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імені О. О. Богомольця

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Обґрунтування необхідності впровадження симуляційного навчання здобувачів стоматологічної освітиза результатами аналізу діяльності Стоматологічного медичного центру Національного медичного університету імені О.О. Богомольця.

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***Анотація**: в роботі проведено аналіз існуючих проблем практичної підготовки студентів стоматологів на клінічних базах профільних кафедр в сучасних умовах реформування системи охорони здоров'я а також впливу пандемії COVID 19 і збройної агресії рф, а також обґрунтовано доцільність симуляційного навчання студентів стоматологічних факультетів. В основу дослідження покладено вивчення статистичних матеріалів Стоматологічного медичного центру НМУ імені О.О. Богомольцята результати анонімного анкетування випускників стоматологічного факультету, лікарів інтернів, що проходили післядипломну підготовку на базі СМЦ, а також вивчення думки експертів-науковців щодо діяльності Стоматологічного медичного центру як науково-навчально-лікувальної бази підготовки майбутніх фахівців у галузі стоматології. Продемонстровано тенденцію до суттєвого зменшення кількості звернень за медичною стоматологічною допомогою до університетської стоматологічної клініки при збільшенні частки пацієнтів, що отримують платні стоматологічні послуги за межами навчального процесу, що суттєво обмежує можливість набуття практичних навичок безпосередньо під час клінічного прийому хворих. Так, загальна кількість звернень в СМЦ склала: в 2012 році–257115 пацієнтів, в 2019 році–181507 пацієнтів, а в 2022 році – 101471 пацієнтів. З них в рамках навчального процесу було прийнято: у 2012 році –94416, у 2019 році –56693, у 2022 році –18382 пацієнта. Суттєве падіння кількості звернень в Стоматологічний медичний центр, відносно стала кількість здобувачів стоматологічної освіти в НМУ імені О.О. Богомольця і реалії останніх трьох років призвели до виникнення певних обмежень та зниження можливостей для практичної підготовки майбутніх стоматологів. Наведені дані дали змогу порахувати середню кількість пацієнтів на одного здобувача медичної стоматологічної осві-*

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ти на рік, яка склала у 2012 році –52,57, у 2019 році –25,85, а у 2022 році всього 9,22 чоловік. Неможливість забезпечити навчання із залученням тематичних пацієнтів є підставою до перегляду підходів до практичної підготовки лікарів-стоматологів з розширенням використання симуляційного обладнання з можливістю комп'ютерного контролю відпрацювання навичок. Результати анонімного анкетування також підтверджують необхідність підвищення ефективності практичної підготовки студентів стоматологів та лікарів-інтернів, зокрема за рахунок впровадження нових форм навчання, таких, як – симуляційна підготовка. Обговорюються переваги та недоліки даної форми практичної підготовки за різних умов організації навчального процесу.

Ключові слова: догляд за зубами, стоматологія**,** симуляційне навчання, стоматологічна клініка, групова практика.

Вступ

Сучасний стан галузі охорони здоров'я в Україні вимагає підвищення якості практичної підготовки майбутніх лікарів. В умовах значного відтоку пацієнтів у приватний сектор медицини, набуття державними ЗОЗ статусу неприбуткових комунальних підприємств (НКП), а також невизначеним статусом науково-педагогічних працівників клінічних кафедр, які функціонують на базах НКП, вимагають перегляду підходів до навчання на додипломному етапі, зокрема розвитку симуляційного навчання, що має ряд суттєвих переваг і покликане забезпечити підготовку здобувачів освіти до роботи в умовах клініки.

Мета

Обґрунтувати доцільність симуляційного навчання студентів стоматологічних факультетів, як основи їхньої підготовки до клінічної роботи на підставі аналізу діяльності Стоматологічного медичного центру Національного медичного університету імені О.О. Богомольця (СМЦ НМУ), аналізу діяльності профільних кафедр та соціологічних досліджень.

