-19 [17], an underlying poorly-controlled thyroid disorder might exacerbate SARS-CoV-2 infection [18,19], however contrasting results have been reported in the reviewed literature across the thyroid disorders. In a study with 50 patients confirmed with moderate to critical COVID-19 with no history of thyroid disease, Chen et al. reported altered thyroid function in more than 60% of patients [20]. A Chinese cohort of 367 patients with predominantly mild to moderate COVID-19 detected abnormal thyroid function in 62 patients (16,9%). Twenty-seven patients (7,4%) had non-thyroidal illness syndrome (NTIS) and 30 patients (8,2%) had biochemical alterations that were suggestive of distinct phases of thyroiditis such as: isolated low TSH and high-normal fT4, isolated slightly elevated fT_3, high-normal Ft4 or isolated low fT4. None had overt thyrotoxicosis. Of these 30 patients with subnormal TSH, 5 presented anti-TPO or anti-TSHR autoantibodies, suggesting an autoimmune component in these cases. Pre-existing autoimmune thyroid disorder was present in 5 patients [21]. In contrast with the previous studies, Khoo and collaborators, did not found any case of overt thyrotoxicosis in a cohort of 334 patients admitted with COVID-19 in intensive therapy unit [22]. Most COVID-19 patients (86.6%) were euthyroid but 5.7% present subclinical hyperthyroidism and a small proportion present overt hypothyroidism (0,6%), which did not differ from non-COVID patients. A small significant reduction in TSH and fT_4 was observed in patients with COVID-19 when compared with non-COVID-19 patients which might be compatible with a nonthyroidal illness syndrome and did not justify any treatment. A retrospective study conducted in the New York City health system evaluated a cohort of 3703 COVID-19 patients, of which 251 patients (6.8%) had pre-existing hypothyroidism. The authors found that hypothyroidism was not associated with increased risk of hospitalization or an increased risk of mechanical ventilation or death [23]. Other studies have also shown that the prevalence of hypothyroidism appears similar in COVID-19 patients compared to the general population, which indicates that hypothyroidism does not increase the chance of COVID-19 infection, and also that hypothyroidism is not associated with a greater COVID-19 death risk [24,25]. Little is known regarding the effect of COVID-19 on the development or progression on thyroid cancer, or the development or progression of thyroid cancer, or susceptibility of people with thyroid cancer to Cancer or COVID-19-related complications [17,41]. Early data suggests that COVID-19 per se does not worsen the outcome of

cancer, but as the pandemic continues, with investigations and treatment delay, morbidity and mortality from thyroid cancer may increase [26-28], controversial results were presented by Guan WJ et al. Based on the study on 1590 hospitalized patients across mainland China between 11 December 2019 and 31 January 2020, Guan WJ et al. concluded that malignancy predisposed to adverse clinical outcomes in patients with COVID-19 [29]. Relatively more consistent results in the reviewed literature were found on thyroiditis. Subacute thyroiditis (SAT; also known as de Quervain thyroiditis) is a self-limiting disorder consisting of three phases: painful swelling of the thyroid, hypothyroidism and euthyroidism. In May of 2020 an Italian case-report provided the first case of subacute thyroiditis (SAT) potentially associated with a prior mild COVID-19 infection [30]. Subsequent studies also reported additional isolated cases of painful symptomatic SAT, developing secondarily to SARS-CoV-2 infection and reinforcing a possible association between SARS-CoV-2 infection and SAT [31-38,13,14]. Studies regarding thyroid function and COVID-19 in adults and children suggest that the virus can contribute to increased rates and severity of thyroid dysfunction [10,38-40]. One systematic review incorporating 1,237 adult patients, identified a positive correlation between thyroid dysfunction and clinical severity of COVID-19, with prevalence of thyroid dysfunction in patients positive for COVID-19 varying between 13-64% [10]. The study on the effect of COVID-19 on the presentation of thyroid disease in children showed that the distribution of thyroid presentation by year increased over the study period; the greatest number of thyroid presentations occurred in 2021 (n=60, 25% of total over time period) and the fewest in 2020 (n=10, 4% of total over time period). There were no statistically significant differences in biochemistry, antibody status or other clinical characteristics between those who presented with hyperthyroidism prior to the pandemic or after [40]. SAT could be a potential long-term complication of COVID-19 [40]. Though prevalence of manifestations of thyroid dysfunction differs by its type across studies, thyroid dysfunction is common [17,16,31,35,43] and SAT could be potential long-term complication of COVID-19. Interestingly, it's of note that several studies have emphasized a relationship/bidirectional impact or interaction between COVID-19 infection and SAT [16-18,31,38]. According to these studies the interaction between the thyroid gland and COVID-19 is complex and bidirectional: on one hand, similarly to other respiratory viruses, thyroid dysfunction is also common in patients with COVID-19 infection.

Conclusion: SARS-Cov2 virus effects functioning of thyroid gland and aggravates existing thyroiditis, there also might be a complex and bidirectional interaction between COVID-19 and thyroiditis.

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SARS-COV2 VIRUS AND THYROID GLAND DISORDERS; A REVIEW

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SUMMARY

The study aimed to identify whether COVID-19 infection impact on thyroid gland function. SAR-CoV-2 virus impacts on thyroid gland function. Thyroid dysfunction is common and subacute thyroiditis is a prevalent thyroid gland disorder tend to be a potential long-term complication of COVID-19. The interaction between the thyroid gland and COVID-19 is complex and bidirectional.

Keywords: SAR-CoV-2 virus, thyroid gland, thyroiditis, relationship

აბსტრაქტები / Abstracts

1. MAIA DATUASHVILI [1], NELI BAKURADZE [2], NINO OTARASHVILI [2]

TOPICAL ANTIANDROGENETIC THERAPY IN THE MANAGEMENT OF ACNE

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Introduction: Prevalence of acne vulgaris is estimated to affect 9.4% of the global population making it the 8th most prevalent disease worldwide. Treatment scheme based on the acne pathogenesis [Gollnick H. et al. JAAD.2003;49 (suppl 1) S1-37] is actual even for today. But not each pathway of acne development has an appropriate active ingredient for topical therapy, especially for regulations of sebaceous glands abnormalities.

The goal of our study was to analyze the results of "Multicenter, randomized, double-Blind, vehicle-controlled study to evaluate the safety and efficacy of clascoterone1 (CB-03-01) Cream, 1% applied twice daily for 12 weeks in subjects with facial acne vulgaris".

Materials and methods: There were involved 708 subjects (age 12 year and older) with mild to moderate acne (24 from our site); During 6 months 353 patients used Clascoterone, 355 - only placebo. IGA (International of Global assessment), inflammatory lesion count (ILC), non-inflammatory lesion count (NILC) and total lesion count (TLC) were assessed in every scheduled visit.

Study results: 2 Point Reduction in IGA & IGA - score of 0 (clear) or 1 (almost clear) was significant and P = 0.0006. Absolute change from baseline in non-inflammatory lesion count (NILC) - P = 0.0009. Absolute change from baseline in inflammatory lesion count (ILC) - P = 0.0027. Treatment emergent adverse events were similar between Clascoterone and vehicle and were mostly mild.

Discussion: Clascoterone cream 1% demonstrated statistically significant efficacy in primary endpoints with side effects similar to vehicle—IGA Success & Absolute Reduction.

Conclusion: Based on the clinical research Clascoterone cream 1% is approved for use as a topical androgen receptor inhibitor indicated for the treatment of acne vulgaris in patients 12 years of age and older. And for nowadays it's indicated as one of the alternative topical medications for mild acne.

2. LALLY MEKOKISHVILI

ACNE – HOW OUR VIEWS HAVE CHANGED

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Acne is one of the most common chronic skin diseases and affects adolescents of both sexes with equal frequency. However, it is a universal condition and can occur at any age. In the last period, the so-called Late acne has become more frequent, affecting almost 40% of adult women.

In recent years, our knowledge of the pathogenesis of acne has improved significantly due to intensive research. According to the modern concept, acne is an Androgen-dependent disease of the pilosebaceous unit, in which the activation of the immune response and the development of inflammation are caused by hyperseborrhea, changes in the composition of sebum, dysbiosis between skin commensal microbes (and not an increase in the number of C acne, as previously thought). It turned out that a specific phylotype C-acne (IA1) plays an important role in pathogenesis.

Although the disease is not considered life-threatening, it significantly reduces a person's quality of life, self-esteem, and can leave live long physical or psychological scars. At a certain age (from 1 year to 7 years), when the level of androgens should be at the lowest, the development of acne can be considered a signal of endocrine disorders with hyperproduction of androgens (early adrenarche, adrenal hyperandrogenism, androgen-secreting tumor), which requires consultation of pediatric endocrinologist. It is important to identify signs in children that predict severe disease in adulthood and require timely and relatively aggressive treatment.

A modern approach to acne treatment involves a combination of local, systemic and procedural methods, the use of appropriate skin care products, restoration of normal skin microbiota, taking into account patient expectations, maximum abstinence from antibiotic therapy, the use of active substances that act

on several pathogenic mechanisms simultaneously, prevention and treatment of post-acne scars and spots. In cooperation with the patient all this makes it possible to obtain an ideal result.
This report will outline modern views on the pathogenesis and treatment of acne, as well as own long-term clinical experience in treating acne patients.

3. NATIA SHEKLASHVILI [1], LALLY MEKOKISHVILI [2]

BASOSQUAMOUS CARCINOMA – A RARE METATYPICAL VARIANT OF BCC (CASE REPORT)

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Introduction: Basosquamous carcinoma (BSC), also called metatypical basal cell carcinoma, is an uncommon and malignant subtype of non-melanoma skin cancer. It has features that are halfway between basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BSC currently represents approximately 2% of all non-melanoma skin malignancies and is predominant in men. It generally affects elderly or older adults; some cases may rarely develop in children too. Clinical manifestations may be a plaque, papule, or nodule with an ulcerating potential, especially on the head and neck or in other sun-exposed areas. Probably due to its very rare occurrence, data on pathogenesis, course and treatment are inconsistent. BSC may behave aggressively, with a propensity for local recurrence and a potential risk for distant metastatic spread. Differential diagnosis includes SCC, BCC, Merkel cell carcinoma, amelanotic melanoma, actinic keratosis.
Case description: We present 73 years' male patient with asymptomatic, solitary, scaly, pink papule on his forearm, measuring 0,5X0,4 cm. The skin rash had developed about one year ago, slow growth was observed. Dermoscopic features were arborizing vessels, keratin masses, white structureless areas, superficial scale and blood spots in keratin masses. The patient was referred to an oncologist with a preliminary diagnosis: Basosquamous carcinoma. A wide excision of the tumor was performed. Histological analysis with hematoxylin and eosin (H and E) stained slides revealed multiple islands of atypical keratinocytes throughout the dermis, exhibiting both basaloid and squamous differentiation. Immunohistochemical (IHC) analysis with p63 and CK5/6 confirmed the diagnosis of a basosquamous carcinoma.
Conclusion: In the differential diagnosis of pink lesions on sun-exposed areas of the body, it is important to consider a rare and aggressive variant of BCC, basosquamous carcinoma, which both dermoscopic and histopathological findings exhibit features of both BCC and SCC. It is vital to appreciate the importance of early resection with free margins, a full workup for lymph node and distant metastases, and a regular follow up to detect a disease recurrence.

4. TINA KITUASHVILI

NAILS – A MESSENGER OF HEALTH

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Changes in the nail plate indicate various diseases of the skin or internal organs which gives it diagnostic value. Sometimes these changes appear before the full manifestation of the disease, sometimes - directly during the course of the disease, or after its resolution. Damage of the nail plate can clinically manifest by changes in its structure or color. There are various known structural changes of the nail, including: onycholysis, koilonychia, irregular pitting, beau's lines, onychauxis, onychogryphosis, onychomadesis, onychorexis, onychomalacia, median canaliform nail dystrophy. Behind each of above-mentioned conditions, another pathology may be hiding, such as the impact of external or internal factors: trauma, contact with chemical substances, nail polish, soap, age (metabolic changes, circulatory disorders), drugs - retinoid or chemotherapy. It may indicate the pathology of other organ systems, such as anemia, hemochromatosis, hypothyroidism, systemic lupus erythematosus, diabetes, lung, heart and digestive system diseases, eating disorders, obsessive-compulsive disorder; Or it may be a manifestation of the following skin diseases: psoriasis, atopic dermatitis, alopecia areata, ichthyosis, tuberous sclerosis, lichen planus, eczema, pemphigus vulgaris, psoriatic arthritis, scleroderma, fungal and bacterial skin infections. Nail deformities with color changes may also indicate any pathology of internal organs, for example, blue

color can be a sign of oxygen deficiency, white - liver disease and diabetes mellitus, light pink - anemia, half pink and half white - kidney disease, yellow color - lung disease, nail infection and tobacco use, red lunula can be seen in lupus, heart disease, alopecia areata, arthritis and dermatomyositis, blue lunula can indicate intoxication. Collection of complete patient history and clinical evaluation helps us in making the differential diagnosis.

5. LIKA TCHUMBASHVILI [1], NELLY BAKURADZE [2], GURANDA GABESKIRIA [1], NELLY KESHELASHVILI [2]

THE ROLE OF THE SCALP BIOPSY IN THE DIAGNOSIS OF ALOPECIA

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Introduction: Alopecia refers to the simultaneous loss of a hair shaft or follicle, or both, on a certain area of the scalp. It is divided into scarring and non-scarring forms, the treatment and outcome of which are different. Correct and timely diagnosis has a great impact on the effectiveness and outcome of treatment. For diagnosis, biopsy is rarely used. In most cases, Trichoscopy is used to clarify the diagnosis along with the evaluation of the clinical picture. Scalp biopsy is used when it's not clear, what type of alopecia we are dealing with - scarring or non-scarring. It is the diagnostic value of biopsy that will be focused on in these two clinical cases.

Case 1: The patient is a 41-year-old woman with a 20-year history of alopecia, untreated, otherwise healthy. Clinically: in the forehead area - baldness characteristic of female androgenetic alopecia; In the occipital region - an oval bald area of 3 cm in diameter. With dermatoscopy: miniaturization of hair strands in the forehead area, variable diameter-anisotrichosis, single yellow dots. There were no miniature strands of hair in the occipital region. Single yellow and black dots, weak exclamation mark-like hair strands, with perifollicular erythema in some places, weak skin atrophy on both sites were observed. Preliminary diagnoses: androgenetic alopecia and combined variant of alopecia areata. At the first stage, the patient refused to do a biopsy. After 3 months of treatment with 2% minoxidil and mometasone furoate topical therapy, as well as triamcinolone acetate injections, the patient had multiple new hair growths on the forehead, while the occipital area remained unchanged. To clarify the diagnosis, the patient agreed to perform a biopsy from the occipital region. Histologically (hematoxylin&eosin) it was revealed: Keratinocyte vacuolization, exocytosis, lymphoid aggregates in the papillary dermis, miniaturization of some hairs and perifollicular lymphoid infiltration in the infundibulum area of the follicle and focal small perifollicular fibroplasia, loss of bordering sebaceous glands, reduction in the number of hair follicles. No significant incorporation of specific antibodies was observed by direct immunofluorescence assay. Based on the obtained results, a diagnosis of Lichen Planopilaris in the occipital area was made. along with local therapy, Hydroxychloroquine 200 mg tablets 2 times a day, for 6 months, was prescribed. 3 months after the treatment, perifollicular hyperemia was no longer observed in the occipital region, the treatment continues.

Case 2: 33-year-old female patient with complaints of hair loss in the frontal-parietal-occipital areas since 2017. In 2021, she consulted a dermatologist and was treated with a diagnosis of Alopecia Areata. She was treated with local corticosteroid ointment (triamcinolone), tacrolimus, castor oil with periodic improvement, however, new lesions appeared, which is why intralesional injections of triamcinolone were performed from March to June 2023, with temporary results, however, an increase in the number of lesions was noted, which is why he referred to our clinic. Clinical Features: multiple 2-3 cm round hairless, hyperemic site on the scalp in the frontal-parietal-occipital areas, skin atrophy in the forehead area. Trichoscopy features: the atrophic area of the skin in the forehead area with a significant capillary network, in the parietal and occipital area, hair follicles are absent in the areas of damage. Based on clinical and trichoscopic findings, a diagnosis of cicatricial hair loss (L66) was made; to clarify the diagnosis, a skin biopsy was performed from an atrophic area of the skin. According to histomorphological and direct immunofluorescence studies, a diagnosis of non-scarring alopecia - alopecia areata was established and treatment with Minoxidil 2% 1 ml rubbed once a day, Bepanthen cream once a day rubbed into atrophic areas of the head for 2 weeks was prescribed. In 1 month after the beginning of treatment the condition

improved. During the treatment of the patient, based on atrophic areas of the scalp and trichoscopy findings, cicatricial hair loss was suspected, which was not confirmed by histomorphological examination. *Conclusion:* Despite its diagnostic value, scalp biopsy is rarely prescribed to determine the form of alopecia, which is sometimes due to the patient's refusal, the cost of the study, also waiting time for result. These two clinical cases clearly confirm the importance of histomorphological investigation for accurate diagnosis and adequate treatment.

6. KAKHA BREGVADZE

A 12-YEAR-OLD BOY WITH MACROCEPHALY AND PIGMENTED MACULES ON THE PENIS

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Pathogenic variants in PTEN are linked with a group of inherited disorders termed PTEN hamartoma tumor syndrome (PHTS). Conditions falling under PHTS, like Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome, can affect numerous body systems, including the skin. Individuals with PHTS have elevated risks of various cancers over their lifetimes, including melanoma, although skin manifestations are generally non-cancerous. Examples of mucocutaneous manifestations associated with PHTS include trichilemmomas, oral papillomas, penile freckling, acral keratoses, and arteriovenous malformations. Due to the wide array of possible clinical presentations and the varying degrees of symptom severity, many individuals with PHTS might remain undiagnosed for an extended period. We describe a case of a male child who received the PHTS diagnosis at the age of 12. His clinical features included macrocephaly, hypertrophy in the left arm, thyroid nodules, penile freckles, developmental delay, and an autism spectrum disorder. Whole exome sequencing revealed a de novo heterozygous variant in the PTEN. The case highlights the diverse and complex nature of PHTS, emphasizing the necessity for early diagnosis, multidisciplinary care, and surveillance protocols, offering the potential for improved prognostic outcomes and enhanced quality of life for affected individuals.

7. KONSTANTINE TSAGAREISHVILI

CUTANEOUS HORN (CORNU CUTANEUM)

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Increasing the number of the geriatric population is a big challenge for both the primary care physicians and dermatologists. The old-age dependency ratio (for both sexes 65 years old and above) was increased 1.5 times in Georgia between 1994 and 2023. The cases of the skin tumors increases and their courses changes in the geriatric age, which significantly affects the quality of life of the patients. The clinical diagnosis - cutaneous horn is more commonly found in the elderly population between 60 to 80 years of age. The causes of the development of cutaneous horn are mainly related to viral wart and seborrheic keratosis in 50% and more cases, in 23-37% cases to actinic keratoses, and only in 20% cases to malignancy. Histological examination is crucial to determine the cause of the cutaneous horn and is necessary to rule out the malignancy. The knowledge and experience of the clinician is also very important to distinguish the malignant and non-malignant processes on the skin. Treatment and supervision of the old-age dermatological patients should be performed considering the central principles of geriatric science.

8. SALOME PATARAIA

PSYCHODERMATOLOGY – INTERACTION BETWEEN THE MIND AND THE SKIN

Kanveni - S/R National Center of Dermatology and Venereology, Tbilisi, Georgia

Psychodermatology is science about interaction between mind and skin. Patients may have many types of mental disorders which are manifested by various, unpleasant sensations on the skin. Although it is a mental illness, patients with a similar diagnosis usually go to a dermatologist because they are convinced that they have a skin problem. For example, delusional disorder in dermatology is one of those health states where observation, patience and correct management are required not only to treat the patient, but also to assess the behavior of his/her family members, as the "Folie a Deux" phenomenon is not so rare.

Among approximately one third of dermatological patients, effective management of the skin diseases involves taking into account psychological factors related to it. Management of such patients requires caution so that they do not lose trust in doctors (as a rule, such patients have a bad experience of communication with doctors due to the fact that doctors do not take their complaints seriously) and in the future receive the treatment they need without any doubts. We have to remember that the dermatologist can be the only doctor from whom the patient will receive recommendations and follow them.

9. KONSTANTINE TSAGAREISHVILI, ALEXANDER TSAGAREISHVILI

GERIATRIC PATIENTS AT THE DERMATOLOGY OUTPATIENT CLINIC

Akaki Tsereteli State University, Kutaisi, Georgia

Background: The elderly population is rapidly growing worldwide. The old-age dependency ratio (for both sexes 65 years old and above) increased 1.5 times in Georgia between 1994 and 2023. In the geriatric age, the number of the certain dermatoses respectively increases, there are changes in their courses, and the presence of polypharmacy and comorbid diseases complicates the process of treatment, significantly affecting the quality of life of patients.

The aim of the study was to determine the prevalence of dermatological diagnoses among geriatric patients during their ambulatory visits to a Dermatology Clinic. This involved a retrospective analysis of the ambulatory patients in 2023, who sought a dermatologist's consultation for their skin disorders for the first time and were aged 65 and older. The study additionally investigated the number of patients in 2023 utilizing the multi-disciplinary ambulatory care services of the Kutaisi Federal Hospital, encompassing both outpatient and inpatient services across all age groups, with a specific focus on geriatric patients.

Results: The total number of ambulatory patients who addressed the dermatologist for the first time at the dermatological clinic was 2,495, of which 219 (8.38%) were aged 65 and older, presenting with various dermatoses. The age distribution of the geriatric patients (219) with dermatoses is as follows: 65-74 years old - 128 (58.4%), 75-84 years old- 77 (35.2%), and over 85 years - 14 (6.4%). Following is the gender distribution: 106 males (48.4%) and 113 females (51.6%), differentiated by residency: urban residents constituted 119 (54%) and rural residents 100 (46%). Among the six most frequently diagnosed dermatoses in elderly patients, dermatitis was the most prevalent (n=86, 39.27%); including Stasis dermatitis (n=15, 17.44%); lichen simplex chronicus (n=6, 6.97%), seborrheic dermatitis (n=3, 3.49%). The Fungal infections were the second most frequently diagnosed dermatological pathology (n=31, 14.15%); including the numbers of onychomycosis (n=7, 25.9%) and Cutaneous candidiasis, (n=4, 12.9%). Xerosis was observed in (n=20, 9. 13%) cases, and pruritus in (n=19, 8.67 %); Zoster was the most frequently diagnosed viral disease (n=17, 7.76%); Psoriasis accounted in (n=9, 4.11 %); and Skin tumors were identified in (n=6, 2.74%), Including basalioma (n=5 83.3%). The study also included an examination of the number of patient visits across all age groups of the multi-disciplinary ambulatory care services of the Kutaisi Federal Hospital, for the year 2023. The total number of those patients was 22,129, which included 1,218 (5.5%) geriatric patients (aged 65 and above). Comparatively, within the hospital during the same period, there were 8,009 patients from all age groups, of which 1,971 (24.6%) were aged 65 and above.

Conclusions: The proportion of geriatric patients (aged 65 and above) who visited the dermatology clinic for the first time constituted 8.38%. In the multi-disciplinary ambulatory clinic, the segment of geriatric patients (aged 65 and over) who were consulting for the first time included 1,218 (5.5%) patients. Among the hospitalized patients, geriatric individuals (aged 65 and over) accounted 24.6%. The main age range of the geriatric patients consulted for the first time at the dermatological clinic was 65-74 years accounting for 128 patients (58.4%). The six most frequently diagnosed dermatoses in these elderly patients and their prevalence were as follows: dermatitis (n=86, 39.27%); fungal infections (n=31, 14.15%); Xerosis (n=20, 9. 13%), pruritus (n=19, 8.67 %); Zoster (n=17, 7.76%); Psoriasis (n=9, 4.11 %); Skin tumors (n=6, 2.74%).

The knowledge and experience of the clinician regarding the most frequent geriatric dermatoses is also very important. Treatment and supervision of the old-age dermatological patients should be performed considering the central principles of the geriatric science. The issue requires further in-depth epidemiological research to reveal the prevalence of the geriatric skin diseases.

10. SOPIKO LILUASHVILI

VITILIGO – PERSPECTIVES IN TREATMENT

Kanveni - S/R National Center of Dermatology and Venereology, Tbilisi, Georgia

Vitiligo is a chronic autoimmune skin disorder caused by lack of pigment melanin. Its etiology is not entirely certain, although there are known contributing factors such as: other autoimmune diseases, worn invasion, intoxication, sun exposure, iron and copper deficiency, chronic inflammatory diseases and endocrinopathies.

Vitiligo is clinically manifested as a single or multiple depigmented areas on the skin, often symmetrically or rarely asymmetrically located on the body, mainly in areas of sun exposure. Segmental, nonsegmental, mixed and unclassified forms are clinically distinguished. Complications include the presence of other types of autoimmune diseases and severe psychological conditions.

Among the treatment methods, local and systemic treatment are distinguished. Steroids, calcineurin inhibitors and vitamin D analogs are mainly used as a local treatment. In systemic therapy are systemic steroids, cytostatics and cyclosporine. Phototherapy is actively used. Fortunately, recently there has been strong evidence for the use of topical JAK inhibitors and their high efficacy. It should be noted that there are fewer side effects and ease of use, which makes the prognosis of vitiligo much more favorable in the future.

11. TAMAR URUSHADZE

PATHOPHYSIOLOGY OF PRURITUS IN ELDERLY

Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

Pruritus represents an unpleasant sensation that may appear at any age and affect the quality of life. Itching developed in elderly represents chronic pruritus in people over 65 years of age. Despite the fact that many different signaling pathways and mediators of both the peripheral and central nervous system in the neuronal sensitivity to pruritus have been identified, the pathophysiology of chronic pruritus is still not fully understood. The neurogenic pathway of pruritus involves a path from the skin to the brain. The transmission of itch signaling is mediated by interactions between histaminergic, nonhistaminergic sensitive C nerve fibers in the skin, keratinocytes, and the immune system. The pathway of itch transmission to the central nervous system includes the dorsal horn of the spinal cord, the spinothalamic tract, and the thalamocortical pathway. In addition, the phenomenon of neuronal sensitization is described, which leads to the initiation of a vicious circle, that affects patient behavior, scratching, and worsens the itch sensation. The high prevalence of pruritus in elderly is closely related to the changes associated with skin aging, including changes in the structure of the skin, altering its regeneration and barrier functions, declining in its normal immune function and changes in the density of nerve fibers which are determined by intrinsic and photoaging factors.

12. TAMAR NIKOLADZE

BIOLOGICS FOR THE TREATMENT OF PSORIASIS – RECOMMENDATIONS FROM BRITISH ASSOCIATION OF DERMATOLOGISTS

New Vision Clinic, Tbilisi, Georgia

“Biologics” are the protein-based drugs derived from living cells, and are designed to target specific areas of the immune system that are over-active in psoriasis, including tumor necrosis factor (TNF) and interleukins (IL) 17 and 23. There are now 11 licensed and NICE-approved biologics for use in psoriasis. This 2020 evidence-based guideline has been developed by a multi-stakeholder guideline group with the British Association of Dermatologists, and provides recommendations on how to use these important drugs effectively and safely to maximize patient benefit. When deciding which biologic to use, clinicians are asked to consider the person’s psoriasis, other medical problems, patient preferences and drug cost. The guideline covers all the new as well as the older biologics, use in children and special groups and new recommendations on what do when treatment fails, when to increase the dose of biologics and preferred options for conception, pregnancy and breastfeeding. To help ensure guideline recommendations are put

into practice, the guideline group have also developed an implementation “tool kit”. This includes a decision-aid, which has been designed to help explain the similarities and differences between the different agents and to support clinicians and patients when deciding which biologic is most appropriate and to help minimize problems when taking these drugs.

13. TINATIN GHIBRADZE

ONYCHOPAPILLOMA – CLINICAL CASE

I. Javakhishvili Tbilisi State University, Kanveni - S/R National Center of Dermatology and Venereology, Tbilisi, Georgia

Onychopapilloma is a rare, benign nail tumor of unknown etiology. It mainly occurs in middle and advanced aged population of all races. For the first time, based on several clinical cases, in 2001, the term "Onychopapilloma" was presented by scientists Baran and Perrin. Onychopapilloma is mainly manifested in the form of Erythronychia, leukonychia and Melanonychia, and in the distal part of the nail there is Onycholysis and subungual warty growth - subcutaneous keratosis. The diagnosis is based on the micromorphological study of the biopsy material, and after formulating diagnosis surgical treatment is recommended.

The clinical case is about a 37-year-old female patient, who came to the clinic because of these following complaints: 3-year history, pain of the nail area of the right thumb, a linear brown spot and a warty growth of the nail area. The patient was not consulted by a dermatologist, and neither systemic nor local treatment was performed. As a result of clinical examination: there was a linear hyperpigmented spot in the central part of the nail area of the first finger of the right hand, on the distal part, a whitish-colored hyperkeratosis with a warty surface was expressed in the area under the nail. According to digital dermoscopy and clinical-laboratory studies, the clinical decision was – Onychopapilloma, and a treatment recommendation was surgery. The performed surgical method included excision of the formation by the curettage method, based on the conclusion of the subsequent pathomorphological study of the material, the diagnosis of Onychopapilloma was confirmed. The patient's condition is stable and there is no relapse.

14. SALOME PATARAIA

TRICHOLOGICAL MANIFESTATIONS OF OBSESSIVE-COMPULSIVE DISORDER

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Trichotillomania is a constant desire of removing hair from the scalp and from different parts of the body. Trichotillomania often begins in childhood, although it can occur in any age group. Different mental disorders, such as depression, multiple types of addictions, and other problems, can aggravate trichotillomania, so it is important to know the conditions in order to be able to properly manage the disease. Trichotillomania is diagnosed mainly as a result of trichoscopic examination. The characteristic signs of trichotillomania are revealed with the help of the above-mentioned research, which allows us to make a differential diagnosis with such alopecia as, for example, Alopecia Areata. In such cases, it is fundamentally important to diagnose Trichotillomania in order to carry out the correct treatment and avoid complications. When diagnosed with Trichotillomania, it is very important to properly inform the patient/patient's family and explain the role of mental health in this situation. Trichotillomania is a diagnosis that, if left without attention, can lead to such a complicated condition as bezoars and require surgical intervention.

15. SOPIKO AZRUMELASHVILI

HYALURONIC ACID – IRREPLACEABLE PRODUCT IN DERMATO-COSMETOLOGY

Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

Hyaluronic acid is a naturally occurring glycosaminoglycan that composes the extracellular matrix of connective tissue, synovial fluid, and other vital tissues. The popularity of hyaluronic acid specifically stems from its effectiveness, ease of administration, and safety profile (low potential for allergic reactions and requires no skin testing). Hyaluronic acid is widely used in Dermato-cosmetology because participates

in the healing process, tissue renewal, skin hydration, and growth factor stimulation. Depending on the concentration, molecular weight, and stabilization of hyaluronic acid, it is used in mesotherapy cocktails, revitalization, and dermal fillers.

16. TINA KITUASHVILI

ONYCHOMYCOSIS – HOW TO RECOGNIZE IT?

I. Javakhishvili Tbilisi State University, Kanveni - S/R National Center of Dermatology and Venereology, Tbilisi, Georgia

The term "onychomycosis" is used to describe dermatophytoses (a fungal disease caused by dermatophytes) of the finger- and toenails. The disease is widely distributed worldwide. In addition to dermatophytes, onychomycosis may be caused by other fungi, such as molds and Candida. Despite this, dermatophytes are the most common cause of onychomycosis in all countries.

Factors that contribute to the development of onychomycosis include wearing closed shoes, chronic nail trauma, genetic predisposition, and the presence of diseases such as diabetes mellitus, peripheral circulatory disorders, HIV infection, and other immunosuppressive conditions. The variety of causes leads to the variety of clinical manifestations, which makes diagnosis difficult. The diagnosis is established, first of all, according to the clinical picture, in addition, following laboratory research methods are used: detection of fungi by direct microscopy with KOH-test, cultural method, molecular (PCR) diagnosis, and in some cases histological research. The results of the research need to be interpreted correctly. The probability of a false negative result when using any test is high, so a negative test does not rule out the presence of onychomycosis. Differential diagnosis should be carried out with such nosologies that occur with nail damage. Treatment of onychomycosis requires correct mycological identification, selection of the correct method of treatment, that is more appropriate for one or another clinical form of onychomycosis and its etiological cause (systemic, local or combined therapy).

17. NIA TOIDZE, ANA GOGUA, ZAZA GABADZE, NINO ADEISHVILI, MARIAM TUTASHVILI, IA PANTSULAIA, IRMA UBIRIA, LAVRITA PACHUASHVILI

COVID-19 AND VACCINE-INDUCED IMMUNE THROMBOTIC THROMBOCYTOPENIA

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Introduction: Vaccine-induced immune thrombotic thrombocytopenia (VITT), also known as thrombosis with thrombocytopenia syndrome, is a catastrophic and life-threatening reaction to COVID-19 vaccines, which occurs disproportionately in response to vaccination with non-replicating adenovirus vector (AV) vaccines. The mechanism of VITT is not well defined and it has not been resolved why cases of VITT are predominated by vaccination with AV vaccines. However, a normal platelet count does not exclude the possibility of this syndrome in its early stages, Positive antibodies against platelet factor 4 (PF4) identified by enzyme-linked immunosorbent assay (ELISA) assay Significantly elevated D-dimer (> 4 times ULN).

Objectives: VITT remains a risk for patients after administering AV vaccines. In addition to COVID-19 vaccination, the first clues point to the possibility that not only adenoviral vector-based vaccines can cause VITT-like symptoms. This review article aims to describe the etiology, epidemiology, pathophysiology, clinical features, diagnosis, and management of COVID-19 vaccine-induced thrombotic immune thrombocytopenia based on the latest available published literature.

Methods: Preceding the approval of these vaccines, the clinical constellation of this new syndrome was not observed in clinical trials of the ChAdOx1 nCoV-19 vaccine, and a single case was observed in the Ad26.COV2. S vaccine trial recipient. Furthermore, the incidence of major adverse effects has remained exceptionally low following the vaccination of more than 400 million people worldwide.

Result: Due to the concern of VITT associated with the Ad26.COV2. S vaccine, the FDA modified the EUA and recommends limiting the use of this vaccine only to individuals > 18 years of age who are otherwise ineligible to receive any other FDA-approved vaccines due to anaphylaxis to mRNA vaccines or its components or are unable/unwilling to receive any other vaccine.

Conclusion: Fortunately, VITT is very rare. However, it can be life-threatening, especially if the diagnosis and treatment are delayed. Adenovirus vectors provide an affordable framework for highly effective vaccines. Unravelling the mechanisms of the anti-PF4 response in VITT has the potential to provide the basis for a more rational approach to developing safer vaccine delivery systems.

18. SHALVA KEVLISHVILI

SOCIO-ECONOMIC FEATURES OF SEXUALLY TRANSMITTED INFECTIONS AMONG MSM IN GEORGIA

New Vision University; Tsitsishvili children's clinic, Tbilisi, Georgia

Objectives. The aim of our study was to investigate correlation between Socio-Economic conditions and prevalence of Sexually Transmitted Infections among MSM in Georgia.
Methods. The study was conducted in 5 main cities in different regions of Georgia (Tbilisi, Batumi, Kutaisi, Zugdidi and Telavi). During 2015-2019, social workers, LGBT community and non-governmental organizations (NGOs), conducted screening of MSM for STI, which was achieved by disseminating required information through electronic and print media, resulting in maximum involvement of MSM in screening programs for STI disseminating. A specially designed questionnaire/survey has been used to investigate the correlations between the following parameters: age, education, income, awareness of STI, sources of information, residence, frequency of safe sex, number of sexual partners and etc.
Results. The results of current study indicated that low income and educational attainment are the key socio-economic risk factors leading to high rates of STI prevalence among MSM. On the contrary, STI rates were inversely associated with the level of education.
Conclusion. Consideration of Socio-economic risk-factors and using of informational data together, screening and prevention programs should be planned, which will lead to a decrease in the number of STIs among MSM in Georgia

19. ALEENA PARVEEN SHAIKH [2], KRISTINA MAKHARADZE [1], MARINA NAGERVADZE [1], MARINA KORIDZE [1], RUSUDAN KHUKHUNAISHVILI [1], SALOME GLONTI [2]

MTHFR C677T GENE POLYMORPHISM AND ASSOCIATION WITH DISORDERS

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The Methylenetetrahydrofolate reductase (MTHFR) is a general and important enzyme in human cells, which is involved in metabolism reactions of homocysteine and folate. The genetic material for MTHFR enzyme synthesis is situated on 1 chromosome p arm in 1p36.3 position. There are a lot of single nucleotide mutations in this mentioned locus, but among them well-studied is the C677T gene mutation. The C677T/MTHFR polymorphisms impact MTHFR enzyme activity, leading to alterations in methionine and folate metabolism, elevated homocysteine levels, and in most cases subsequent effects on DNA methylation.
This literature review compiles information about the MTHFR C677T polymorphism and explores its potential association with various complex, multifactorial disorders, including cancer, cardiovascular complications, neurological conditions, and diabetes mellitus, among others. The review synthesizes findings from diverse global populations, providing valuable insights for master's and doctorate students, as well as researchers specializing in this field.

20. GIORGI BERIANIDZE [1], KRISTINE PURTSKHVANIDZE [1], NATA KIKNAVELIDZE [1], KETEVAN BARABADZE [3,4], NINO ADAMIA [1,2]

IMMUNODEFICIENCY IN PATIENT WITH KEGG DISEASE (X-LINKED CREATINE DEFICIENCY SYNDROME) – A RARE CLINICAL CASE REPORT

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Background. The creatine deficiency disorders (CDDs), inborn errors of creatine metabolism and transport, comprise three disorders: the creatine biosynthesis disorders guanidinoacetate methyltransferase (GAMT) deficiency and L-arginine: glycine amidinotransferase (AGAT) deficiency; and creatine transporter (CRTR) deficiency. Creatine transporter deficiency is an X-linked genetic disorder caused by a variant in the SLC6A8 gene located on the X chromosome (Xq28). This condition varies in severity with features often including intellectual disabilities, speech delay, autistic features, attention deficit hyperactivity, gastrointestinal issues and immunodeficiency.

Case report. On August 20, 2021, a 5-month-old male was admitted to Ingorokva High Medical Technology University Clinic with a significant birth history. The main complaints during this admission were T-36.8 C; P-164; R-68; T/A - 80/49mm.Hg; SaO_2-89%. Tachypnoe, dyspnoea, desaturation, excessive bronchial mucus production - hard to evacuate. The patient had a history of recurrent hospital admissions for the same presenting complaint. On physical examination the patient exhibited pallor of the skin and circumoral cyanosis. Capillary refill time-2. Turgor and elasticity were reduced. Auscultation revealed a systolic murmur at the heart's apex, although the heart's tones were unclear. Shallow, rhythmic breathing accompanied by retraction and wheezing. Palpation revealed a smooth and painless abdomen, spleen and liver at normal size. Normal diuresis combined with normal intestinal function. Patient was on an enteral tube feeding. Based on this condition genetic disorder was suspected and performed testing for mucoviscidosis, which was negative. CT scan excluded congenital tracheal abnormalities. Immunological indicators were studied and in blood serum was detected low range of immunoglobulins: IgM - 0,43g/l (0,55-2,2g/l); IgA - 0,36g/l (0,8-2,2g/l). It demonstrated a malfunction in humoral immunity, which led to the diagnosis of congenital primary immunodeficiency. After that, the patient was administered intravenous immunoglobulins. Blood tests also showed low creatinine level (normal - 0.39mg/dl), genetic testing for SLC6A8 gene (This gene, located on the X chromosome, encodes the creatine transporter protein responsible for transporting creatine into cells, particularly in the brain and muscles) was performed. Genetic analysis revealed KEGG Disease (X-linked Creatine deficiency syndrome). SLC6A8 gene inactivation impairs CD8+T cell survival, Slc6a8 or Ckb ablation compromises CD8+ T cell expansion in response to infection and Slc6a8 or Ckb deletion weakens TCR-mediated activation of mTORC1 signaling.