Матеріали і методи

Проведено аналіз стану системи стоматологічної допомоги в Україні, показників діяльності СМЦ НМУ імені О.О. Богомольця та кафедр стоматологічного профілю НМУ впродовж 2012–2022 рр., аналіз та узагальнення соціологічних досліджень (анкетування) випускників Стоматологічного факультету, експертної оцінки діяльності СМЦ.Також вивчено світовий та вітчизняний досвід щодо переваг застосування симуляційних методів навчання за даними літературних джерел.

Результати

Зміни в системі надання стоматологічної допомоги населенню України, які відбулись в останні роки, свідчать про значне скорочення кількості державних закладів охорони здоров'я (далі ЗОЗ), в яких вона надавалась, з відповідним скороченням штатних одиниць лікарів-стоматологів. Натомість суттєво зросла кількість приватних стоматологічних клінік і кабінетів та збільшилась кількість лікарів-стоматологів, які в них працюють (Chopchik V.D., Kaniura O.A., 2019).

Окремі державні стоматологічні поліклініки, які в силу наявних запобіжних механізмів на законодавчому рівні не могли бути скорочені, переведені на повне самозабезпечення шляхом перетворення в державні комунальні неприбутковіпідприємства, що дало можливість запровадження фінансових відносин між такими ЗОЗ і пацієнтами. Фактично відбулась тотальна комерціалізація стоматологічної допомоги з переведенням останньої в категорію «стоматологічна послуга» і відповідними фінансовими очікуваннями надавачів та очікуваннями споживачів таких послуг щодо їх доступності і якості.

Такі реалії останнього часу вимагають подальшого підвищення якості підготовки майбутніх лікарів-стоматологів на клінічних базах профільних кафедр вищих медичних навчальних закладів, в тому числі в університетських стоматологічних клініках, таких, як Стоматологічний медичний центр Національного медичного університету імені О.О. Богомольця, а саме – досконалого оволодіння практичними навичками, які за усталеною

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традицією протягом десятиліть засвоювались студентами стоматологічного факультету під час прийому пацієнтів на практичних заняттях, починаючи з 4 семестру навчання. Очевидно, що рівень оволодіння практичними навичками при роботі з реальними пацієнтами напряму залежить від їх кількості.

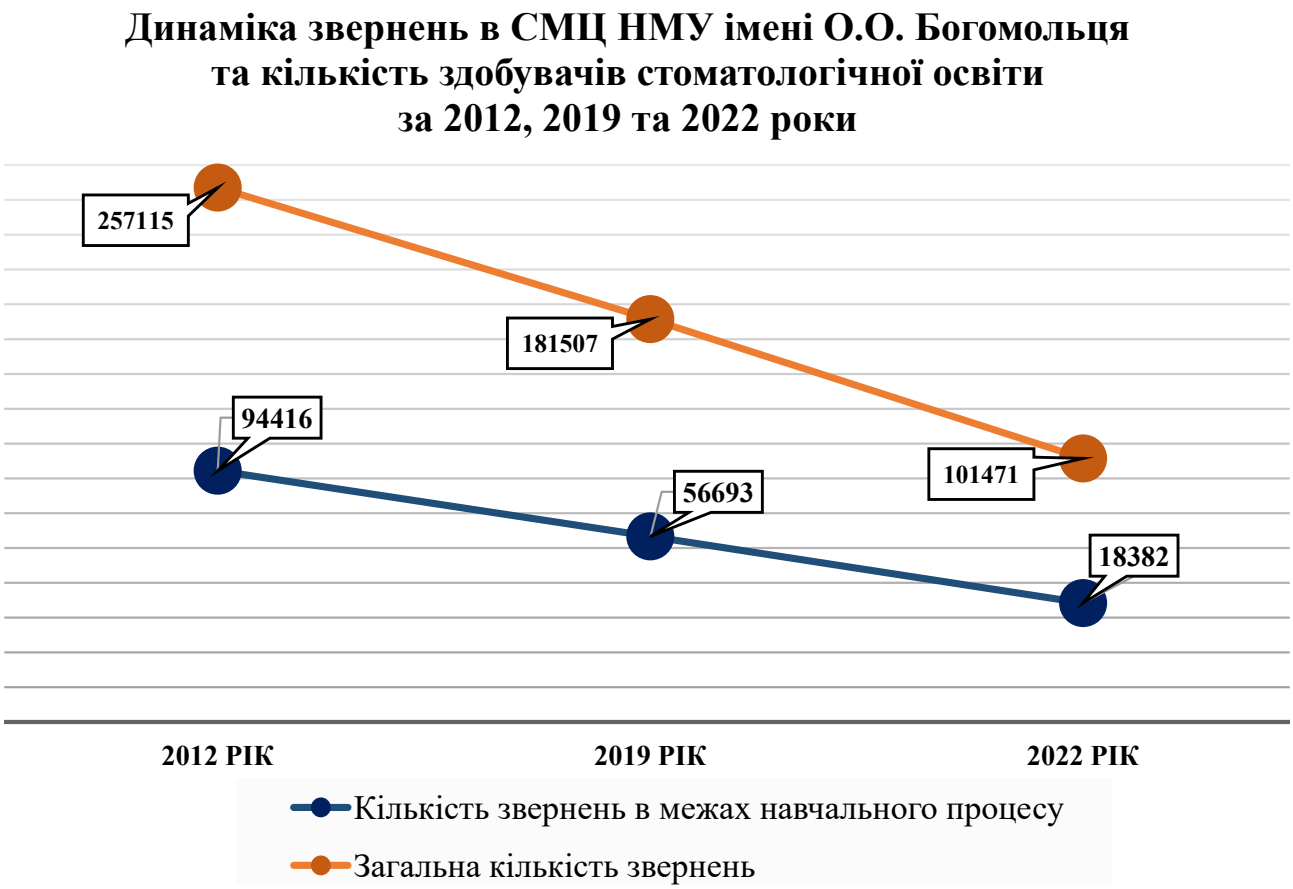
Проведена у 2019 році експертна оцінка показала, що СМЦ володіє потужними умовами для організації навчання студентів та лікарів-інтернів-стоматологів. Експерти відзначили за 10-бальною шкалоюнаявність достатньої матеріально-технічної бази в СМЦ для забезпечення навчального процесу(8,7±0,09) та наявність можливості отримання лікарями-інтернами та студентами практичних навичок в умовах СМЦ (8,8±0,07) (Chopchik V. D., Kaniura O. A., 2019).

Водночас статистичний аналіз діяльності СМЦ свідчить про суттєве зменшення кількості звернень за стоматологічною допомогою. Так загальна кількість звернень в СМЦ склала: в 2012 році–257115 пацієнтів, в 2019 році–181507 пацієнтів, а в 2022 році – 101471 пацієнтів.З них в рамках навчального процесу прийнято: у 2012 році –94416, у 2019 році –56693, у 2022 році –18382 пацієнта (Рис. 1).

Така усталена тенденція значною мірою пов'язана переважно з відтоком пацієнтів в приватний сектор стоматології (Chopchik V.D., Kaniura O.A., 2019).

Крім того, починаючи з 2020 року різке падіння кількості звернень відбулося за рахунок локдауну через пандемію COVID-19, а в 2022 році – з початком воєнних дій та евакуацією значної частини населення Київського регіону (Жарікова Ю.В., 2020). Суттєве зниження кількості прийнятих пацієнтів в рамках навчального процесу на кафедрах стоматологічного профілю обумовлене вимушеним запровадженням дистанційного навчання, пов'язаним з карантинними обмеженнями і початком во-

Рис. 1. Порівняльна характеристика кількості звернень в СМЦ НМУ імені О.О. Богомольця за період з 2012 по 2022 рік.



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єнних дій.Слід також зазначити, що у СМЦ постійно зростає частка пацієнтів, що отримають допомогу на основі надання платних стоматологічних послуг, оскільки з року в рік збільшується обсяг фінансових надходжень СМЦ за надання таких послуг – за досліджуваний період на тлі різкого зменшення кількості звернень в 10 раз зросло виконання фінансових показників за рахунок обслуговування пацієнтів, що відбувається в основному поза межами навчального процесу.