Conclusion. Our case particularly highlighted creatine transporter deficiency (CRTR) as an X-linked genetic disorder. CRTR deficiency affects the transport of creatine, leading to creatine deficiency. While it primarily impacts neurological functions, it's not linked to immunodeficiency. Due to absent of neurological symptoms and presence of immunodeficiency was revealed, which gave us suspicion that patient has SLC6A8 gene mutation. In the context of the patient's lack of neurological symptoms alongside the presence of immunodeficiency, the possibility that the patient had an SLC6A8 gene mutation was raised.

21. GIORGI BERADZE [1], VALERI SHARVASHIDZE [1], NINO ADAMIA [2]

FIRST APPROVED CRISPR/CAS9-BASED TREATMENT FOR SICKLE CELL DISEASE

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Background: Sickle Cell Disease is an inherited red blood cell disorder that causes anemia, severe pain and other complications. People with SCD have decreased quality of life. So, it is crucial to create treatment for this disorder. Over decades scientists have tried to create a drug that can solve this problem and now by unifying old knowledge with modern technologies they created a revolutionary therapy for SCD

treatment. *Objectives:* Since the discovery of the CRISPR-Cas system in bacteria, it has become a major field of study. It is a very promising tool that gives us the opportunity to discover new therapeutics. After years of hard work, in December 2023 FDA approved the first drug.
Methods: Scientists used the CRISPR-Cas9 system to "knock out" a gene called BCL11A. This is a transcription factor that is located on the second chromosome and silences γ-globin gene after birth the of a person. When BCL11A is deactivated, the organism produces fetal hemoglobin instead of mutated sickle-shaped cells. HbF can take over the supply of oxygen to the body. The process consists of a few steps: Firstly, the doctor collects patients' blood stem cells, then cells will undergo genetic editing in the laboratory. The next step is to remove existing blood stem cells from the bone marrow to make room for newly edited cells, for this patient goes under chemotherapy and finally receives an IV infusion of the drug.
Results: Firstly, 44 people were enrolled in the study, but only 31 remained long enough to collect data. 29 out of 31 did not have severe Vaso-occlusive crises. None of the patients needed hospitalization. After the treatment patients can have low levels of platelets and white blood cells, which can cause bleeding and high risk of infections. Also, treatment can cause mucositis and febrile neutropenia.
Conclusions: Despite all side effects and high price, this revolutionary discovery can change people's lives. Based on results, it can be said that after some time the CRISPR-Cas9 system will be used to treat many other diseases too.

22. KETEVAN KIMADZE[1], NINO ADAMIA [2], LALI SILAGADZE [2], IRMA UBIRIA [2]

BRONCHIAL ASTHMA IN THE PEDIATRIC POPULATION AND ITS GENETIC PREDISPOSITION

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Introduction: Bronchial asthma is the most common chronic disease in children and affects 14.2% of the world's child population. The disease is characterized by reversible airway obstruction and chronic inflammation. Asthma exacerbations are a significant cause of morbidity and hospitalization in children, with a mortality rate of 0-0.7 per 100,000 children. Consequently, it represents a large financial burden for both the family and the healthcare system. 1-2% of the health budget of developed countries is spent on disease management.
Research material: we made a map - a questionnaire based on which we had to determine the genetic factor of allergic diseases in the children's population, we took as research contingent 150 children aged 6 to 17 years. The questionnaire included: - family anamnesis, tobacco use in the family, pets, dust collectors, food allergens, the period of the year was focused on - the season, environmental conditions, sports, overweight, age.
Research Discussion: The pathogenesis of asthma is based on the interaction of genetic and environmental factors. In recent years, for the development of appropriate preventive or therapeutic measures, special attention has been paid to determining the influence of genetic factors, which, although observed in adult patients, significantly prevails in pediatric age. The genetic and epigenetic mechanisms underlying bronchial asthma in children are not fully understood. To date, more than 100 genes have been associated with asthma, related to the immune system, airway mucosa and lung structure and function, including specific cytokines, Toll-like receptors, sphingolipid biosynthesis regulator 3, gasdermin B, filaggrin protein, genes encoding the major histocompatibility complex and the cysteine-leukotriene metabolism pathway.
Conclusion: the expression of some genes depends on environmental factors based on epigenetic mechanisms. Histone modification at certain loci, DNA methylation, and micro-RNA production regulated by environmental factors (tobacco and alcohol consumption, obesity, stress, etc.) have been reported in pediatric patients with asthma.

23. NINO TIKARADZE, REZIKO TAPATADZE, NINO ADAMIA

LEUKOENCEPHALOPATHY WITH BRAIN STEM AND SPINAL CORD INVOLVEMENT AND LACTATE ELEVATION

Tbilisi State Medical University, Tbilisi, Georgia

Background: Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation, (LBSL) according to MR-spectroscopy is a rare, slowly progressive, hereditary neurodegenerative disease. Dystrophic changes in the nervous tissue are observed, which will lead to a decrease in the volume of the white matter of the brain and functional limitation. The disease is related to the mutation of the DARS2 gene, which provides instructions for making an enzyme called mitochondrial aspartyl-tRNA synthetase. This enzyme is important in the production (synthesis) of proteins in cellular structures called mitochondria, the energy-producing centers in cells. A decrease in the activity of mitochondrial aspartyl-tRNA synthetase leads to the non-inclusion of aspartic acid residue in the structure of all mitochondrial proteins and to the disruption of redox processes in the cell, as well as to the activation of the histotoxic hypoxia mechanism. Clinically, LBSL manifests symptoms of damage to the pyramidal tract, cerebellum, and posterior columns of the spinal cord. Neurological dysfunction affects the legs more than the upper limbs. It is characterized by slowly progressive cerebral ataxia, and later learning problems, cognitive impairment and deterioration of the general neurological status appear. MRI reveals diffuse damage of cerebral hemispheres, brain stem, and spinal cord white matter. The exact number of people diagnosed with this disease is unknown, but based on reported clinical cases, there are less than 200 cases of LBSL worldwide. The disease is considered a pediatric pathology, adult forms are sporadic. Here we present a clinical case of LBSL.

Clinical case: a man is 56 years old, and currently presents with a typical neuromuscular clinical picture with complaints: weakness in the legs, leg muscle cramps at night, lethargy, and blurred vision. The patient has been under observation since the age of 15.

24. NINO KIKVADZE [1], GIORGI KHAKHALEISHVILI [2], NINO ADAMIA [3,4]

ASSOCIATION OF ALLERGIC RHINITIS AND ATOPIC DERMATITIS WITH BRONCHIAL ASTHMA IN A PEDIATRIC POPULATION

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Introduction: Allergic rhinitis, atopic dermatitis (AD) and asthma constitute the triad of atopic diseases, which are common in infants and children and represent a major concern because of leading to a heavy economic burden as well as poor quality of life. More specifically, childhood allergic diseases cause sleep disorders, impede growth, disrupt education and etc.

Aim: The aim of our current research is to study and specify how frequent the coexistence of the mentioned three diseases or any two of them is in population of students of a Georgian public school. In addition, through a specially designed questionnaire, we have the opportunity to study in the case of each patient at what age and which allergic disease was diagnosed for the first time and whether it caused later the development of any other disease with an allergic mechanism, in order to asset the prevalence of the association of AR, AD and BA in the study cohort. Because our research is still in process, to date, our study group includes 109 children, from them there are 65 boys and 44 girls.

Results: Because the prevalence of allergic diseases is closely related to age and dependent on the type of these ailments, the symptoms manifest at different ages. On average, the rate of atopic dermatitis is highest in children under 5 years of age, asthma symptoms are highest in children between 2 and 9 years of age and allergic rhinitis – in those between 6 and 11 years of age. According to the results of our current study, we can highlight that the prevalence of rhinitis in patients with previous AD (42%) is about 22% more than in the individuals without AD (20%). The co-existence of Asthma and allergic rhinitis (AR) is found in 39% of patients, but the prevalence of having both rhinitis and asthma is about 9-10% in patients with AD.

Discussion: When it comes to the association of allergic rhinitis and atopic dermatitis with bronchial asthma in a pediatric population, some studies appear to support the atopic course, according to which allergic diseases occur following a time-based order from atopic dermatitis and food allergy to asthma and allergic rhinitis. But, meanwhile, there are several other researches, the results of which seem to support that the atopic march is less frequent than classically considered. According to our current data, we can say, that there is an association between AD and allergic rhinitis, but as our results show, less than 10% of children with atopic dermatitis or eczema follow the trajectory of the classic atopic march, while Asthma and AR co-exist more often.
Conclusion: At the end of our study, the obtained data will allow us to more accurately assess the relationship between the manifestations of allergic rhinitis, atopic dermatitis and bronchial asthma and their frequency in the study population.

25. GURI KUPRASHVILI, TAMAR KHMALADZE, NINO ADAMIA, IRMA UBIRIA

VIRAL INFECTION: COVID-19 IN THE POPULATION OF CHILDREN SUFFERING FROM BRONCHIAL ASTHMA

TSMU, Faculty of Medicine, M.Iashvili Children's Central Hospital, Tbilisi, Georgia

A unique clinical approach is required for children with asthma who are susceptible to SARS-CoV-2 infection. This approach should take into account the clinical characteristics of the infection, as well as the safety, effectiveness, and efficiency of the COVID-19 vaccine. The purpose of this study is to evaluate the impact of SARS-CoV-2 and the COVID-19 vaccine on pediatric patients with asthma. Through specific search queries, we conducted a thorough investigation of the major medical databases from March 2023 to early global spread of COVID-19, along with relevant data from significant national and international organizations.
Although there was no statistically significant difference in the incidence and morbidity of SARS-CoV-2 between pediatric asthmatic patients and pediatric non-asthmatic patients, it was found that uncontrolled asthmatic children had a higher risk of experiencing severe illness during SARS-CoV-2 infection. A growing body of research suggests that COVID-19 vaccinations are safe, effective, and useful for children with asthma, regardless of the severity of their illness. Since evidence of novel viral variations driving epidemic waves shows that the existing paradigm is out of date, more cohort-based research is needed.

26. NATIA ALIEVI, DAVIT VASADZE, NINO ADAMIA

DEVELOPMENT OF CYTOKINE STORM DURING INFECTION WITH COVID-19

Tbilisi State Medical University, Faculty of Medicine, M. Iashvili Children's Central Hospital, Tbilisi, Georgia

Objective: To describe clinical features, diagnostic findings, treatments and outcomes in patients with new-onset postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders following SARS-CoV-2 infection (COVID-19).
Methods: We retrospectively reviewed medical records for patients who presented with persistent neurologic and cardiovascular complaints between April and December 2020 following COVID-19 infection.
Results: Twenty patients (70% female) were included in this study. 15 had POTS, 3 had neurocardiogenic syncope and 2 had orthostatic hypotension. Six patients had abnormalities on cardiac or pulmonary testing, and 4 had elevated autoimmune or inflammatory markers. All patients were treated with non-pharmacologic therapies and most required pharmacologic therapies. 6 to 8 months after COVID-19, 17 (85%) patients had residual autonomic symptoms, with 12 (60%) unable to return to work.
Conclusions: POTS can follow COVID-19 in previously healthy patients. Appropriate diagnostic investigations and therapies are necessary to identify and treat autonomic dysfunction after Covid-19.

27. ANA KAMKAMIDZE

INFECTIOUS DISEASES OF ANIMALS: A FUTURE TREND

Georgian Agricultural University

In my presentation I will discuss the following topics: what are RNA vaccines, how they are developed and what types of RNA vaccines are available. Presentation also includes the topic of the advantages of RNA vaccines as well as the difference between DNA and RNA vaccines.
RNA vaccines differ from traditional vaccines, unlocking a new era of veterinary medicine. My topic includes how mRNA vaccine works and how it induces immune responses This approach can allow for faster, cheaper development of vaccines. I will speak about mRNA vaccine trials for diseases of importance in veterinary medicine, for example: rabies virus and influenza virus. All issues are accompanied by photos and diagrams which will make the information easy to grasp. There will be a discussion on why RNA vaccine production is so important for veterinary medicine.

28. ANA KAKHNIASHVILI, MARIAM TUTASHVILI, IA PANTSULAIA, NINO ADAMIA, IRMA UBIRIA

BRONCHIAL ASTHMA AND ROLE OF VITAMIN D IN THE IMMUNE SYSTEM IN A PEDIATRIC POPULATION

TSMU, Faculty of Medicine, Tbilisi, Georgia; M. Iashvili Children's Central Hospital, Tbilisi, Georgia

Introduction: Although we can name genetic predisposition as the cause of the development of bronchial asthma in children, its complex interaction with environmental factors is noteworthy.
Objectives: The main goal of the study is to describe the role of vitamin D in the immune system of the children's population, whether the amount of maternal vitamin D and the lifestyle are important for the development of the children.
Methods: This was a series of observations and cohort studies based on which we can discuss the specific numbers of disease formation and their prevalence. Reliable data provides research such as The Vitamin D Antenatal Asthma Reduction Trial (VDAART) and The Copenhagen Prospective Studies on Asthma in Childhood (COPSAC2010).
Results: While the results of the above trials did not meet statistical significance, the effect of prenatal vitamin D3 supplementation was of similar magnitude and direction in both trials (HR of 0.8 for VDAART and 0.76 for COPSAC2010), suggesting a true effect. One possible explanation is that baseline vitamin D status may affect the response to vitamin D supplementation, and since baseline vitamin D level was not a criterion for entry in either trial, this may have biased the results toward the null.
Conclusion: Accumulating evidence suggests a relationship between maternal vitamin D deficiency and the risk of childhood asthma. High-dose vitamin D supplementation during pregnancy appears to reduce the risk of early life wheeze/asthma, but not long-term asthma, in the offspring.

29. TINATIN MIGINEISHVILI, ANA KOBAKHIDZE, NINO ADAMIA, LASHA TCHELIDZE

IDIOPATHIC THROMBOCYTOPENIC PURPURA AND ROLE OF THROMBOPOIETIN-RECEPTOR AGONISTS IN THE PEDIATRIC PRACTICE OF HEMATOLOGISTS

TSMU, Department of Hematology and Oncology of M. Iashvili Children's Central Hospital, Tbilisi, Georgia

Background: Idiopathic thrombocytopenic purpura (ITP, also called immune thrombocytopenic purpura) is an acquired disorder in which there is immune-mediated destruction of platelets and possibly inhibition of platelet release from the megakaryocyte. Treatments of ITP continue to challenge medical doctors because of a lack of well-tolerated and effective drugs. Children who develop chronic ITP may benefit from splenectomy. Immunosuppressive therapy with glucocorticoid drugs and intravenous immunoglobulin is the classical initial treatment for ITP. A novel class of thrombopoietin agonists has recently been developed. Eltrombopag is an oral thrombopoietin-receptor agonist that stimulates thrombopoiesis, increasing platelet production. Eltrombopag produced a very outstanding response in adult and pediatric patients with severe chronic ITP.

Methods: From M. Iashvili Central Pediatric Clinic (Tbilisi, Georgia) with the hematology and oncology department, we analyze 5 patients, suitable according to the study criteria. The study aims to evaluate the clinical and laboratory manifestations. Additionally, we discuss the best way of treatment.
Results: We built charts showing that the median age of our five patients is 11 years. They all have chronic idiopathic thrombocytopenic purpura and platelet counts of less than 30,000 per microliter of blood. All patients have been hospitalized several times in Iashvili Central Pediatric Clinic and have received standard treatments. Two of them have had splenectomy. However, after reducing the dose or stopping the treatment, the relapse occurred soon. In three of them COVID-19, Helicobacter, and Staphylococcus exacerbated ITP. Along with other basic drugs, they were prescribed Eltrombopag 50 mg per day. In 4 patients, the number of platelets increased after taking the drug. Only one patient is resistant to this medication. It responds only to intravenous immunoglobulin. Side effects of Eltrombopag were not detected in the patients studied by us.
Conclusion: The results of our study show that Eltrombopag is well tolerated in raising platelet counts in patients. Additionally, Eltrombopag is an effective treatment option for pediatric patients with chronic ITP and who have an increased risk of bleeding.

30. ANA MAGHRADZE, IVANE CHKHAIDZE, NANI KAVLASHVILI

EPIDEMIOLOGY, CLINIC AND OUTCOME OF MULTISYSTEM INFLAMATORY SYNDROME (MIS-C) IN GEORGIA

Tbilisi State Medical University, International Faculty of Medicine and Stomatology, Pediatric Department, Georgia

Aim of the study was to assess the clinical and lab characteristics and outcomes of MIS-C in Georgia. The study comprised 126 children with MIS-C admitted to Iashvili children's central hospital from December 2020 to February2024. Data were obtained from medical record retrospectively.
Results: For today, 126 cases have been diagnosed in our hospital, about 200 throughout Georgia, Concurrently, the most common presenting symptoms include fever (100%), gastrointestinal (GI) symptoms (86%), cardiac symptoms (66%), rash (48.1%), respiratory (39%) and neurological (28%) symptoms. The average duration of fever was observed to be 8,5 days, ranging from 4 to 12 days. Shock and/or hypotension were common occurrences among patients with MIS-C (24%). In total, 38.7% of the patients admitted to pediatric intensive care unit and 19.3% received vasopressor support. 20% of patient had depressed left ventricular ejection fraction. Cardiac symptoms (69%) predominated over respiratory (40%) and neurological (32%) symptoms. Admission lab findings - elevated CRP - 99.8%, procalcitonin - 97.1%, erythrocyte sedimentation rate - 98%, D-dimer - 98.8% and ferritin - 78%; Lymphopenia - 98.9%, neutrophilia - 96% and hypoalbuminemia 40.3%. High level of 38% received IV Intravenous immunoglobulin, 98.2% - corticosteroids; Anakinra was not used in our clinic. Median duration of hospital length of stay was 14.5 days. Comorbidities were present in 1.1% of the patients. No mortality was recorded.
Conclusion: While being rare MIS-C has very severe presentation that need early recognition and aggressive treatment. The increasing number of MIS-C cases shows that this phenomenon is more common than was thought at the beginning of pandemic. Here is not enough evidence about the long-term consequences yet and we conduct monitoring and evaluation of patients in dynamics.

31. MAYA KHELADZE, NINO CHANKOTADZE

CELLULAR AND HUMORAL IMMUNE RESPONSES TO COVID-19

Sachkhere Medical Center, Sachkhere, Georgia

At the Sachkhere Medical Center in 2021, for the first time in Georgia, a evaluation of immunity in Covid-19 patients was conducted on Elispot. The Elispot analysis was used for the assessment of T-cell immunity in persons exposed to the Covid-19 or SARS-CoV-2 virus vaccinated individuals. To assess the stability of the immune response against SARS-CoV-2, especially those who have no antibodies against the virus. Elispot is an imaging technology to measure the active effects of the immune response to infection. In order to use venous blood to isolate T-lymphocytes, we added the SARS-CoV-2 antigen mixture to the

gel. If the lymphocytes and the virus met each other earlier, then the lymphocytes release cells, visually this is expressed in the so-called varnish. In the central clinic, 24 patients were examined for both humoral immunity (IgM & IgG) and cellular immunity in the form of interferon gamma and interleukin-2. Research has found a proportional position between immunities, namely in those organisms with high antibodies, low cellular immunity and resistance; It was noteworthy that in 2 patients with lethal interferon gamma and interleukin-2, the dynamics decreased sharply, while the level of antibodies increased. Answers To conclude that the presence of T-cell immunity against Covid-19 is not difficult, the immunity is solid from 6 months to 1 year.