Кількість студентів, які здобували освіту на Стоматологічному факультеті НМУ та осіб, які навчались в інтернатурі, загалом складала в 2012 році –1796, в 2019 році –2193, в 2022 році –1987 чоловік.

Суттєве падіння кількості звернень в Стоматологічний медичний центр, відносно стала кількість здобувачів стоматологічної освіти в НМУ імені О.О. Богомольця і реалії останніх трьох років призвели до виникнення певних обмежень та зниження можливостей для практичної підготовки майбутніх стоматологів, про що свідчать зокрема результати анонімного опитування студентів і випускників останніх років. Наведені дані дали змогу порахувати середню кількість пацієнтів на одного здобувача медичної стоматологічної освіти на рік, яка склала у 2012 році –52,57, у 2019 році –25,85, а у 2022 році всього 9,22 чоловік.

Якщо врахувати, що на базі СМЦ функціонує 7 кафедр стоматологічного профілю, очевидно, що у 2022 році 1 здобувач стоматологічної освіти мав можливість працювати на окремо взятій кафедрі лише з 1–2 пацієнтами, відпрацювавши при цьому орієнтовно від 1 до 5 практичних навичок впродовж року лише один раз.

Тим не менше і досить парадоксальним є той факт, що за результатами проведеного нами у 2019 році соціологічного дослідження (анонімного опитування) серед лікарів-інтернів,організація роботи СМЦ щодо створення умов для навчання задовольняє 52,1%, не задовольняє 47,9% опитаних. Задоволеними отриманими у СМЦ практичними навичками виявили 81,0% опитаних, незадоволеними – 19,0% опитаних. Організацію самостійної роботи на практичних заняттях у СМЦ позитивно оцінили 64,1%, негативно – 35,9% опитаних.Згідно з результатами того ж опитування відсоток лікарів-інтернів, які не мали можливості навчатися на високотехнологічному імітаційному обладнанні, оснащеному якісними відео- і аудіо- реєстраторами, склав 99,0±0,5%, а на комп›ютерах з використанням сучасних цифрових технологій – 97,0 ± 0,9 % опитаних (Chopchik V.D., Kaniura O.A., 2019).

Також за результатами опитування лікарів-інтернів, проведеним Сектором моніторингу НМУ імені О.О. Богомольця у 2021 році,більшість респондентів зазначала потребу у збільшенні практичної підготовки. На їхню думку нестача практичних навичок була пов’язана з дистанційнимнавчанням в умовах пандемії (Сектор моніторингу).

Ще драматичніше з початком медичної реформи склалися обставини на кафедрах, клінічні бази яких розташовані в комунальних закладахохорони здоров›я, в яких доступ викладачів і студентів до практичної діяльності суттєво обмежений або взагалі неможливий: викладачі не представлені в електронних медичних інформаційних системах (МІС), установчі документи таких ЗОЗ і посадові інструкції лікарів не передбачають проведення практичних занять зі студентами, а модель фінансування галузі ніяким чином не враховує педагогічну складову.

Така тенденція беззаперечно спонукає до пошуку альтернативних форм оволодіння практичними навичками. Такі форми навчання вже тривалий час використовуються в системах підготовки лікарів у провідних навчальних закладах за кордоном, стали для них традиційними і довели свою ефективність. До них, зокрема, відноситься і симуляційне навчання, яке дозволяє здійснювати відповідний комп’ютерний контроль правильності виконання необхідних маніпуляцій (Бойчук Т. М., 2018; Гресько, М. Д., 2022).

В даний час симулятори використовуються для навчання та об›єктивної оцінки у багатьох областях діяльності людини, які передбачають високі ризики. Тому поява можливостей в організації фантомного і симуляційного навчання медичних працівників бачиться як розумний і необхідний напрям у навчальному

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процесі (Zhdan, V. & Katerenchuk, O., 2020).

Симуляційне навчання на доклінічному етапі, на думку багатьох дослідників(Гресько, М. Д., 2022, Гринзовський, А. М. & Черненко, Л. М., 2022), має цілий ряд переваг, а саме:

- дозволяє багаторазове відпрацювання навички;
- дає можливість навчання в будь-який зручний час;
- спонукає здобувача освіти до підвищення і закріплення теоретичних знань;
- не залежить від наявності тематичного пацієнта в клініці;
- усуває страх при відпрацюванні навички на реальному пацієнті;
- не передбачає непорозумінь між пацієнтом та студентом на комунікативному рівні;
- унеможливлює ризики ускладнень при роботі з пацієнтами;
- дає можливість відпрацювати рідкісні види практичних навичок;
- отримати навички роботи в команді
- дати об›єктивну оцінку виконанню процедур і маніпуляцій.

Компоненти симуляційного навчання використовувались і використовуються при навчанні студентів-стоматологів НМУ імені О.О.Богомольця протягом тривалого часу. В СМЦ обладнані симуляційні класи для відпрацювання практичних навичок з різних стоматологічних дисциплін. Проте, зважаючи на вищенаведене, постає нагальна потреба розширення і централізованої організації симуляційного навчання. Може бути два підходи до здійснення даної задачі: створення окремої кафедри пропедевтики стоматології, відповідальної за оволодіння практичними навичками на фантомах з усіх напрямів стоматології, або організація окремого стоматологічного симуляційного центру з окремим штатом технічних працівників і графіком роботи, який дозволяв би студентам відпрацьовувати навички у відведений для цього час під керівництвом чергових фахівців із реєстрацією виконаної роботи у спеціально розробленій документації. Обидві моделі мають позитивні і негативні сторони. Перша забезпечує оптимальну спадкоємність викладання пропедевтичних дисциплін, можливість створення більш якісної теоретичної бази та навчально-методичної документації, проте вимагає значного навантаження і розширення вимог до науково-педагогічного персоналу (або введення до складу кафедри представників суміжних спеціальностей, а також інженерно-технічний персонал) і обмежує час і тривалість відпрацювання практичних навичок на кафедрі. Другий підхід розширює можливості практичної роботи студентів, забезпечує облік виконаних маніпуляцій, проте певною мірою обмежує контроль якості їх виконання і не забезпечує логічну послідовність їх виконання. Постає питання про необхідність аналізу і обрання оптимального підходу до симуляційного навчання, виходячи з потреб і можливостей Університету з урахуванням кадрового забезпечення, контингенту здобувачів освіти, матеріального забезпечення тощо.

Висновки

Сучасний стан медичної галузі, особливості надання стоматологічних послуг, які призвели до різкого падіння кількості звернень, зокрема в СМЦ, і, як наслідок, неможливість забезпечити навчання із залученням тематичних пацієнтів є підставою доперегляду підходів до практичної підготовки лікарів-стоматологів з розширенням використання симуляційного обладнання з можливістю комп’ютерного контролю відпрацювання навичок. Університет має обрати найбільш доцільну модель симуляційного навчання, що дозволить здобувачам вищої освіти в повній мірі оволодіти практичними навичками як підґрунтям фахових компетентностей лікаря-стоматолога.

Фінансування

Це дослідження не отримало зовнішнього фінансування.

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Substantiation of the need to implement simulation training for dental students based on the analysis of the activities of the Stomatological Medical Center at O. Bogomolets National Medical University

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Abstract: the article analyzes the existing problems of practical training of dental students at the clinical bases of specialized departments in the modern conditions of the health care system reforms, as well as the impact of the COVID-19 pandemic and armed aggression of the russian federation, and also substantiates the feasibility of simulation training for students of dental faculties. The research