32. NATIA CHKHAIDZE

EPIDEMIOLOGY AND RISK FACTORS OF HOSPITAL-ACQUIRED PNEUMONIA IN TERTIARY PEDIATRIC HOSPITAL, TBILISI, GEORGIA

Tbilisi State Medical University, Iashvili Central Children Hospital, Tbilisi, Georgia

Introduction. Hospital-acquired pneumonia (HAP) is one of the most common complications among hospitalized children. This study aimed to determine the epidemiology and risk factors of HAP in the tertiary pediatric hospital in Tbilisi, Georgia.
Methods. The study included pediatric patients admitted to the Iashvili Central Children's Hospital from March 2023 to January 2024. The following data were recorded: age, sex, hospital ward, and risk factors, including comorbid disease, Hb<10 g/dL, pH<7.35, invasive techniques, surgery, hospital admission in the previous month, and interval from admission to presentation of HAP.
Results. The study was performed on 36 patients with a median age of 36 months. Most of the patients (58%) were males. The most common causes of the admission were upper respiratory tract infection (9 patients, 25%), fever (7 patients, 19%), and bronchitis (5 patients, 14%). 17 patients (47%) had histories of hospitalizations within the last 30 days. Most cases (20 out of 36) were late-onset HAP. The median time of HAP onset was 8 days. The median length of the hospital stay was 17 days. 22 out of 36 patients experienced a prolonged length of hospital stay of more than ten days. Most of the patients (24 patients, 67%) had comorbidities. The most frequent comorbidities were developmental delay (6 patients) and epilepsy (5 patients). Logistic regression showed a significant relationship between HAP and the presence of comorbidities, prior hospitalization, prolonged hospitalization, and anemia.
Conclusions. Early identification of risk factors may be useful in identifying patients at high risk of HAP development.

33. NINO DATASHVILI

AUTOIMMUNE SKIN DISEASES IN DOMESTIC ANIMALS

Agrarian University of Georgia

Immune-mediated skin diseases driven by either autoantibodies or self-reactive T cells are commonly encountered by veterinarians. Origin of some of these diseases are identified while others have unknown pathogenesis. Major groups of immune-mediated skin diseases are Blistering Diseases, Melanocyte Diseases and Hair Follicle Diseases. They have commonalities and differences in clinical signs, pathological mechanism and tropism. Participants in immune-mediated skin diseases are autoantibodies such as IgG, IgA, together with complement and other inflammatory molecules as well as white blood cells: neutrophils, macrophages, mast cells, T and b cells, plasma cells, and NK killers. Their target is amongst 50 different skin proteins, such as Desmoglein, Desmcollin and others. Major symptoms include lesions of epidermal and dermal layers, blisters, vesicles, pustules, alopecia, pruritus. Treatment is combination of immunosuppressive therapy.

34. VAKHTANG BERIDZE [1,2], SOPHIO BERIDZE [1], TAMAR BAKHTADZE [1,2], MEGI KHABAZI [1], JOSHUA LEWSON [3], JANE ZEJDA [4]

SCREENING OF DIAGNOSED AND UNDIAGNOSED PEDIATRIC ASTHMA IN BATUMI, GEORGIA

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Background and Objective. A population-based survey including 3239 urban children (age: 9.0±2.4 y.) in Batumi, Georgia showed a low prevalence of asthma in children (1.8%). One potential explanation is underdiagnosis of asthma. To investigate this, we conducted a follow up to the survey with the objective of estimating the level of childhood asthma underdiagnosis and to describe factors related to it.

Methods. Subjects included 437 survey participants who had a history of asthma-like symptoms and no diagnosis of asthma. All children underwent clinical examination (spirometry, skin prick tests, FeNO measurement) to identify new cases of asthma. The distribution of host and environmental factors was compared between the group with newly identified asthma and a group of 59 children with previously known asthma (diagnosed asthma).

Results. Clinical investigation identified 107 cases of undiagnosed asthma. The corrected asthma prevalence estimate was 5.1% (95%CI: 4.4%-5.9%) suggesting that 65% of asthma cases were undiagnosed. Compared to children with diagnosed asthma, children with undiagnosed asthma were younger (8.2±1.6 vs 9.3±2.1; p=0.0005), had less frequent history of allergic disorders (38.3% vs 64.4%; p=0.001), and a lower prevalence of parental asthma (1.8% vs 8.4%; p=0.04). The groups did not differ in terms of environmental characteristics except for more exposure to passive smoking in the undiagnosed asthma group (p=0.01). Multivariate analysis confirmed results of simple analyses.

Conclusion. In Batumi, 65% of children with asthma remain undiagnosed. Older age of a child, coexisting allergic disorders, and parental asthma seem to facilitate diagnosis. Implementation of current diagnostic guidelines should improve diagnostic accuracy of pediatric asthma in Batumi

35. N. GAGUA, L. MOKVANIDZE, N. KEKENADZE

MEASURING LDL-C LEVELS: COMPARING DIFFERENT METHODS

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Introduction. In modern medical practice, there are many routinely done tests. Based on these test results, patients are diagnosed and appropriate treatments are chosen. For the measurement of LDL-C levels, the most commonly used methods are - centrifugation (Direct Method) and Friedewald formula. The aim of the study is to determine the accuracy of the Friedewald equation compared to centrifugation.

Material and Methods. The study was retrospective. Data was taken from Medcapital Laboratory. The laboratory used centrifugation and directly measured LDL-C. We manually calculated LDL-C levels with the Friedewald equation. Those two results after-centrifugation and Friedewald equation-were compared. Patient data was taken from 2019-2021. Patients whose lipid profile lacked any component of lipid profile were excluded from the research.

Results. In total 500 patients were included. Their date of birth ranged from 1930 to 2008. Analyzing data showed that the Friedewald equation overestimates data compared to centrifugation. It displayed underestimation only in two cases.

Conclusions. Although there is controversy about LDL-C measuring techniques, it is acknowledged that the Friedewald formula cannot estimate LDL-C levels correctly when TG≥400 mg/dl and LDL-C levels are <70 mg/dl. In the data we reviewed only a minority of patients displayed these changes in lipid profile. We also compared the number of patients who had abnormal LDL-C levels. After centrifugation 160 patients had elevated LDL-C, but when reevaluating the same patients with Friedewald equation 238 showed elevated LDL-C. In these 78 patients, LDL-C levels were overestimated, which could be a reason for unnecessary pharmacological intervention and other medical complications.

36. G. TCHOLADZE [1], I. PANTSULAIA [1], T. BOLOTASHVILI [2], R. JORBENADZE [2]

INFLAMMATORY INDICES ROLE IN PREDICTING THE SEVERITY OF COVID-19

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*Introduction.*The severity of COVID-19 patients can be predicted by evaluating various clinical parameters; however, the identification of time-consuming and cost-effective biomarkers is still relevant. Inflammatory indices (neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), eosinophil and neutrophil ratio (ENR), Systemic inflammatory index (SII, platelet X neutrophil count/lymphocyte count), due to their reflection of the body's inflammatory response and potential prognostic value are among the potential indicator. Previous studies have provided conflicting findings about the validity of these coefficients, with some studies indicating a significant association and others indicating the opposite. Our study aims to gain a deeper understanding of the significance of inflammatory indices (NLR, PLR, ELR, SII) in the assessment of disease severity in patients with various severities of covid-19.

Methods: Our study included 100 COVID-19 patients who were divided according to clinical classification into: mild (n=60, CT score <8), moderate (n=19, CT score>8 and <12) and severe (n=21, CT score >12) categories. Inflammatory indices were calculated in all patients. Through statistical analysis, including logistic regression and ANOVA, the relationship between these hematological ratios and the clinical severity of COVID-19 was examined.

Results: Our analysis revealed statistically significant differences in the studied parameters in patients with severe and mild form ($p<0.05$). In severe patients, the SII index is especially elevated after hospitalization, while this index does not change in mild and/or moderate patients. Also, CRP and ferritin were statistically higher in patients with severe disease compared to patients with mild or moderate disease.

Conclusion(s): SII was found to be an important marker of severity progression in COVID-19 patients and could be used as an independent prognostic factor. At the same time, SII is low-cost and time-consuming blood test for COVID-19 patients. Additionally, this study contributes to a growing body of evidence that calls for a holistic approach to patient evaluation that includes clinical and laboratory parameters to accurately predict COVID-19 prognosis.

37. I. KUKHIANIDZE, S. GAMKRELIDZE, M. SHAVIANIDZE

RHEUMATIC ARTRITS CONTROL AND REHABILITATION IN BALNEOLOGY RESORT "TSKALTUBO"

Faculty of Medicine, Akaki Tsereteli State University, Kutaisi, Georgia

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis in the UK and affects around 1% of the population. Approximately 10,000 people receive a diagnosis of RA every year. Rheumatoid arthritis is a long-term condition that causes pain, swelling and stiffness in the joints. The condition usually affects the hands, feet and wrists. Rheumatoid arthritis is an autoimmune disease. This means your immune system (which usually fights infection) attacks the cells that line your joints by mistake, making the joints swollen, stiff and painful. Over time, this can damage the joints, cartilage and nearby bone. It's not clear what triggers this problem with the immune system, although you're at an increased risk if: you are a woman, you have a family history of rheumatoid arthritis, you smoke.

To combat this problem, balneotherapy with various hydrotherapy is successfully used in the Tskaltubo balneological resort. Today, modern medical and rehabilitation facilities allow us to treat, prevent and raise the tone of the body. It is generally recognized that in the conditions of modern rehabilitation of patients, a great role is assigned to non-drug treatment methods, and balneology, in particular, radon therapy, plays a leading role in these methods. It has been proven that radon increases the protective functions of the body, strengthens the immune system, activates blood circulation, regulates blood pressure, promotes cell recovery and regeneration (after wounds and burns), has an analgesic and anti-inflammatory effect, has a pronounced sedative (relaxing) effect, Activates cognitive functions.

Based on the above, the Tskaltubo resort is the best base for highly effective treatment with natural healing factors. Taking radon procedures leads to reduction of inflammatory processes and increase of flexibility in damaged joints and reduction of pain syndrome.

38. GIORGI VADACHKORIA

HEART HEALTH AND IMMUNE CHECKPOINT INHIBITORS (ICIs) – WHAT WE ARE LEARNING AND HOW TO HELP

Faculty of Medicine, David Tvildiani Medical University, Tbilisi, Georgia

Millions worldwide fight two health conditions: Cancer and Cardiovascular diseases. The correlation between these two have been demonstrated, as advances in the treatment of malignancies prolong the lives of patients while posing a threat to their cardiovascular health.

Cancer Therapy Induced Cardiotoxicity (CTIC) is an effect of chemotherapies and immunotherapies on the heart. CTIC is defined as an asymptomatic reduction in EF by less than 55% but more than 10% and in the presence of symptoms and signs of heart failure (HF) a decrease in EF by 5 % or more to less than 55%. A rare, but fatal cause of CTIC is Immune checkpoint Inhibitors (ICIs). ICIs are monoclonal antibodies that non-specifically block immunosuppressive checkpoints on cytotoxic T-cells: CTLA-1, PD-L1, and PD-1. Therefore, they can initiate T-cell-mediated immunity against tumor cells. Unfortunately, with widespread activation of the immune system, ICIs can induce off-target immune-related adverse effects (irAEs) that can manifest as CTIC.

While the mechanism of ICIs induced CTIC is still incompletely understood, it is believed to be caused by several processes: in mouse models, PD-1 plays an important role in cardiac immune tolerance and in human individuals with fulminant myocarditis PD-L1 expression is increased in cardiomyocytes, which is consistent with the increased level of this marker found in human studies and mouse models. This suggest that PD-1 plays part in protecting myocytes against immune attacks. As this immunosuppressive mechanism is inhibited during ICIs treatment, robust T cells attack cardiomyocytes and cause irreversible damage. Activated T- cells also target unknown common antigen shared by cancer cells and cardiomyocytes further augmenting the damage, also they infiltrate the myocytes and directly kill the cells and increase cytokine production. The most common cytokines produced include granzyme B, TNF, IF-gamma.

Based on Pathomorphological analyses of cancer patients' hearts after cancer treatment, cardiotoxic effects were grouped into two categories - irreversible (type I) and reversible (type II). Type I is usually associated with loss and injury of cardiomyocytes, while in type II there are dysregulation of cardiomyocyte functions without cell death. Anthracyclines cause type I injury by formation of Reactive Oxygen Species (ROS) which damage mitochondria, alter metabolism of the cell and induce apoptosis. Alkylating agents mediate type I toxicity by damaging vasculature and/or thromboembolic ischemia. Tyrosine kinase inhibitors (TKI) or monoclonal antibodies are usually implicated in type II toxicity and their effect stem from damaging signaling pathways of cardioprotective factors such as Neuregulin-1.

Although the rate of occurrence of cardiac irAEs is 1%, the mortality rate can reach up to 50-60%. The most common manifestation is myocarditis (14.1%), followed by pericarditis (13.6%).

The standard treatment of cardiac irAEs is discontinuation of ICIs and high-dose corticosteroids. If the response to the treatment is adequate, the patient can be switched to 1mg/kg/day corticosteroids and the dose should be tapered over several weeks. With no symptomatic improvement, other immunomodulatory drugs should be started. One serious problem is that T-cells can become resistant to steroids and if this happens other treatments may not be effective. Considering these complications, researchers suggested: that instead of using corticosteroids to initiate nonspecific immunomodulatory effects, cardiac irAEs should be treated by specifically targeting T-cells. To achieve this, they proposed using two drugs - Abatacept which binds costimulatory molecules CD80 and CD86, and Ruxolitinib - an inhibitor of jak 1 and jak 2 proteins. Rutoximab does not provide a long-lasting effect, it commences working immediately, while abatacept has long-lasting effect but takes several weeks to achieve efficacy. To test this, they enrolled 40 patients with ICIs-induced cardiotoxicity. 10 were treated with standard care, while 30 were with a new treatment plan. The 3-month survival rate for group I was 40% and after

6 months 20%, while in the experimental group, the 3-month survival rate was 77% and 6 months - 70 %.

To conclude, ICIs have revolutionized cancer treatment and have prolonged millions of lives, one of the most feared side effects of these drugs is cardiotoxicity, but with new experimental treatment there is hope that not many people will succumb to this complication.

39. GIGI GORGADZE [1], RAIMONDA PISKINIENE [2]

IMMUNOLOGICAL BIOMARKERS IN OPHTHALMOLOGY – RECENT ADVANCES AND THEIR APPLICATION IN DISEASE DIAGNOSIS, PROGNOSIS AND PERSONALIZED TREATMENT

[1]Faculty of Medicine, Tbilisi State Medical University, Georgia; [2] Clinical department of Ophthalmology, Lithuanian University of Health Sciences, Lithuania

Recently, immunological biomarkers have been particularly effective and useful in elucidating the pathogenesis of ophthalmic diseases, assessing progression and appropriate management. Recent advances in immunological research have revealed the utility of such biomarkers as cytokines, chemokines, and autoantibodies.

For example, cytokine profiling in aqueous humor and tear samples has made it possible to differentiate between infectious and non-infectious uveitis, thus facilitating the choice between antimicrobial treatment and immunosuppressive therapy. Antibodies to retinal antigens are useful as diagnostic markers of autoimmune retinopathy, which is very useful for timely identification and classification of the disease. New diagnostic tools such as high-throughput multiplex assays and point-of-care testing especially contribute to fast and accurate diagnosis by means of immunomarkers.

Regarding prognostic value, for example, elevated levels of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are associated with poorer outcomes and increased risk of relapse in diseases including diabetic retinopathy and age-related macular degeneration. Chemokine gradient in neovascular age-related macular degeneration correlates with disease severity and response to anti-VEGF therapy.

Obviously, immune biomarkers alone are insufficient to draw conclusions, but integrating data with clinical parameters and other laboratory-instrumental research results is useful.

Current research is focused on exploring the importance of new biomarkers, including micro-RNAs, extracellular vesicles, and immune cells, which will greatly refine the understanding of disease phenotypes and thus contribute to better diagnosis, treatment, and prognosis.

Thus, the development of a precision medicine approach, such as the management of ophthalmic diseases using immunological markers, offers unprecedented opportunities and has great potential to revolutionize clinical practice.

40. NIA GORGADZE

EXPERIMENTAL AUTOIMMUNE DISEASE MODELS

Agricultural University of Georgia

Autoimmune diseases in veterinary medicine pose significant challenges for diagnosis and treatment. This abstract provides an overview of experimental models used in veterinary research to understand autoimmune diseases, their mechanisms, and potential therapeutic interventions.

These models, adapted for veterinary medicine, replicate autoimmune conditions seen in animals, such as autoimmune hemolytic anemia (AIHA) or immune-mediated polyarthritis (IMPA). They involve inducing immune responses against self-antigens or tissues, often through immunization or genetic manipulation.

Studying these models has shed light on the underlying mechanisms of autoimmune diseases in animals, including the roles of autoantibodies, immune cell dysregulation, and tissue inflammation. Additionally, they have served as platforms for testing novel treatments, such as immunosuppressive drugs or biologics, tailored for veterinary patients.

Advancements in experimental techniques, including the use of genetically modified animals and advanced imaging technologies, have improved the accuracy and relevance of these models in veterinary research. By leveraging these models, veterinarians aim to develop better diagnostic tools and more effective treatments for autoimmune diseases in companion animals, ultimately improving their quality of life.

41. KETEVAN GOTSADZE, NINO ADAMIA, IA PANTSULAIA, DAVID TOPHURIA, MAIA MATOSHVILI, IRMA UBIRIA, NERIMAN TSINTSADZE, MARIAM TUTASHVILI, LAVRITA PACHUASHVILI, NANA NAREKLISHVILI, KHATIA KHACHIDZE, DAREJAN KHACHAPURIDZE, NINO JOJUA, DALI SHOVNADZE, EKA LILUASHVILI, SOFO JAPIASHVILI

ELIMINATION OF DEPENDENCE ON THE NASAL VASOCONSTRICTION AGENTS

Tbilisi State Medical University, Clinic Raymann, Akaki Tsereteli Kutaisi State University

Introduction: Rhinosinusitis is a global problem, its prevalence is quite high, occurring in 28% of the population. Therefore, consumption of the nasal vasoconstriction medicines is high as well, every third individual all over the world (68%) consumes the nasal vasoconstriction agents and hence, it is the most sold medicine. Its wide consumption is caused by both, local nasal pathologies and various general diseases, including consumption of certain medicines and global air pollution. It is widely known that the patient can consume nasal vasoconstriction medicines for 7 days but no more than 10 days and people do not comply with this requirement. Hence, dependence on the nasal vasoconstriction sprays is quite high. These medicines have local and general side effects. Thus, the issue of their reasonable consumption is of significance.

Research design: open controlled research data processing was provided by SPS V/12 method.

Goal of the work: elimination of dependence on nasal vasoconstriction medicines by means of the nasal steroids. Two groups were compared, for the main group was used two-component combined medicine Fluticasone propionate and Azelastine nasal spray, for the control group there was used single-component nasal steroid Fluticasone furoate. Effectiveness of these two nasal sprays was compared, with respect of elimination of dependence on vasoconstriction agent.

Research result: the patients selected for the research were the individuals with pure nasal vasoconstriction agents' dependence, i.e., the patients, whose nasal vessel dependence was caused not but the other pathologies, among them, the patients with allergic rhinitis were not involved in the research. The sample included 186 patients aged from 18 to 54, it was divided into two groups: in the main group there were 96 patients and they were treated with two-component combined nasal steroid – Fluticasone propionate and Azelastine. The control group included 90 patients treated with single-component nasal spray Fluticasone furoate. As a result of six-month observations, high effectiveness of the combined medicine was revealed, in comparison with the single-component Fluticasone furoate, with respect of elimination of the dependence on nasal vasoconstriction agents. After use of the combined medicine, in maximum 30 minutes, the breathing through nose improved, in 80% of cases, in 10% cases, symptoms disappeared in 3 days and in the remained 10% of cases, treatment did not yield any results. For the single-component nasal spray, breathing through nose improved in 12 hours, in 40% of cases, in 20% of cases, the symptoms disappeared in 48 hours and in 40% of cases no result was yielded (dependence was not eliminated).

Conclusion: effectiveness of two-component nasal steroid is much higher than that of single-component nasal steroid, with respect of elimination of nasal vasoconstriction dependence, as the combined preparation eliminates more rapidly and it is much more effective, compared with the control group, $P>0.05$; also, combined preparation has less side effects (drying of mucous tunic, bleeding in case of medicine consumption).

42. BEKA JALABADZE

HOW WE BATTLE CANCER EVERYDAY

QSI Tbilisi, Georgia

Healthy cells turning into tumor cells is quite common when it comes to humans. It can happen any time as long as the needed circumstances are met. People are developing cancer all the time; however, the immune system is doing a great job keeping an eye over it. Without cancer immunosurveillance these malignant cells would pose an even bigger risk to our health. In this presentation we will expand about immunosurveillance; the damage that leads to cancer; and how the immune system, precisely the natural killer and cytotoxic T-cells take care of cancer cells. Furthermore, we go over how tumors can develop strategies to evade detection from such cells, leading to immune escape and progression. The concept of immunosurveillance is now well established and has a solid foundation. To sum up everything that has been stated so far, learning about immunosurveillance is crucial so we can understand cancer development better.

43. KETEVAN MACHAVARIANI, ALEXANDER TELIA, MARIAM TUTASHVILI, MANANA SHAVGULIDZE, ALEXANDER (DAVID) TELIA

ALLERGEN-SPECIFIC IMMUNOTHERAPY MECHANISMS, STAGES OF DEVELOPMENT AND FUTURE PERSPECTIVES

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Introduction. Allergen-specific immunotherapy (AIT) is considered one of the leading directions in its influence on the course of allergic diseases. The main goal of AIT is to reduce the symptoms caused by the allergen and prolong the remission of the disease. It is the only identified disease-modifying intervention for allergic diseases, developing both rapid de(hypo)sensitization and subsequent allergen-specific immune tolerance and suppression of allergic inflammation in damaged tissues. AIT is considered the only treatment option capable of inducing cure and long-term tolerance even after cessation of therapy. It was first used in 1911 and later took a special place in allergy practice as "subcutaneous immunotherapy" (SCIT). AIT has undergone significant changes to address issues of standardization, effectiveness, safety, duration of treatment, and cost.

Although modern research confirms the effectiveness of SCIT for bronchial asthma and rhinitis, an alternative method, sublingual immunotherapy (SLIT), has been increasingly used over the past 20 years. Original, replicative, and secondary studies conducted in this direction cannot prove the feasibility of routine implementation to date, there is insufficient evidence in the medical literature regarding the effectiveness and of sublingual immunotherapy in medical practice.

Materials and Methods: We conducted a prospective cohort study to evaluate the efficacy, safety, and cost-effectiveness of SLIT. Patients included in the study (patients with polysensitization to seasonal and non-seasonal allergens, allergic rhinitis, and asthma, aged 6-60 years, both sexes) were divided into two parallel groups (active/test and control). Patients in the active group received SLIT therapy for at least 18 months with three 6-month periods.

The results of our study revealed sufficient arguments to consider SLIT as a promising, albeit non-standard approach to the treatment and prevention of allergic rhinitis and asthma.

44. MAIA KHERKHEULIDZE

MODERN APPROACHES TO ATOPIC DERMATITIS. BEYOND THE SKIN

Tbilisi State Medical University, Tbilisi, Georgia

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder, with periods of exacerbation and remissions, that is affecting approximately 7 to 20% of children and 5–8% adults. AD clinical presentation with severe pruritus and recurrent eczematous lesions often results sleeplessness, stress, poor self-esteem and school achievement, that has a great impact on child's and family's quality of life and psychological and social well-being. AD is a complex and multifactorial disorder that combines skin barrier dysfunction, increased transepidermal water loss, changed skin microbiome, environmental factors

and immune dysregulation with prevalence of the T2-mediated immune pathway. The exact mechanisms of the pathogenesis of AD are still unclear, but recent research shows that AD can be considered as an inflammatory skin disease with a systemic component. The main goal of treatment of AD includes relief of symptoms, improvement of quality of life and reduction of relapses. The classical treatment includes nonpharmacological emollients and use of topical corticosteroids and calcineurin inhibitors, with antihistamines, antibiotics, adding of phototherapy, and immunosuppressant drugs in severe cases.
Recent understanding of the pathogenesis of AD has allowed the development of new drugs targeting different mechanisms and cytokines that have changed the treatment approach. A lot of new agents are approved by FDA for treatment of pediatric AD, including topical crisaborole (PDE4 inhibitor), topical ruxolitinib (JAK 1/2 inhibitor), oral upadacitinib (JAK 1 selective inhibitor), and injected dupilumab (anti-IL-4/13 monoclonal antibody). The resent studies showed effect of topical PDE4 inhibitors, topical and oral JAK inhibitors, and the injectable biologic treatments as well as using the bacteriophages for modulation of the skin microbiome and specific nanoparticle skin delivery systems, but more research is needed to prove the efficiency and safety of new approaches.

45. LIZI KAISHAURI

AUTOINFLAMMATORY DISEASES IN ANIMALS

Agricultural University of Georgia

Immune-mediated diseases usually involve a mixture of both dysfunctional innate and adaptive immune responses. The importance of these responses varies among diseases. Thus, there is a continuum from purely autoinflammatory disease at one extreme and purely autoimmune at the other. Innate autoimmunity or autoinflammation at one point was believed to be a set of monogenic human diseases marked by recurrent episodes of systemic and organ-specific inflammation caused by dysregulation of the innate immune system. While initially encompassing only innate immunity, it is apparent that many such systemic diseases play an important role in both autoimmune and even immunosuppressive disorders. Many autoinflammatory disorders have complex genotypes and phenotypes, and overproduction of proinflammatory cytokines is the most characteristic feature. Such diseases that will be discussed are: Shar-Pei fever syndrome, canine hypertrophic osteodystrophy, sweet syndrome, sterile nodular panniculitis, type 1 and type 2 autoimmune pancreatitis. We will talk about specific immune factors involved in the development of these disorders as well as clinical signs, and existing diagnostic methods and treatment plans.

46. LASHA TCHELIDZE, TINATIN MIGINEISHVILI, LALI SAGINADZE, NINO ADAMIA

STEVENS-JOHNSONS SYNDROME: A CASE STUDY

Tbilisi State Medical University, M. Iashvili Children's Central Hospital, Tbilisi, Georgia

Background: Stevens-Johnson syndrome is an acute, rare, immune-complex-mediated disease involving the skin and the mucous membranes. It is considered a minor form of toxic epidermal necrolysis, with less than 10% of the body surface area evidencing detachment. Various etiologic factors such as infections and drugs have been implicated in the etiology. Physicians must therefore consider Stevens-Johnson syndrome as a potential complication of treatment, especially when the use of medication is questionable. Diagnosis relies mainly on clinical signs together with the histological analysis of a skin biopsy. The differential diagnosis includes drug hypersensitivity reactions, staphylococcal scalded skin syndrome, acute generalized exanthematous pustulosis, and autoimmune bullous dermatoses. Immunosuppressive medications have been used with some success in patients. Our case report underscores the imperative of teamwork, vigilance, and thorough patient examination to prevent any unfortunate oversights.
Case report: A 6-month-old boy was hospitalized at M. Iashvili Central Pediatric Clinic in Tbilisi, Georgia. According to the parents, nasal obstruction, rhinorrhea, and restlessness started two days before hospitalization. The pediatrician assessed it as a respiratory infection and prescribed an antiviral spray and nasal drops. On examination in the hospital, there was a diffuse maculopapular rash on the neck and face, Swelling of the soft tissues of the face, large painful erosions, and blistering rash on the face, trunk, limbs,

and mucosal surface. He also had blepharoconjunctivitis. The patient was diagnosed with Stevens-Johnson syndrome. A council was held, where the patient's condition was assessed as critical, and the patient was managed with supportive care. The patient was prescribed dexamethasone, atarax, and sodium chloride. He was consulted by an ophthalmologist and was prescribed Tobrex and Ophtaquix.

Despite the treatment, on the third day after hospitalization, the general condition of the patient worsened. Hyperemia and desquamation of the skin expanded and spread to the dorsal surface, the groin area became swollen and hyperemic. The patient had adynamia, vomiting, and widespread skin pain, which is why Infulgan was prescribed. Under active observation, the treatment continued unchanged, and from the seventh day, the patient's condition gradually improved. On the ninth day, the desquamation of the necrotic areas of the patient's skin was completed, and the picture of blepharoconjunctivitis was not expressed. Paraclinical studies showed positive dynamics. Due to the positive dynamics, the patient was discharged with the appropriate prescription on the tenth day.

Discussion: Our case shows that Stevens-Johnson syndrome is a rare disease, especially, at this age. It remains a significant challenge for pediatricians, as it requires accurate anamnesis collection, rapid and accurate differential diagnosis, adequate management, and active monitoring during treatment.

47. KETEVAN LOMIDZE, NINO KIKODZE, MARINE GORDELADZE, TINATIN CHIKOVANI, NINO CHARKVIANI

WHOLE BLOOD CELL COUNT DERIVED BIOMARKERS OF THYROID DYSFUNCTIONS ASSOCIATED WITH THE TREATMENT OF NON-SMALL CELL LUNG CANCER AND CERVICAL CANCER WITH IMMUNE CHECKPOINT INHIBITORS

Tbilisi State Medical University, Tbilisi, Georgia

Background: Treatment with immune checkpoint inhibitors (ICIs) for advanced malignancies has been associated with developing immune related adverse events (irAEs) severe enough to require the cessation of life-saving tumor immunotherapy.

Objectives: The present study aimed to identify predictive inflammatory markers of the development of immune-related thyroid dysfunctions in patients with cervical cancer (CC) and non–small cell lung cancer (NSCLC) treated by ICIs.

Methods: A retrospective study was conducted on twenty-seven patients with CC and NSCLC treated by ICIs. The data were collected before and 12 weeks after treatment. Complete blood count-derived inflammatory markers: dNLR (derived neutrophil to lymphocyte ratio), NLR (neutrophil to lymphocyte ratio), SSI (systemic inflammation index), PLR (platelet to lymphocyte ratio), WHR (white blood cells to hemoglobin ratio) were calculated. In addition, thyroid functional tests were collected. Data statistical analysis was performed by STATISTICA (Stat soft, Inc, USA).

Results: Five patients out of twenty-seven with CC treated by PD-1 and CTLA-4 inhibitors who developed hypothyroidism showed significantly high baseline PLR and low WHR compared to patients without clinical symptoms of hypothyroidism and reference levels TSH and FT4. Association between NLR, dNLR, SSI, and thyroid dysfunction was not observed.

Conclusions: Our findings show a strong correlation between hypothyroidism and WHR and PLR biomarkers. As a result, using these biomarkers for early identification of hypothyroidism helps treat thyroid dysfunction and improves cancer immunotherapy outcomes.

48. NINO KVIRTIA [1], SOPHIO BERIDZE [2], MARIKA MORTULADZE [1], KAKHABER KASHIBADZE [2]

LIVER TRANSPLANTATION IMMUNOLOGY: IMMUNOSUPPRESSION AND REJECTION

[1] Batumi Shota Rustaveli State University; [2] Avicenna Batumi Medical University; Georgia

Background: Liver transplantation (LT) is a critical intervention for patients with end-stage liver disease, offering hope where conventional treatments fail. The key challenge lies in balancing the efficacy of immunosuppressive therapy with its adverse effects to optimize graft longevity and patient survival. Initiated during the anhepatic phase and continued long-term, immunosuppressive therapy varies across centers, with early post-transplantation period vigilance crucial to mitigate rejection risk.

This study *aims* to evaluate rejection rates post-liver transplantation and explore management strategies.
Methods: We conducted a retrospective analysis of medical records from liver transplant recipients at our center. The study subjects were adult liver recipients who underwent liver transplantation at our center (Batumi Referral Hospital - Medcenter, Georgia) since 2014, including December 2023, totaling 95 recipients, with a median age of 49.5 years. Perioperative survival was observed in 98% of cases, and a five-year follow-up demonstrated a survival rate of 75%. Cross-sectional study analysis was employed to examine rejection episodes, focusing on both acute and chronic rejection.
Results: Among the 95 liver transplant recipients, our analysis identified instances of rejection. Specifically, one patient experienced chronic rejection, while acute rejection occurred in another patient. These occurrences led to adverse outcomes, resulting in patient mortality. Our findings highlight the significance of vigilant management of rejection episodes post-transplantation.
Conclusion: In summary, our study emphasizes the importance of effective immunosuppressive strategies. Our findings underscore the need for ongoing research to refine protocols and enhance graft survival. Collaboration and innovation in transplant medicine are essential for addressing the complexities of rejection and improving patient outcomes. Ultimately, our pursuit of excellence in liver transplantation relies on both clinical expertise and scientific advancement.

49. GIORGI LOLADZE

GENETIC FACTORS IN AUTOIMMUNITY

Agricultural University of Georgia

The development of autoimmune diseases in animals is influenced by both environmental and genetic factors. More commonly, interactions between multiple genes and the environment contribute to autoimmunity. Possessing several common risk gene variants collectively increases susceptibility. Notably, autoimmune diseases often result from MHC gene interactions. MHC molecules play a crucial role in antigen presentation and immune responsiveness. Genetic predisposition plays a crucial role in autoimmunity. There are numerous loci associated with autoimmune risk. These shared loci may reveal common pathways, but their effects are often small. For instance: In mice, over 25 gene loci contribute to autoimmunity, including those related to cytokines, apoptosis, and antigen clearance. Some diseases result from single gene defects, while others involve complex interactions. Breed predisposition is one important topic to discuss, as we know dogs are descended from wolves. This process was achieved by inbreeding and loss of genetic diversity which caused certain types of autoimmune diseases in animals. Monogenic Diseases - specific gene mutations encoding crucial regulatory proteins can trigger autoimmune diseases. For example - AIRE mutations leading to autoimmune polysystemic syndrome-1. Sex Hormones and Autoimmunity is an important factor. Estrogen and prolactin promote B-cell proliferation, while testosterone has the opposite effect.
In conclusion, Autoimmunity results from complex interactions between genetic predisposition and environmental factors. Genome-wide studies identify multiple risk loci, often with small effects. Breed predisposition highlights the impact of genetic diversity loss. Monogenic diseases and sex hormone influence play roles, with certain gene mutations triggering specific conditions.

50. R. SEPIASHVILI, D. KHACHAPURIDZE, K. BARABADZE, N. ADAMIA, N. TOTADZE, I. PANTSULAIA, L. SAGINADZE, N. JOJUA, T. ARAKHAMIA, E. KHURTSIDZE, G. KHAKHALEISHVILI

DEFICIENCY OF COMPLETE NUTRITIONAL MICRONUTRIENTS, DISEASE PREVENTION

National Institute of Allergology, Asthma and Clinical Immunology of Georgian National Academy of Sciences, Tskhaltubo, Georgia; Tbilisi State Medical University, Tbilisi, Georgia; A. Tsereteli University, Kutaisi, Georgia; M.Iashvili Children Hospital, Tbilisi, Georgia

Introduction: The World Health Organization systematically makes recommendations for the need for a complete, balanced diet for children in order to prevent their normal growth, development and disease in children, considering all age incisions.

The aim of our study (2019-2021) is to strengthen the monitoring of micronutrient deficiencies in the nutrition of 986 children aged 1 day to 16 years of age in children.
Research objectives: We developed the target groups: children from 1 day to 2 years of age (354 children) (145 girls and 209 boys), school children (632 children, 256 girls and 367 boys). 3 nutritional indicators were selected: iron, iodine, and folate.
The results of the study: - It was found that out of 589 children from 1 day to 6 years from whom blood was taken from a vein for ferritin testing - 35.7% were anemic, and 64.3% were without anemia and from 397 children (from 7 to 16 years) from whom blood was taken from a vein for ferritin and folate tests, 43.2% had anemia and 56.8% had no anemia.
Based on the results of the research, a recommendation was issued; Improving the promotion of exclusive breastfeeding during the first 6 months of life. Many adequate steps are still needed as it is still a problem to continue breastfeeding after 3 months of age; Getting a product Fe in I and other essential micronutrients and vitamins for children, a study based on medical practice over the last 2 years - on the example of 986 patients. Deficiency of essential nutrients in children - 0-16 years.
Conclusion: Observations have shown that iron deficiency anemia, vitamin D and calcium deficiency are still a significant problem. Especially during the pandemic period.

51. TAMAZ MAGLAKELIDZE

DIAGNOSIS AND MANAGEMENT OF COPD EXACERBATIONS IN INPATIENT SETTINGS

Respiratory Association of Georgia, Chaphidze Emergency Cardiology Center, Iv. Javakhishvili Tbilisi State University, WHO-GARD, Tbilisi, Georgia

Introduction: In this presentation we discuss COPD exacerbations, explore their prevalence, diagnostic challenges, and the latest treatment strategies that is pressing concern in healthcare today.
Objective: To inform healthcare providers about COPD exacerbation management, covering diagnosis, comorbidities, and treatment options.
Content: We discuss the growing prevalence of COPD and the over and underdiagnoses it often faces, also covers nuances of COPD exacerbations, including their frequency and diagnostic intricacies. We place emphasis on recognizing comorbidities and their impact on exacerbation frequency and management, treatment strategies, incorporating both pharmacological and non-pharmacological interventions to optimize patient care.
Conclusion: By understanding the complexities of COPD exacerbations and implementing tailored treatment approaches, healthcare providers can improve patient outcomes and alleviate the burden of this condition.

52. NESTAN GVETADZE [1], TINATIN CHIKOVANI [1], LEVAN SHALAMBERIDZE [2], NINO KIKODZE [1]

COMPLETE BLOOD COUNT DERIVED BIOMARKERS OF METHOTREXATE RESPONSE IN NEWLY DIAGNOSED RHEUMATOID ARTHRITIS PATIENTS

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Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation of the synovium, leading to joint damage and systemic complications. Methotrexate (MTX) is commonly used as a first-line treatment for RA due to its immunosuppressive properties. However, a significant proportion of patients exhibit resistance to MTX therapy. Lately, certain complete blood count (CBC) derived biomarkers such as RDW, HGB/PLT, and HGB/MON ratios have emerged as promising indicators in various inflammatory conditions, providing insights into disease prognosis and therapeutic response. However, there is currently limited data available on the effectiveness of the abovementioned biomarkers as prognostic ones to predict treatment outcomes in newly diagnosed RA patients who are initiating MTX treatment.
Objective: This study aimed to determine the potential of RDW, HGB/PLT, and HGB/MON as prognostic biomarkers in newly diagnosed RA patients commencing MTX therapy. Additionally, to investigate their

possible correlation with the Disease Activity Score of 28 joints (DAS-28), which is a widely accepted tool to monitor and assess disease activity and treatment response in RA patients.
Methods: We conducted a comprehensive analysis involving 64 RA patients categorized into Methotrexate-resistant (MTXR) and Methotrexate-sensitive (MTXS) groups and 28 age- and sex-matched healthy individuals. ANOVA analyses were employed to assess differences in hematological biomarkers between groups. Standard T-tests were used to compare specific biomarkers between MTXR, MTXS, and control groups. For the comparison of categorical variables between the groups Chi-square test was employed. Furthermore, we examined correlations with Pearson's correlation test between RDW, HGB/PLT, HGB/MON ratios, and DAS28 in both groups. To determine the predictive capabilities of these biomarkers, Receiver Operating Characteristic (ROC) curve analysis was performed.
Results: No statistically significant difference was observed between the biomarkers of interest in MTXR and MTXS groups, according to an unpaired t-test. No significant positive correlations were identified between CBC-derived biomarkers and DAS-28 in either the MTXR or MTXS groups. Additionally, The ROC curve analysis showed that their predictive capability was insignificant.
Conclusion: Based on our findings, we cannot support the use of RDW and HGB/PLT and HGB/MON ratios as predictors of methotrexate response in newly diagnosed RA patients. Also, our study cohort has shown that they cannot replace DAS-28 for assessing disease activity in RA patients.