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is based on the study of statistical materials of the Stomatological Medical Center in O. Bogomolets NMU (SMC), the results of an anonymous survey of graduates of the Dental Faculty, interns and doctors who underwent post-graduate training at the SMC. A tendency to a significant decrease in the number of applications for dental care to the university dental clinic has been demonstrated with an increase in the proportion of patients receiving paid dental services who were excluded from the educational process. Such tendency limits the possibility of acquiring practical skills directly during the clinical diagnostics and treatment of patients. Thus, the total number of patient visits to the SMC was: in 2012–257,115 patients, in 2019–181,507 patients, and in 2022–101,471 patients. Of these, 94,416 patients were admitted as part of the educational process in 2012, 56,693 in 2019, and 18,382 patients in 2022. A significant drop in the number of patients who visited the Stomatological Medical Center, a relatively constant number of dental students at O. Bogomolets NMU and the realities of the past three years have led to the emergence of certain restrictions and reduced opportunities for practical training of future dentists. The presented data made it possible to calculate the average number of patients per student of medical and dental education per year, which was 52.57 in 2012, 25.85 in 2019, and only 9.22 people in 2022. The limited possibility of training with the involvement of thematic patients is a reason to revise the approaches to the practical training for dentists with the expansion of the use of simulation equipment with the possibility of computer control of practicing skills. The results of the anonymous survey also confirm the need to improve the effectiveness of the practical training of dental students and interns, in particular through the introduction of new forms of training, such as simulation training. Advantages and disadvantages of this form of practical training under different conditions of organization of the educational process are discussed.

Keywords: dental care, dentistry, simulation training, dental clinics, group practice.

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Living in a Pandemic: Social Isolation and Mental Health

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Abstract: *the novel coronavirus disease of 2019 (COVID 2019) has gripped the world with fear, anxiety and confusion, and it is spreading as fast as a virus. In addition to the negative consequences of the infection of COVID-19 for health, the implementation of strict quarantine also affected the world economy. As a result, there is growing concern that the pandemic has harmed the mental health of the general population. Fear, anxiety, and stress are normal responses to perceived or real threats, and when we are faced with uncertainty or something unknown. Thus, it is normal and understandable for people to feel fear in the context of the COVID-19 pandemic. Together with a fear of being infected with a virus during a pandemic like COVID-19, there are significant changes to our daily lifestyle: our movements somewhere is restricted in support of efforts to contain and slow down the spread of the virus. As the COVID-19 pandemic and lockdown measures continue, there is growing interest in the long-term effects on mental health. In this article, we aim to review and summarize the results of various studies that have examined the psycho-sociological consequences of the pandemic and its impact on the mental well-being of population in a general.*

Key words: COVID-19, pandemics, quarantine, patients, mental health.

Introduction

At the end of December 2019, the first case of pneumonia caused by the coronavirus was detected in the Chinese city of Wuhan. The disease is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the condition is known as coronavirus disease 2019 (COVID-19) according to the World Health Organization (WHO, 2020).

Novel coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, has become a pandemic with increasing cases worldwide. After its initial outbreak, the coronavirus disease spread rapidly throughout the world community, affecting countries in Europe, the United States, the United Kingdom, Asia, the Middle East, and North Africa, prompting the World Health Organization (WHO) to declare COVID-19 a global pandemic in March 2020 (WHO, 2020). Countries around the world have implemented disease containment strategies aimed at disrupting the transmission chains of the virus. These strategies are collectively referred to as nonpharmacological interventions (NPIs) (Ferguson et al.,

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2020). NPIs are mitigation strategies designed to reduce physical contact between individuals in a community in order to reduce the reproduction number, the average number of secondary cases generated by each positive case. The term NPIs is commonly used interchangeably with physical or social distancing protocols. A variety of NPIs are concurrently implemented worldwide, and many countries have implemented strict strategies, including quarantines (e.g., physical closure of schools and universities), social distancing from peers and community activity, quarantine and isolation, to reduce transmission rates in their communities (Ebrahimi et al 2021). Given the fact that many of these interventions are simultaneously operating worldwide, their potentially harmful association with the health status of the general public has now become a major concern for clinicians, academics, and health policy-makers (Holmes et al. 2020).