53. KH. MIKELADZE, N. CHIKADZE, N. GACHECHILADZE

ANTIBACTERIAL TREATMENT ALTERNATIVES STUDIES IN CLL PATIENTS

Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

Introduction: Chronic lymphocytic leukemia (CLL) is an oncohematological disease characterized by accumulation of a large number of lymphocytes in the central and peripheral lymphatic organs and tissues that results in decline of humoral and cellular immunity and development of opportunistic infections, the most common cause of death for CLL patients. The identification of infectious agents and effective methods of their elimination is one of the key aspects of CLL patient's therapy. Antibiotic treatment still remains one of the main approaches, but nowadays, selection of an effective antimicrobial drug is problematic because of increased antibiotic resistance. Phage therapy is considered as a promising, safe alternative to antibiotics, although it's potential for treatment or prevention of bacterial infections in patients with CLL hasn't been investigated.
The aim of the study was to identify opportunistic infectious agents and their antibiotic and phage sensitivity in patients with CLL. Additionally, we aimed to detect anti-phage natural antibodies that could potentially hinder phage effectiveness.
Research methodology: Swabs from the nasopharynx of 20 CLL patients (both-males and females, age 60-67) were subjected to standard bacteriological analysis, through primary 4 quadrant striking on SBA and TSA plates followed by sub-culturing of developed colonies on a number of selective - differential media. The phenotypic identification was done using API test systems (bioMerieux, France). Antibiotic sensitivity was studied by Kirby-Bauer disc-diffusion method according to the EUCAST standards, and phage susceptibility (6 commercial phages, produced by Eliava Biopreparations) - by Spot-Test technique. The control group comprised 6 healthy donors matched for age and gender parameters with the study group. The presence of anti-phage antibodies in the sera of CLL patients was examined via EIA using Sigma-Aldrich reagents. The control group for this study comprised healthy donors matched for age and gender parameters.
Results: A total of 46 bacterial strains were collected from 40 nasopharyngeal swabs of CLL patients and identified at species level. Among these, 37 strains were classified as opportunistic pathogens such as P.luteola; S.epidermidis; S. salivarius; S. lentus; S. capitis; S. warneri; S. hominis; S. xylosus; S. heamolyticus; S.saprophyticus; S. cohnii spp; Kocuria varians/rosea; A.viridans; B.subtilis, while 9 were identified as pathogens (S.aureus, E.coli).
The antibiotic sensitivity testing involved the following antibacterial drug groups: tetracyclines, glycopeptides, oxazolidinones, cephalosporins, fluoroquinolones and aminoglycosides. Our study indicated that the most effective antibiotics against isolated pathogenic agents (S.aureus; E.coli) were

tetracyclines, fluoroquinolones, and aminoglycosides (susceptibility range – 89-100 %). For the isolates of opportunistic flora (P.luteola; S.epidermidis; S. salivarius; S. lentus; S. capitis; S. warneri; S. hominis; S. xylosus; S. heamolyticus; S. saprophyticus; S. cohnii spp; Kocuria varians/rosea; A.viridans; B.subtilis) the promising susceptibility was shown towards all antibiotic groups (≥56% susceptibility), with the higher efficacy of oxazolidinones (86%). However, for pathogenic agents (S.aureus; E.coli), high resistance (up to 100%) to glycopeptides was registered while susceptibility to other antibiotic classes remained high.
None of the commercial phages exhibited activity against the isolated strains, prompting an investigation into natural anti-phage antibodies in CLL patients' sera. Our study revealed that the titers of natural anti-phage antibodies were significantly high in CLL patients' sera, rendering phage treatment ineffective with standard commercial phages.
Conclusions: Study results showed the possibility for elimination of bacterial colonization in CLL patients by rational use of antibiotics. At the same time, it became clear that in case of need a customized phage treatment of CLL patients, it can be done through selection of active phages (monophages, or mixtures) from the Eliava Institute's collection and preparing autophages, since the standard commercial phages, cannot replace antibiotic treatment for the effective elimination of infectious agents in CLL patients.

54. MOHAMED ABDALLA AHMED, AHMED ELSHENNAWI SELIM, AHMED MOHAMED KESHK, SALEM MOHAMED SALEM MOUSSA, ZAID ISSAM SALEH ALHAMARSHEH, MOHAMED AHMED TALAAT MAHDEY, NINO DIDBARIDZE

IMPACT OF CLIMATE CHANGE ON HUMAN IMMUNE RESPONSE: A COMPREHENSIVE REVIEW

Tbilisi State Medical University, Tbilisi, Georgia

Climate change is not only jeopardizing the health of our planet but is also increasingly affecting our immune health. This comprehensive review investigates the potential impacts of climate change on human immunity, focusing on a broad range of climate-related exposures such as air pollution, heatwaves, wildfires, extreme weather events, and biodiversity loss. These exposures disrupt the functioning of the human immune system by affecting the physical integrity and functional efficacy of the epithelial barrier. Additionally, they can hyper stimulate the innate immune system and influence adaptive immunity, leading to the development of noncommunicable diseases such as autoimmune conditions, allergies, respiratory illnesses, and metabolic disorders. The loss or failure of immune tolerance can instigate a wide spectrum of health issues.
There is an urgent need for additional research in climate change and immunology, spanning diverse environments and utilizing modern biologic and epidemiologic tools. Understanding the complex interactions between climate change and human immunology is crucial for developing effective strategies to enhance human immune resilience and mitigate adverse health impacts.

55. KARAMAN PAGAVA, TEMURI MIKELADZE

PRIMARY IMMUNIDEFICIENCIES IN GEORGIA. CURRENT SITUATION

Tbilisi State Medical University, Tbilisi, Georgia

The lecture presents modern views on primary immunodeficiencies (definition, classification, diagnosis, management). It is emphasized that this group of diseases includes cellular and humoral immunodeficiencies, combined immunodeficiencies with associated syndromes, primarily antibody deficiencies, immune dysregulation syndromes, phagocytosis disorders, innate immune disorders, complement deficiencies and also auto-inflammatory disorders. Currently, a study is being conducted with the Molecular Medicine Research Center Primax (Tbilisi) and ViennaLabDiagnostics (Vienna, Austria) to create a registry of patients with familial Mediterranean fever (the registry already includes more than 200 patients), a study is also underway to create a registry of patients with other primary immunodeficiencies (so far it includes 11 genetically confirmed cases). In order to raise the level of awareness of primary immunodeficiencies in Georgia, special conferences are held (6 conferences have already been held) within the framework of the J project. At the international level, the J project

publications with the participation of Georgian authors serve the same purpose (Front Immunol. 2022, J Clin Immunol. 2020, 2022).

56. NANA SISAURI

AUTOIMMUNE EYE DISEASES

Agricultural university of Georgia

Autoimmune eye diseases are conditions where the body's immune system mistakenly attacks eye tissues, causing inflammation and vision problems. This abstract provides a simplified overview of these diseases, including how they develop, how doctors diagnose them, and the available treatments. These conditions occur when the immune system malfunctions and targets parts of the eye like the uvea, retina, or cornea. Factors like genetics and environmental triggers can contribute to their onset.

Common autoimmune eye diseases include chronic superficial keratitis, uveitis, uveodermatologic syndrome. Symptoms vary but often include eye pain, redness, sensitivity to light, and blurred vision. Diagnosis involves eye exams and sometimes additional tests like scans or blood work. Treatment aims to reduce inflammation and protect vision. Options range from eye drops and pills to more specialized therapies like immunomodulatory drugs or surgery in severe cases.

In conclusion, while autoimmune eye diseases present challenges, advancements in understanding and treatment offer hope for better outcomes and improved quality of life for affected individuals.

57. S. RIGVAVA, L. GUBELADZE, M. NATIDZE, N. KARUMIDZE, L. KVACHADZE, T. DALAKISHVILI, D. BOLKVADZE, D. GOGIASHVILI, L. KAVTARADZE

POLYCLONAL IMMUNOGLOBULIN FOR TREATMENT OF COMPLICATED STAPHYLOCOCCAL INFECTION

George Eliava Institute of Bacteriophages, Microbiology and Virology; European University, Tbilisi, Georgia; Ltd "Immunogen", Tbilisi, Georgia

The aim of the Project is to obtain an anti-staphylococcal polyclonal immunoglobulin with high therapeutic (healing) properties, and the Laboratory and Experimental study thereof. The works and studies to develop immunoglobulin were including the following: selection of Staphylococci, Immunogens – alpha-anatoxin, receiving of PV-leukocidin, hyaluronidase and determining an activity; Immunization of Producer animals (goats) with immunogens; reception of hyperimmune serum and release of immunoglobulin fraction; enzymatic processing of antibodies to obtain a harmless medicine (preparation); received final product controls. 30 strains having the stable characteristics were selected out of 102 strains gathered from Tbilisi and Kutaisi Clinics. (Staphylococcus aureus - 24, Staphylococcus epidermidis - 6). In order to obtain immune serum, the producer animals, have been vaccinated according to a pre-developed Immunization Schedule, with increasing doses of immunogens, with the addition of adjuvants. In the normal (K), immune serum and immunoglobulin we have determined the protective Antibody Titer. For this purpose, we have used hemolysis reaction (Lh), passive hemagglutination test (using dry diagnostic test systems), Immunoenzymatic analysis ("Sandwich-ELISA" method). Antibody titer in immune preparations in hemolysis reaction to alpha-toxin it was 150 IU/ml, in normal serum -0.5-1.0 IU/ml; The titer of Antibacterial Antibodies in the passive hemagglutination reaction was found to be as -1:6400 - 1:12800, of the anti-leukocidin antibodies - 1:640-1:1280, and for hyaluronidase - 1:160-1:320, the titer of the same antibodies in normal serum ranged from 1:10 to 1:40. These antibodies were determined by immunoenzymatic method in the analysis. Medium values of normal serum against alpha-toxin were 0.081; The index of positivity to the same toxin in immune serum amounted to 10.08; The index of positivity of antibacterial antibodies was equal to 9.2517. PV-leukocidin positivity index - 4.3968, and hyaluronidase -0.9214. To remove anaphylactogenic Fc fragments from antibody molecules, we used enzyme (Pepsin) treatment with a special kit ,,PierceTM Fab Preparation Kit, USA".

The medicine (preparation) tested in accordance with the requirements of the European Pharmacopoeia was found to be sterile, non-toxic, reactogenic, stable, non-pyrogenic. Purified immunoglobulin 5 IU/ml -0.5 ml subcutaneous injection protected 91.7% of white mice from an unconditionally lethal (Dcl) dose

of pathogenic staphylococcus. Mortality in animals under the control amounted to 100%. Thus, a harmless medicine (preparation) with high healing properties have been obtained - Antistaphylococcal purified Polyclonal Immunoglobulin.

"This work was supported by Shota Rustaveli National Science Foundation of Georgia", Grant #AR-18-306: "Development of Polyclonal Immunoglobulin for the Treatment of the Complicated Staphylococcal Infections".

58. NONA JANIKASHVILI[1], KAKHABER ODISHARIA[2], VLADIMER ODISHARIA[2], TINATIN CHIKOVANI[1]

COMPUTER MODELING OF AUTOIMMUNITY AND ITS TREATMENT

[1]Tbilisi State Medical University, Tbilisi, Georgia; [2]Iv. Javakhishvili Tbilisi State University, Tbilisi, Georgia

Computer models of immune mediated disorders provide an analytic framework in which the specific questions concerning the disease immune components and the management strategies are addressed. We have developed the mathematical models of autoimmune diseases using non-linear differential equations which accurately decipher the interactions of immune cells and their soluble mediators in the pathogenic process. Disease management using diverse treatment options is also explained in these models. Herein, we present a novel computer model that describes the dynamics of T helper and T regulatory cells subsets in the pathogenesis and treatments of autoimmune arthritis. The model explores the functional polarization of opposite T cell fates based of IL-6 value. The interaction of T and B lymphocytes is also reflected in the present model. Of importance, our model provides a mechanistic interpretation of a real patient data and the disease intervention options.

59. SALOME BADIASHVILI

BOVINE MUCOSAL VACCINES: CHALLENGES AND PERSPECTIVES

Agricultural University of Georgia

Mucosal vaccines have been used in cattle for almost five decades, primarily via intranasal and oral delivery routes. There is an increasing interest in the use of mucosal vaccination in cattle for several reasons. In newborn calves, Intranasal mucosal vaccination provides a strategy to reduce vaccine interference by maternal antibodies and enhance disease protection as maternal antibodies diminish. Additionally, mucosal vaccines offer advantages in controlling both clinical disease and reducing transmission of mucosal pathogens. Mucosal vaccines may offer opportunities to activate both innate and adaptive mucosal effector cells and improve control of mucosal infections while preserving mucosal barrier integrity and vital mucosal functions.

Greater understanding of host-microbiome interactions may inform vaccine strategies to control opportunistic pathogens residing within the commensal microbiome. Comprehension of the unique aspects of the bovine mucosal immune system are crucial in optimizing vaccination approaches. The potential for new vaccine delivery vehicles and vaccination strategies to improve mucosa vaccine efficacy are discussed, considering limitations and opportunities. Refinement of mucosal vaccination aims to address current infectious disease challenges in cattle, ultimately bolstering herd health and productivity.

60. SHORENA KARTVELISHVILI, NINO ADAMIA, TAMAR TABATADZE, ANA ADAMADZE

CHRONIC ASTHMA

Tbilisi State Medical University, M.Iashvili Children Hospital, Tbilisi, Georgia

Introduction: childhood bronchial asthma is an important public health problem worldwide. it is one of the most common chronic diseases in childhood, which affects the quality of life not only of the child, but of the entire family. Despite effective and safe treatment, bronchial asthma imposes a significant burden on a child's health-related quality of life. Asthma symptoms and lung function tests are very important for the diagnosis of the disease, however, determining the health-related quality of life (hrqol) can lead to an important and more comprehensive assessment of the impact of asthma on the child's quality of life.

Objective: to improve the quality of management of a child with bronchial asthma by introducing quality of life assessment questionnaires into clinical practice.
Methods: the study was observational, cross-sectional. data were collected from 2017 to 2020 from 3 clinics of the evex hospital network: - M.Iashvili central children's hospital, Batumi mother and child center and Zugdidi referral hospital. The research tool was a collection of questionnaires, which consisted of the following questionnaires: 1) general questionnaire - a basic, general questionnaire that included information about the participants' asthma; 2) pediatric quality of life inventory (pedsql), asthma module (version 3.0, short form. pediatric quality of life inventory (pedsql), asthma module (version 3.0, short form); 3) pedsql multidimensional fatigue scale. pedsql multidimensional fatigue scale; 4) pedsql family impact module. pedsql family impact module; 5) asthma control test (act) and the childhood asthma control tests (cact). The pedsql asthma module and the multidimensional fatigue scale were completed independently by parents and children from 5 years of age. Age-appropriate versions of the questionnaires were used (2-4; 5-7; 8-11; 12 and 13-18 years). The younger children were interviewed, and the older children filled out the questionnaires independently. Visual aids were used for 5- to 7-year-old children. The form and severity of asthma were determined by a pediatrician and an allergologist using the British thoracic society (bts) asthma management step approach, with stage 4–5 asthma being classified as severe asthma. In addition, children over 6 years of age were assessed for external breathing by computer spirometry, determining the following parameters: fev1, fvc, fev1/fvc, fef 25-75.
Results: 507 children aged 2 to 18 and their parents were included in the study. The quality of life was evaluated both by children with asthma and by their parents. As a result of the research, it was revealed that bronchial asthma affects the quality of life not only of the child, but also of the whole family. Assessments of qol by children and their parents are correlated; the mean score for both children's and parents' qol assessment was 43.6. Severe asthma, poor asthma control, smoking, presence of dampness, child overweight and obesity were associated with lower qol scores. The qol score was also related to socioeconomic status and family education level. Qol was not related to the age and gender of the study participants, spirometry results, pet ownership and concomitant allergies. Qol assessment revealed that asthma limits the child's daily activities.
This was the first study in Georgia that examined bronchial asthma symptoms, severity, and control using currently used childhood asthma qol instruments and questionnaires in clinical practice. "Asthma-related quality of life" refers to the perceived impact (perception) of asthma on the patient's quality of life. Qol assessment will help us understand the subjective impact of the disease on the patient's daily life. This type of analysis is very important for a comprehensive and complete assessment of bronchial asthma, for planning the correct management of the disease and for prognosis. Properly managed asthma provides symptom control, treatment efficacy, reduced risk of adverse outcomes and complications, eliminates the need for hospitalization, all of which significantly reduces health care costs.

61. NINO NANAVA[1], VLADIMER ODISHARIA[2], TINATIN CHIKOVANI[1], NONA JANIKASHVILI[1]

DIGITAL TRANSFORMATION IN UNDERSTANDING AND MANAGING OF IMMUNE MEDIATED DISORDERS – BENEFITS AND CHALLENGES

[1]Tbilisi State Medical University, Tbilisi, Georgia; [2]Iv. Javakhishvili Tbilisi State University, Tbilisi, Georgia

Exploring the pathogenesis of immune diseases is a critical task for their therapeutic management. Effective monitoring of immunopathological mechanisms in an individual patient is crucial for accurate diagnosis and the selection of personalized treatment strategy. In recent years, personalized treatment approaches have been the main focus of pharmaceutical companies and clinics worldwide. However, the experimental research for such investigations requires expensive experimental bases and long research processes, that entails a heavy economic burden on the country. Therefore, an innovative approach is to create the mathematical models of immunopathogenesis and immunotherapy. Such models serve as alternatives to experimental biomedicine and allow for the theoretical determination of disease dynamics and treatment outcomes.
Our interdisciplinary team of immunologists and applied mathematicians developed mathematical models of the immunopathogenesis and treatments of widespread immune mediated disorders. These models are

based on non-linear differential equations, with variables reflecting the dynamics of measurable immune parameters over time during the progression of the disease and the course of its treatment. The creation of corresponding computer programs is also addressed by our team. The mathematical and computer models are regularly tested with real patient data and evaluated for their challenges and benefits. As a result, such models, representing a digital transformation in the understanding and managing of immune-mediated disorders, contribute to the creation of new knowledge and technological products in a competitive interdisciplinary direction.

62. ZVIAD KALICHAVA [1], VLADIMER ODISHARIA [2], NONA JANIKASHVILI [3]

MATHEMATICAL MODELING OF T LYMPHOCYTE CROSS-TALK IN RHEUMATOID ARTHRITIS

[1]N. Muskhelishvili Institute of Computational Mathematics, Tbilisi, Georgia; [2] Iv. Javakhishvili Tbilisi State University, Tbilisi, Georgia; [3] Tbilisi State Medical University, Tbilisi, Georgia

Rheumatoid arthritis is a systemic autoimmune disease characterized by the joint inflammation and the cartilage destruction. Autoreactive B lymphocytes represent integral elements of the pathophysiology of rheumatoid arthritis. Immune balance between the effector and the regulatory T cell subsets guide the production of autoantibodies by B lymphocytes and, therefore, play a cardinal role in disease severity. Mathematical models of immune mediated disorders provide an analytic framework in which we can address specific questions concerning disease immune dynamics to dictate the choice of treatment. Herein, we present a novel mathematical model that describes the immunopathogenesis of rheumatoid arthritis using non-linear differential equations. The model explores the functional dynamics of cartilage destruction during disease progression, in which a system of differential equations deciphers the interactions between autoreactive B lymphocytes and T helper cells. Moreover, immunomodulatory effects of IL-6 that deviates the fate of T cells towards pro-inflammatory vs. regulatory subsets is also solved in these equations. In conclusion, we propose a novel mathematical model that best describes the immunopathogenic cross-talk of T lymphocytes in patients with rheumatoid arthritis and, therefore, may take a rapid pace towards its individualized testing schemes.

63. VLADIMER ODISHARIA [1], ZVIAD KALICHAVA [2], KAKHABER ODISHARIA [1], NONA JANIKASHVILI [3]

MATHEMATICAL MODELING OF TREATMENT OF RHEUMATOID ARTHRITIS WITH METHOTREXATE AND TOCILIZUMAB

[1]Iv. Javakhishvili Tbilisi State University, Tbilisi, Georgia; [2]N. Muskhelishvili Institute of Computational Mathematics, Tbilisi, Georgia; [3]Tbilisi State Medical University, Tbilisi, Georgia

Mathematical models of immune mediated disorders provide a platform in which we can address specific treatment choice in the vast personalized manner. Our interdisciplinary research team has created a mathematical model of rheumatoid arthritis, which determines the level of cartilage damage in the patient and, accordingly, the progression of rheumatoid arthritis over time with a system of equations that calculates the interaction variables between B and T lymphocytes. Inter-relation between different CD4+ T lymphocyte subsets is also solved in this model. The proposed mathematical model is a nonlinear system of ordinary differential equations and describes immunopathogenic dynamics in patients with rheumatoid arthritis. As part of the further tasks, based on the mathematical model of the pathogenesis of the disease, again using non-linear differential equations, we created a mathematical model of disease treatment. In this novel model features of treatment with methotrexate and tocilizumab in a separate or combined scheme are taken into account as variables. In conclusion, we propose a novel mathematical model that best describes the readouts on the treatment outcomes in patients with rheumatoid arthritis and, therefore, may take a rapid pace towards its implementation in biomedical and clinical research.

64. BESARION LASAREISHVILI

EXPLORING PHAGE THERAPY AS A SOLUTION TO ANTIMICROBIAL RESISTANCE: CURRENT LANDSCAPE, PROSPECTS AND HURDLES

Agricultural University of Georgia; Eliava Institute of Bacteriophage, Microbiology and Virology, Tbilisi, Georgia

Antimicrobial resistance poses a significant challenge in healthcare, particularly among opportunistic pathogens, which exhibit complex diagnostic hurdles and an escalating prevalence of multiple drug resistance, often leading to mixed and endogenous infections. Obligate pathogens, by contrast, present a milder concern, with early diagnosis facilitated, effective vaccines available, and limited avenues for dissemination, coupled with a lack of antimicrobial resistance.

Addressing antimicrobial resistance necessitates a multifaceted approach, including adherence to rational antimicrobial therapy principles and exploring alternative biological therapeutics such as phages. Phages offer distinct advantages over antibiotics, including lack of adverse effects, ability to penetrate bacterial biofilms, adaptability to resistant strains, and environmental safety and cost-effectiveness.

There is a burgeoning interest in phage therapy globally. Western European nations are observing a steady increase in the establishment of enterprises and laboratories specifically dedicated to producing phage preparations.

Phage therapy employs virulent phages, typically in cocktail formulations, and offers a broad therapeutic spectrum against various tissue purulent infections and intestinal diseases. Prior to treatment initiation, phage sensitivity testing via phage-gram is essential. Personalized phage preparations (autophages) may be employed in cases of phage resistance.

Phages are administered over 2-3 weeks, with a dosing regimen of 2-3 times daily, typically ranging from 10^5-10^8 phage particles per administration. Additionally, phages exert an indirect immune-modulating effect, augmenting their therapeutic efficacy and showcasing adjuvant and vaccine-like actions.

Large-scale technologies for endotoxin purification, notably tangential filtration, are imperative to facilitate the widespread adoption of phage therapy. Furthermore, future phage formulations should incorporate low-immunogenic variants to mitigate humoral immune responses.

The abundant diversity of phages in the environment ensures the availability of effective options against antimicrobial-resistant bacteria. Legalizing phage therapy and refining treatment protocols are pivotal for its continued advancement and clinical utility.

65. BESARION LASAREISHVILI [1,2], LANA MTVARELIDZE [1], NIA GACHECHILADZE [1], MARIAM BERISHVILI [1], LELA DUMBADZE [1], EKATERINE JAIANI [2], VOLODYMYR TARABARA [3], ZUZANNA KAZMIERCZAK [4], KRYSTYNA DABROWSKA [4]

EXPLORING THE IMPACT OF PHYSICOCHEMICAL PROPERTIES ON PHAGE IMMUNOGENICITY: A STUDY OF E. COLI PODOVIRIDAE PHAGES AND THEIR DNA

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Introduction & Objectives: Phage therapy holds promise against antimicrobial resistance. However, developing anti-phage neutralizing antibodies poses a challenge for chronic infections, limiting long-term efficacy. To address this, phage drugs need a broad lysis spectrum and low immunogenicity. We hypothesize that physicochemical properties like size, morphology, charge, and hydrophobicity influence phage immunogenicity, aiding preliminary prediction. During therapy, phage DNA, a ligand for Pattern Recognition Receptors, accompanies phage particles, necessitating the study of its host impact.

Materials & Methods: We analyzed the hydrophobicity, charge, and hydrodynamic diameter of ten E. coli-specific Podoviridae phages. Three bacteriophages (BL-2, ECC, BS) with distinct properties were selected for immunogenicity assessment. Phage preparations underwent endotoxin purification via tangential filtration and EndoTrap. Intraperitoneal administration of 5x10^8 phage particles to CD1 outbred female mice (n=7/group) ensured endotoxin levels stayed below 0.01 EU. Blood serum collected at intervals (0-100 days) measured anti-phage IgM and IgG class antibodies via ELISA. The impact of

purified phage DNA was evaluated through intravenous injection (5 ng) in plasma samples obtained at 6, 12, 24, and 72 hours. Cytokine levels, lipid profiles, liver enzymes, creatinine, and leukocyte count were assessed. Liver and kidney histological analysis was conducted on days 5, 10, 15, and 30.

Results: Anti-phage IgM antibody levels peaked on day 5, stabilizing thereafter. IgG antibody levels rapidly increased until day 25-30, followed by a slower rise. Notable differences in IgG levels were observed until day 25, diminishing thereafter. Further studies should compare phages differing significantly in each trait to minimize confounding factors. Administration of phage DNA had no impact on the examined parameters.

This work was supported by Shota Rustaveli National Science Foundation of Georgia (SRNSFG) №YS-21-3118

66. TSITSINO ZHORZHOLIANI

INCREASE IN CASES OF GASTROENTERITIS NOSOLOGY DEPENDING ON THE SEASON IN CHILDREN (0-10 YEARS OLD)

Batumi Medical University "Avicenna", Tbilisi, Georgia

This study aims to investigate the rise in cases of gastroenteritis among children aged 0-10 years during the holiday season in Batumi, comparing it with other medical conditions. We analyze the epidemiological situation in Batumi during the holiday season, particularly focusing on the surge in gastroenteritis cases. Methodologically, this research utilizes data from St. Batumi Central Hospital for Mothers and Children and Batumi Republican Clinical Hospital. We employ a quantitative approach to process data related to gastroenteritis and other medical conditions during the holiday season. Specifically, we use correlation analysis and calculate the Pearson correlation coefficient.

The results indicate a significant increase in gastroenteritis cases during the holiday season, primarily attributed to the influx of tourists during this period, resulting in a higher number of children. Additionally, the rising number of infections can be linked to improper food preparation, unhealthy lifestyles, unfavorable living conditions, and dietary habits that do not adhere to recommended guidelines. This paper aims to complement preventive measures. Our focus is on ensuring food safety by implementing good hygiene practices throughout food production, processing, and preparation. Public awareness campaigns addressing safe food handling, proper cooking temperatures, and personal hygiene also play a pivotal role in reducing the incidence of this infection. The recommendations we propose are designed to lower the risk of gastroenteritis among children aged 0-10 years and enhance the effectiveness of children's healthcare during the summer season.

67. NINO GVAJAIA, LIKA KUTCHAVA, LEVAN ALAVIDZE, SAI PRATIBHA YANDAMURI, ELENE PESTVENIDZE, VASO KUPRADZE

ARTIFICIAL INTELLIGENCE IN THE MEDICAL FIELD: DIAGNOSTIC CAPABILITIES OF GPT-4 IN COMPARISON WITH PHYSICIANS

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GPT-4 is an extensive language model designed to understand and generate human-like text, with the ability to accomplish complex tasks such as data analysis and decision-making. This study aimed to evaluate the effectiveness of GPT-4 in making medical diagnoses comparable with those of experienced physicians across various medical specialties. We conducted a retrospective observational study, which involved preprocessing 340 clinical cases, the contents of which included medical history, physical findings, laboratory, and instrumental data. We provided this information to GPT-4, which was instructed to give us the top five most likely differential diagnoses.

The discrepancies between AI's five differentials and the physician's final diagnosis were analyzed regarding different specialties and laboratory/instrument data inclusion. Before we integrated laboratory data, GPT-4 showed a 60% diagnostic match with physicians on the first differential and 86% in all five. After we integrated the instrumental and laboratory findings, these percentages grew to 72% and 92%, respectively. The integration of laboratory and instrumental data increased GPT-4's diagnostic accuracy,

evidenced by an odds ratio factor of 2.1 and McNemar's test chi-squared value of 10.76, highlighting the substantial impact of this data on AI's diagnostic precision.
This study highlighted the potential of using GPT-4 in medical diagnostics, provided a basis for integrating AI tools with clinical judgment, and opened avenues for future research, particularly in developing AI models tailored to the diagnostic needs of different medical fields.

68. NANA TSKHAKAIA, DALI STURUA, NINO ADAMIA

BRONCHOPULMONARY DISPLASIA – ETIOLOGY, CLINICAL AND RADIOLOGIC FEATURES, DIAGNOSIS

M. Iashvili Children's Central Hospital, David Tvildiani Medical University, Tbilisi State Medical University

Bronchopulmonary dysplasia (BPD), also known as neonatal chronic lung disease is an important contributing factor in the increased risk of mortality and morbidity in the preterm population. BPD is a lung disease characterized by disruption of pulmonary development and/or lung injury in the context of preterm birth. Clinically, BPD is defined as an ongoing need for supplemental oxygen and/or respiratory support at either 28 days postnatal age or 36 weeks postmenstrual age in a preterm neonate with radiographic evidence of parenchymal lung disease.
Various criteria are used to define the severity of BPD. Severity categories in the 2019 definition (Jensen definition) are based primarily on the mode of respiratory support administered at 36 weeks PMA, regardless of whether the infant requires supplemental oxygen and are classificated in three categories: mild, moderate and severe categories. The severity of BPD increases with decreasing gestation age.
The etiology of BPD is multifactorial and involves disruption of lung development and injury due to antenatal (intrauterine growth restriction, maternal smoking) and/or postnatal factors (eg, mechanical ventilation, oxygen toxicity, infection) that cause inflammation and damage to the vulnerable premature lung. The physical examination is variable. Infants with BPD usually are tachypneic. Depending upon the extent of pulmonary edema and/or atelectasis, they may have mild to severe retractions, and scattered rales may be audible. Intermittent expiratory wheezing may be present in infants with airway narrowing from scar formation, constriction, mucus retention, collapse, and/or edema. Chest radiograph — As BPD evolves, the chest radiograph also changes from clear lung fields to findings that include diffuse haziness and a coarse interstitial pattern, which reflect atelectasis, inflammation, and/or pulmonary edema. Lung volumes are normal or low. With further evolution of the disease, there may be areas of atelectasis that alternate with areas of gas trapping, related to airway obstruction from secretions or bronchiolar injury.

69. D. STURUA, N. TSKHAKAYA, N. ADAMIA, N. JOJUA, L. SAGINADZE, T. ARAKHAMIA, I. UBIRIA

LUNG ABSCESSES IN CHILDREN

M. Iashvili Children's Clinical Hospital, David Tvildiani Medical University, Tbilisi State Medical University

Pulmonary infections continue to be a leading cause of morbidity and mortality in children. This was due to the advances in radiological imaging in recent years and the emergence of new lung infections. The clinical picture of diseases and the results of treatment have changed. Thus, we considered it necessary to evaluate the updated results on this topic. In this review article, we will discuss the complicated forms of lung infections in children, in particular, several cases of rare forms of pneumonia with a destructive process, which are caused by new pathogens - coronavirus disease, as well as bacterial and parasitic infections. We will introduce you to the current stages of the abscess process and visualization findings based on the data of our clinic.
Lung abscess is a localized volumetric formation of pus in the lung. It is often difficult to control and treat, and in some cases can be life-threatening. Since the clinical presentation of pulmonary infections in children is often nonspecific, radiological imaging evaluation plays an important role in initial detection, follow-up of disease progression, and assessment of potential complications.

70. SOPIO TSERTSVADZE [1,3], TAMAR KOKASHVILI [2], NINO JANELIDZE [2], NINO SIRADZE [1], ELENE DIDEBULIDZE [2], MARINA TEDIASHVILI [2], IVANE CHKHAIDZE [1,3]

POTENTIAL OF BACTERIOPHAGE – BASED STRATEGY TO COMBAT HEALTHCARE ASSOCIATED INFECTIONS IN PEDIATRIC HOSPITALS

[1]M. Iashvili Children's Central Hospital, Tbilisi, Georgia; [2]George Eliava Institute of Bacteriophages, Microbiology and Virology, Tbilisi, Georgia; [3] Tbilisi state Medical University, Tbilisi, Georgia

Healthcare associated infections (HAI) represent a big challenge to clinical medicine, including pediatric services, worldwide. Gram negative bacilli (GNB), primarily Pseudomonas aeruginosa, Acinetobacter baumannii and Enterobacteriaceae species in addition to Staphylococcus aureus and coagulase-negative (CoN) staphylococci are important HAI pathogens with high potential for horizontal spread. Their elimination remains difficult because of resistance of infectious agents to many antibiotics. Bacteriophages are considered as effective and safe tool for control of multidrug resistant bacterial infections.

Our long-term study was undertaken to identify the dynamics of prevalent bacterial flora in the respiratory department with ICU of a large children's hospital, and to analyze their antibiotic and phage susceptibility profiles. The various samples from patients with respiratory disorders and from fomites were collected during multiple sampling series. The obtained isolates were identified by biochemical profiling and using API systems (Biomereux, France), followed by PCR confirmation. The susceptibility to specific sets of antibiotics was determined by disc diffusion method according to the EUCAST guidelines, phage susceptibility was studied by spot test followed by EOP determination.

Among GNB isolates collected at the children's hospital P. aeruginosa was most frequently isolated, followed by Serratia marcescens, A. baumannii, K. pneumoniae etc. Among gram- positive bacteria S. aureus and CoN staphylococci remained dominant. Majority of GN clinical isolates, primarily P. aeruginosa, A. baumannii and other nonfermentes, also K. pneumoniae were shown to be multidrug resistant, frequently resistant to carbapenems. S. aureus strains showed variable profiles of antibiotic susceptibility with obvious resistance to Beta- lactams and in a few cases - warning signs of vancomycin resistance.

The isolates of prevalent clinical pathogens were screened against 6 commercial phage preparations ("Eliava Biopreparations") and more then 50 individual phages from Eliava collection active to P. aeruginosa, A. baumannii, S. aureus and CoN staphylococci, K. pneumoniae. Up to 90 % of S. aureus strains in were lysed by Sau phages. The high cumulative lytic activity (>80%) of phages was demonstrated towards multidrug resistant clinical isolates of P. aeruginosa, A. baumannii and K. pneumoniae. Based on the obtained results 4 individual phages P. aeruginosa with broad host range, also 4 phages of A. baumannii and 5 - of S. aureus were selected as candidate phages. The developed experimental mixtures showed extended lytic activity against multidrug resistant pediatric hospital strains thus demonstrating obvious potential of bacteriophages to combat HAI in this critical era of antibiotic resistance.

71. RICHARD TAVDGIRIDZE

IMMUNE-MEDIATED ENTEROPATHIES IN ANIMALS

Agricultural University of Georgia

The gastrointestinal tract has a special role to play in the relationship between the body's immune responses, the commensal microbiota, and invading pathogens: The immune system has to be discriminating – it cannot react very strongly to everything foreign that it encounters, especially if it does not pose a threat. As a result, the gastrointestinal tract is home to many regulatory and tolerance-inducing mechanisms, that ensure that immune-mediated responses to all these antigens are either totally suppressed, as in the responses to foods, or at the very least, are carefully regulated, as in the responses to the microbiota. Food allergies can be considered as a failure in immune regulation. Autoinflammatory diseases that affect the intestine and other enteropathies, represent another consequence of a loss of peripheral tolerance; In this topic, there will be discussed loss of food tolerance and as a result, induced Gluten-Induced enteropathy.

We will also cover other immune-mediated enteropathies, such as Canine inflammatory bowel disease (IBD), in dogs characterized by chronic inflammation of the gastrointestinal tract. It's thought to be caused by a complex interplay of genetic predisposition, immune system dysregulation, and environmental factors.
Equine Inflammatory Bowel Disease is a condition in horses characterized by chronic inflammation of the gastrointestinal tract, like its equivalent in canines. However, IBD in horses is less commonly diagnosed compared to other species.
In this topic, it will be discussed the causes of such immune-mediated enteropathies, the clinical features, diagnostic methodologies, and therapeutic approaches of those diseases mainly in dogs and horses.

72. MARINA SHAVIANIDZE

TSKALTUBO RESORT, ITS MINERAL SPRINGS AND OUTSTANDING PEOPLE – OTARI SHAVIANIDZE (1926-1999)

ATSU Medical University

Tskaltubo is one of the ancient resorts. It is mentioned in 1245 in the charter of the Gelati monastery. Therefore, we must assume that the resort has a 1000-year history. Tskaltubo located is in the Colchis plain 100 meters above sea level. The resort has a terraced layout. In the center there is a balneological zone where mineral springs are concentrated. Tskaltubo mineral springs do not contain toxic or potent substances, which is, of course, their advantage. Of the physical properties of water, the most important is high flow rate and natural temperature. Flow rate is 15-18 million liters per day. Because of this, a special treatment method is used in Tskaltubo – a flow bath. The water temperature is 33-34 degrees, the acid-base balance is 7,2, water mineralization is 0,8 g/l. Water contains 6 ions – natrium, calcium, magnesium, bicarbonate, sulfate, and chlorine. Water also contains gases- nitrogen, radon, argon, and helium. In addition, the water contains biologically active microelements iodine, zinc, lithium, bromine, manganese, and silica. Based on the above, the method of treatment with Tskaltubo mineral baths is determined by a 20-day course of treatment, 20 -minute baths, 20-25 baths rep course. Tskaltubo mineral baths have a wide range of effects, they have a beneficial effect on cardiovascular, musculoskeletal, diseases of the peripheral and central nervous system, skin, gynecological and endocrine diseases.
One of the outstanding figures at the Tskaltubo resort was Otari Shavianidze who made a significant contribution to the development of the resort. He was born in 1926. In 1948 he graduated from the Tbilisi state medical institute. Worked as director of the Scientific Research Institute of Balneology and Physiotherapy for 30 years. Candidate of medical sciences, academic Doctor of Medicine, professor, senior researcher, doctor of the highest category, published more then 180 scientific papers, 10 monographs, numerous articles in magazines and newspapers. His monographs include "Tskaltubo", "Tskaltubo children resort", "Tskaltubo – 1000 years" and others. He was the first in world literature to study the effect of Tskaltubo mineral baths on tumors and proved the stimulating effect. He was also the first to develop differential treatment for children at the resort. His works are fundamental in the field of pediatrics. He is considered the founder of children balneology.

73. SHORENA KITSMARISHVILI

DISCOVERER AND EXPLORER OF SUBTERRANEAN MARVELS

Infectious Diseases and AIDS Center, Tbilisi, Georgia

Jumber Jishkariani was a Georgian geographer and journalist, renowned for being one of the early explorers of Prometheus Cave. He held the esteemed title of honorary member of the Geographical Society of Georgia and was recognized as a distinguished journalist, earning the honor of being a laureate of the Sergey Meskhi Prize. Additionally, he was a member of the Phasis Secular Academy and was granted the status of honorary citizen of Tskaltubo. Since his student years, Jumber actively engaged in various expeditions, dedicating his entire life to the underground investigation. From 1959 until the end of his life, he served in the karstology-speleology department of the Vakhushti Bagrationi Institute of Geography. In 1986, he assumed the role of scientific researcher, and from 1997 to 1999, he held the

position of the head of the department. His involvement led to the exploration of over 400 caves and abysses, including the New Athos Cave, for which he created the initial plan. In 1984, Jumber led a team of speleologists from the institute in discovering a cave in the village of Kumistavi, Tskaltubo district, which stands out as one of the unique caves in Europe. He played an active role in advancing speleotherapy. Mr. Revaz Sepiashvili, the director of the Scientific Research Institute of Allergology, Asthma, and Clinical Immunology of the Georgian Academy of Sciences, made significant contributions to studying the healing properties of the cave's microclimate. In addition to his dedication to speleology, Jumber pursued journalism with great passion, authoring over 1000 publications in various journals and newspapers.

From 1999 to 2008, he embarked on a business trip to the United States of America to gain expertise in cave improvement. This endeavor served as a connecting and unifying bridge for Georgians dispersed across different parts of the world. Upon returning to his homeland, he fervently continued his pursuits despite facing vision impairment (having lost an eyeball), yet remaining spiritually resilient. With the assistance of generous individuals, he successfully published five books: "Our Otia," "Treachery in the Dal Valley," "Above Envy and Slander," "Fragments from an American Diary & Letters," and "Amazing Subterranean." Until the end of his life, Jumber upheld the life motto of the great writer Levan Gotua: "I don't desire any happiness if it comes at the expense of my homeland."

74. LELA TSAKADZE, IVANE CHKHAIDZE

RESPIRATORY VIRUSES IN THE PRE- AND POST-PANDEMIC PERIODS IN M. IASHVILI HOSPITAL

Tbilisi State Medical University, M. Iashvili Children's Central Hospital, Department of Pediatrics

Background: The COVID-19 pandemic has had a major impact on healthcare systems throughout the world. The precautions taken to prevent COVID-19 have seemingly had an indirect effect on the seasonal variations of viral diseases and the frequency of relevant viruses. Therefore, the aim of this study is to evaluate the impact of the COVID-19 pandemic on the frequency and seasonal variation of common respiratory viruses in children pre- and post-pandemic.

Methodology: A cross-sectional retrospective cohort study was conducted by analyzing the electronic database of the M. Iashvili Children's Clinic. A total of 3,640 samples were collected from children under the age of 17 who were hospitalized in the M. Iashvili Children's Hospital between January 2018 and December 2023. A study was conducted to assess the impact of the COVID-19 pandemic on the frequency and seasonal variation of common respiratory viruses in children pre- and post-pandemic.

Results: All nasopharyngeal swabs (NPS) for viral Polymerase chain reaction (PCR) multiplex that were done for all admitted children of age up to 17 years were included, and the total samples amounted to 3640, There were 2270 (62.4%) positive samples for viruses and 1370 (37.6%) negative samples. The number of positive samples pre-COVID-19 pandemic was 493 (60%), and the number of positive samples -COVID-19 pandemic was 797 (35%) and post pandemic period was 980 (57%). The frequency of different viruses has decreased post-COVID-19 and seasonality has changed; Although Rhinovirus, and influenza viruses have no big changes, but HMPV (Human Metapneumovirus) has increased frequency post-COVID-19 (13%), while post-COVID-19 it was (2 %). The seasonal peak for Respiratory Syncytial Virus (RSV) pre-COVID-19 showed mainly in winter (70%), while post-COVID-19 it showed no peak.

75. TAMAR DANDURISHVILI, IA KHURTSILAVA

THE ROLE OF VITAMIN A SUPPLEMENTATION ON WEIGHT IN OBESE CHILDREN AND ADOLESCENTS

Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia

Introduction: The prevalence of overweight children and adolescents in Georgia has raised concerns regarding their health. Evidence shows that vitamin A has been found to reduce concentrations of adipocytokines, such as leptin and resistin and have great impact on obesity. This study aimed to investigate the association between vitamin A supplementation and weight loss in Georgian population.

Methods: We conducted a cross-sectional study involving 40 obese children and adolescents. It was prospective research. BMI >90 percentile. Age range was 5-17. All participants received dietary guidance, and those with insulin resistance were treated with metformin. We used therapeutic dose of vitamin A. Additionally, 20 patients received daily vitamin A supplementation for three months.
Results: The results indicated a significant reduction in weight for all participants, with those who received vitamin A supplementation experiencing nearly twofold greater weight loss compared to those who did not.
Conclusion: These findings suggest that vitamin A consumption may be an effective strategy for facilitating weight loss in overweight children and adolescents. This research contributes valuable insights that can inform future interventions and public health strategies in Georgia. The study was small, and the conclusions can't be very clear, but this small study shows that expanded research is required in this direction, as vitamin A supplementation can be promising when dealing with children and adolescents with obesity.

76. KETEVAN TSANAVA

THE POTENTIAL OF BACTERIOPHAGES IN THE TREATMENT OF IRRITABLE BOWEL SYNDROME (IBS)

George Eliava Institute of Bacteriophages Microbiology and Virology, Georgia

Irritable Bowel Syndrome (IBS), affecting approximately 10-15% of the global population, is a multifactorial gastrointestinal disorder. Its etiology is attributed to various factors including heightened visceral sensitivity, dietary intolerances, ingestion of lipid-rich foods, psychosocial stressors, and alcohol consumption. Emerging evidence underscores a significant correlation between dysbiosis of the gut microbiota and the pathogenesis of IBS, highlighting the critical role of microbial imbalances in its development. Traditional pharmacotherapy for IBS often involves the administration of antibiotics. Although efficacious in certain contexts, this approach is fraught with numerous adverse effects, including but not limited to, anxiety, vesical discomfort, hematuria, and increased respiratory rate. Moreover, antibiotic treatments precipitate disruptions in the microbiome's equilibrium and foster antibiotic resistance among bacterial populations over time.
In light of these challenges, bacteriophages, or phages, represent a novel therapeutic avenue. These viruses exhibit bactericidal activity with high specificity, targeting select bacterial species while sparing the broader microbiome. This specificity minimizes the collateral damage associated with broad-spectrum antibiotics and mitigates the risk of disrupting the gut's microbial harmony. Consequently, there is a burgeoning interest in the exploration of phage biology and the application of phage therapy in treating IBS. Unlike antibiotics, phage therapy is associated with a markedly lower incidence of adverse effects, rendering it a potentially promising alternative for managing this complex disorder.

77. ANA-MARIAM KVACHADZE, KHATIA MENTESHASHVILI, NINO CHIKADZE, TAMAR TSERTSVADZE

SURFACE EXPRESSION OF CD180, MD-1, IGM AND IGD AND THEIR TURNOVER AT VARIOUS TIME POINTS AND CELLULAR CYCLE PHASES IN CLL-DERIVED MEC1 CELL LINE

Tbilisi State University, Faculty of Exact and Natural Sciences Division of Immunology and Microbiology, Georgia

Introduction: Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world and represents expansion of CD19+CD5+CD23+ cells. CLL cell proliferation and expansion is driven by B cell receptor ligation with (auto)antigens and by interaction with the microenvironment through a variety of receptors. One of these receptors is the CD180 toll-like receptor. Our team has shown, that it is expressed on about 60% of CLL cells, is involved in the regulation of CLL cell proliferation and apoptosis and correlates with overall patients survival. Since all normal B cells express CD180, its absence from 30% of the CLL samples is puzzling. The MD-1 satellite molecule, which is essential for CD180 expression on the cell surface, may play a role in this heterogeneity. We have shown high CD180 expression is associated with a favorable disease outcome and superior overall survival emphasizing the importance of

understanding the modulation of CD180 expression in CLL. We therefore characterized the surface expression of of CD180, MD-1, IgM and IgD by the MEC1 cells over 72-hours.
Methods: For this purpose, MEC1 CLL-based cell line was used, which was grown in special cell culture RPMI-1640 medium, which consisted of inactivated bovine serum, L-Glutamine and Pen strep in 37°C. Synchronised MEC1 cells were assessed for surface expression of CD180, MD-1, IgM and IgD -24h, 48h, and 72h using flow cytometry. The viable cells were selected through a parallel identification of cell-cycle phases using propidium iodide. To assess the effect of MD-1 on the expression of CD180, after stimulating MEC1 24–72-hour culture cells with IgM and IgD CD19+/MD1+//CD180+ expression alteration was measured.
Results: In MEC1 the increase in expression of MD1 correlated with increasing of expression of CD180 positively. As we can see at 48hrs, CD180 expression dropped, but regained its level of expression after 72hrs. After 24hrs, MD1 expression significantly increased, but then dropped in 48h cell culture, but regained its expression level in $CD180^+$ 72h cell culture. After 72hrs the expression of IgD drastically dropped compared to $CD180^+$ 24h and 48h cell cultures. After 48-72hrs the expression of IgM decreased compared to $CD180^+$ 24 cell culture. As we can see, MD1 and CD180 expression level drastically dropped in 48hr cell culture. We were inquisitive about the reason and factors that caused such decreasement in the expression of following proteins. We decided to assess the effect of MD-1 on the expression of CD180, after 24 hours stimulating MEC1 24–72-hour culture cells with IgM and IgD $CD19^+/MD1^+//CD180^+$ expression alteration was measured. The stimulation of MEC1 24-hour culture by bindings with IgM or/and IgD decreased $CD19^+CD180^+$ expression, but $CD180^+MD1^+$ remained the same level by binding with IgD as in unstimulated 24-hour cell culture, unlike by binding with other antibodies. The stimulation of MEC1 48-hour culture by bindings with IgM or/and IgD increased $CD180^+MD1^+$ expression, but $CD180^+$ population decreased compared to unstimulated and stimulated 24-hours cells. The stimulation of MEC1 72-hour culture by bindings with IgM or IgD didn't cause any alterations in the immunophenotype of cells.
Conclusion: As a result of our research, it was concluded that MD1 in MEC1 cell culture is a positive regulator of CD180 receptor; MEC1 72-hour cell culture is anergic to IgM, IgD and joint binding of B cell receptor. In result, the impact of MD1 expression was determined on the expression of CD180 and its functions, which modulation is followed by leukemic cell apoptosis. This research will allow us to determine new approaches to CLL immunotherapy.
This work was supported by Shota Rustaveli National Science Foundation of Georgia (SRNSFG) [grant number FR-22-9689]

78. TSISANA UGULAVA, DAVID TSKHOMELIDZE

WHY IDENTICAL TWINS ARE NOT IDENTICAL: GENETIC TRAITS OF ALLERGIC INHERITANCE

Tbilisi State Medical University, Tbilisi, Georgia

Introduction and Objectives: As we know, there are two main theories around allergy inheritance: hygienic theory and genetic theory. Identical twins share not only the same genetic code but also the same environment. That's why it's very interesting for us to learn why twins develop different allergies throughout their lives and why identical genetic codes don't guarantee the same diseases. That's where epigenetics comes in.
Materials and Methods: Through five years of research, we have used questioning as the main resource for our work, as well as longitudinal research. While doing research, we were making blank questions and saying that we were looking after couples. In terms of developing allergies further in life, while researching, we found a correlation between older and younger twins developing allergies. Also looking for correlation between c-sections and allergies.
Results: from 70 pairs of twins, 20.2% of cases developed allergies in both (but it was a different kind of allergy for most cases, 87%); in 12.8% of cases, allergies developed in the A twin; and in 24.2%, twin B was allergic. In other cases (42.8%), both kids were healthy. Also, those born due to c-sections developed allergies more often (68%).

Discussion and Conclusion: In conclusion, we can say that B twins develop allergies more often and have more severe forms, while Twin A is usually less responsive to allergens.

79. ZAAL KOKAIA

NEUROINFLAMMATION IN ISCHEMIC STROKE – PROS AND CONS!

Lund University, Sweden

Stroke is currently the third leading cause of disability-adjusted life-years and mortality worldwide, with a projected 23 million cases and 7.8 million deaths in 2030. As the risk of stroke increases sharply with age, incidence, and prevalence are expected to rise even further as a result of an aging population. This disease affects about 3.5 million people in the EU, with 700 000 new cases yearly. More than half of the patients suffer significant residual impairments, causing huge economic and societal burdens. Acute clinical intervention, typically surgical removal or dissolution of the clot by administration of tissue plasminogen activator (tPA), aims to restore blood flow in the affected brain areas. Unfortunately, these interventions are only possible within a very short time window after stroke onset, and as a result, 10% of all stroke patients are eligible for this treatment. The spontaneous functional outcomes appear to be consistent with a degree of rewiring of surviving neural networks and recruitment of intact synapses, which tends to occur mainly in the contralateral brain hemisphere but also ipsilateral to the lesion. Ischemic stroke leads to brain tissue lesions triggering inflammation, activation of resident immune cells, i.e., microglia, as well as infiltration of immune cells from the blood, including monocytes. Activated microglia and monocytes produce pro- and anti-inflammatory mediators. Thus, neuroinflammation serves as a double-edged sword in the context of ischemic stroke, exerting both detrimental and beneficial effects on stroke-induced damage as well as post-stroke regeneration and recovery. Understanding the mechanisms underlying neuroinflammation-mediated regeneration is crucial for developing targeted therapeutic strategies aimed at promoting functional recovery in stroke survivors.

ავტორთა საყურადღებოდ!

1. ორიგინალური სტატია უნდა წარმოადგინოთ ერთ ეგზემპლარად, დაბეჭდილი 1,5 ინტერვალით, შრიფტის ზომა - 12 პუნქტი; ქართული, რუსული და ინგლისური ტექსტი აკრეფილი უნდა იყოს შრიფტით Sylfaen, ფორმატში Microsoft Word.
2. სტატიის მოცულობა არ უნდა იყოს 5 გვერდზე ნაკლები და უნდა შეიცავდეს ციტირებული ლიტერატურის სიას, ცხრილებს და გრაფიკებს.
3. პირველ გვერდზე მიუთითეთ: 1) ავტორის (ავტორების) სახელი და გვარი სრულად; 2) სტატიის სათაური; 3) კათედრა, ლაბორატორია ან ორგანიზაცია, ქალაქი, ქვეყანა.
4. სტატიას უნდა დაერთოს რეზიუმე ინგლისურ და ქართულ ენებზე, თითოეული მოცულობით არა უმეტეს 0,5 გვერდისა.
5. ტექსტში ბიბლიოგრაფიული მითითებები აღნიშნეთ ნომრით, კვადრატულ ფრჩხილებში, ლიტერატურის ნუსხის შესაბამისად. მიუთითეთ ნაშრომის სახელწოდება, გამომცემლობა, წელი, ტომი, ნომერი და გამოშვება, გვერდების აღნიშნვით.
6. სტატიას ბოლოში ერთვის პირველი ავტორის ხელმოწერა, სამეცნიერო ხარისხი და წოდება, მისამართი და ტელეფონის ნომერი.
7. ჟურნალის სარედაქციო კოლეგია იტოვებს უფლებას შეასწოროს და შეამოკლოს ჟურნალში გამოსაქვეყნებელი სტატია რეცენზენტის შენიშვნების გათვალისწინებით.
8. ჟურნალის სარედაქციო კოლეგია პასუხს არ აგებს გამოქვეყნებული მასალის შინაარსზე.
9. ხელნაწერები, რომლებიც არ შეესაბამება აღნიშნულ წესებს, უბრუნდება ავტორს განხილვის გარეშე.

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1. A single copy of an original article should be typed 1.5-spaced, font size 12, on sheets of paper with standard margins. It's desirable to submit an article typed in Microsoft Word.
2. The articles submitted should not be less than 5 typed pages, including list of references, tables and figures.
3. Page 1 should include: 1) the authors' full names; 2) the title of the article; 3) the department, laboratory and institution where the work has been carried out, city, country.
4. Abstract in English and Georgian (0.5 typed page in size) should be sent with the article.
5. References cited in the article text should be numbered in square brackets and according to the list of references where the authors are enumerated in alphabetical order. The author, title of the article, place of publication, publishing house, publication year, volume, number, edition number, pages (from-to) should be indicated.
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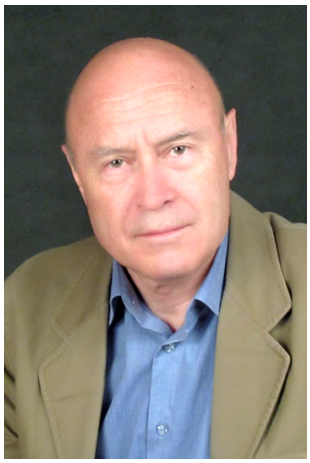
მთავარი რედაქტორების გვერდი
Page of Editors-in-chief

ნინო ჯავახიშვილი - მთავარი რედაქტორი 1999-2012 წლებში
გამოჩენილი ქართველი მეცნიერი და საზოგადო მოღვაწე. დიდი ანატომი. საქართველოში კლინიკური მორფოლოგიის ფუძემდებელი. თბილისის სახელმწიფო სამედიცინო ინსტიტუტის კურსდამთავრებული (1935). მედიცინის მეცნიერებათა კანდიდატი (1941). მედიცინის მეცნიერებათა დოქტორი (1949), პროფესორი (1953), საქართველოს მეცნიერებათა დამსახურებული მოღვაწე (1965), საქართველოს მეცნიერებათა აკადემიის აკადემიკოსი (1979). საქართველოს მეცნიერებათა აკადემიის ექსპერიმენტული მორფოლოგიის ინსტიტუტის დირექტორი (1959-2006), საპატიო დირექტორი (2006-2012). ჯილდოები: ღირსების ორდენი, ლენინის ორდენი, შრომის წითელი დროშის ორდენი, ხალხთა მეგობრობის ორდენი, საპატიო ნიშნის ორდენი. 300-მდე სამეცნიერო ნაშრომის, 9 მონოგრაფიის ავტორი.

Nino Javakhishvili - Editor-in-Chief in 1999-2012
Prominent Georgian scientist and public figure. Great anatomy. Founder of clinical morphology in Georgia. Graduate of Tbilisi State Medical Institute (1935). Candidate of Medical Sciences (1941). Doctor of Medical Sciences (1949), Professor (1953), Honored Worker of Science of Georgia (1965), Academician of the Georgian Academy of Sciences (1979). Director of the Institute of Experimental Morphology of the Georgian Academy of Sciences (1959-2006), Honorary Director (2006-2012). Awards: Order of Honor, Order of Lenin, Order of the Red Banner of Labor, Order of Friendship of Peoples, Order of Merit. Author of about 300 scientific works, 9 monographs.



ბორის კორსანტია - მთავარი რედაქტორი 2013-2020 წლებში
გამოჩენილი ქართველი მეცნიერი, იმუნოლოგი. საქართველოში ვირუსოლოგიის ერთ-ერთი ფუძემდებელი. ვიტებსკის სახელმწიფო სამედიცინო ინსტიტუტის კურსდამთავრებული (1964). ლენინგრადის ექსპერიმენტული მედიცინის ინსტიტუტის ასპირანტი (1964-1967), მედიცინის მეცნიერებათა კანდიდატი (1967), ლენინგრადის სსრკ ჯანდაცვის სამინისტროს გრიპის ინსტიტუტის დოქტორანტი (1972-1975), მედიცინის მეცნიერებათა დოქტორი (1975), პროფესორი (1980), მედიცინის და ბიოლოგიურ მეცნიერებათა აკადემიის აკადემიკოსი. საქართველოს ექიმთა პოსტდიპლომური განათლების ასოციაციის დამფუძნებელი, ვიცე-პრეზიდენტი, კონფერენციების სამეცნიერო დირექტორი.
290 სამეცნიერო ნაშრომის და 5 მონოგრაფიის ავტორი.

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ექიმი დერმატოვენეროლოგი. თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის, კანისა და ვენერიულ სნეულებათა დეპარტამენტის ასოცირებული პროფესორი. თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის კურსდამთავრებული (2001). საქართველოს მეცნიერებათა აკადემიის ბიოტექნოლოგიის ინსტიტუტის ასპირანტი იმუნოლოგიასა და ალერგოლოგიაში (2001-2003), თსსუ დერმატო-ვენეროლოგიის რეზიდენტი (2002-2005).
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