Due to the rapid spread of COVID-19, efforts by scientists and clinicians are currently focused on understanding the epidemiology, clinical features, mode of transmission, countering the spread of the virus, while the critically important mental health has been overlooked in these efforts, and providing effective strategies to protect public health. (Legido-Quigley et al. 2020; Shamasunder et al. 2020).

Aim

This article aims to summarize the current information on the factors that contribute to mental distress in isolation, anxiety and despair, and consider the mental health of vulnerable groups such as children and teens, the elderly, and healthcare professionals.

Materials and methods

To carry out this review, we searched the published articles in PubMed and Google Scholar using the keywords “COVID-19”, “SARS-CoV-2” or “coronavirus disease 2019” and “mental health” in the abstract or title, of analyzed articles published in scientific journals. Research included literature reviews, systematic reviews, meta-analyses, randomized controlled trials, cohort studies, case reports, and studies in English. We also look for related articles in the reference lists of the articles we have read.

Review and discussion

A new coronavirus disease 2019 (COVID-19) has become a pandemic that has affected health and well-being worldwide. Apart from the consequences of physical health, of economy, and influence on society, the psychological impact of this pandemic is increasingly being reported in the scientific articles (Kalcev et al. 2020; Nicola et al. 2020; Lei et al. 2020). Current information in articles suggests that people suffered from COVID-19 may have a high burden of mental health problems, including depression, anxiety disorders, stress, panic attacks, irrational anger, impulsivity, somatic disorders, sleep disorders, emotional disorders, post-traumatic stress symptoms, and suicidal behavior (Pfefferbaum and North 2020; Wang et al. 2019; Karadağ et al. 2022)

There are numerous evidence of neurological, cognitive, and emotional disturbances in patients with COVID-19. Acute neurological symptoms such as neuro-inflammation, cognitive impairment, loss of smell, and stroke are common direct sequelae among patients infected with SARS-CoV-2. Work-related stress, quarantine measures, social distancing and quarantine in order to diminish SARS-CoV-2 infection have also affected the mental health of large populations, regardless of age. Health emergencies have affected individuals and communities, causing emotional responses and unhealthy behaviors (Pandey et al. 2021). Social isolation and its impact on mental health is perhaps the most difficult aspect that many people have faced in recent years. Despite the quarantine policy in place effectively reduced the spread of the infection, the social isolation caused by the quarantine caused an increase in negative emotions and psychological consequences, including confusion, anger, anxiety and depression of population in the general (Galea et al. 2020; Brooks et al. 2021; Banerjee and Rai 2020). Social communication is vital to human well-being, and while online media and applications such as Zoom, Skype, WhatsApp and FaceTime can ensure continued social interactions, they do not replace the need for face-to-face human contact. It is possible that people may begin to experience temporary mild to moderate symptoms of depression under current circumstances (Haider et al. 2020).

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Psychosocial impact of quarantine and isolation

Enforced mass quarantine, as applied by nationwide quarantine programs, can cause mass hysteria, anxiety, and distress through factors such as feelings of being cornered and loss of control (Rubin et al. 2020).

The psychological impact of quarantine can range from immediate consequences such as irritability, fear of being infected and spreading of the infection to family members, anger, embarrassment, frustration, loneliness, denial, anxiety, depression, insomnia, despair, to extreme consequences including suicide (Brooks et al . 2020; Robertson et al. 2004; Barbisch et al. 2015).

Impact on various layers of society

Children

A child's response to a crisis depends on his physical and mental health, family socioeconomic circumstances, and cultural background (Dalton et al. 2020; Landoni et al. 2022; Radanović et al. 2021). Stress factors such as monotony, frustration, lack of personal contact with classmates, friends, and teachers, lack of sufficient personal space at home, and family financial losses during quarantine can potentially trigger unpleasant and even long-lasting negative psychological consequences in children (Wang et al. 2020 ; Jiao et al. 2020). Likewise, children during COVID-19 may develop phobias, PTSD (post-traumatic stress disorder), etc. when they found out information about risk of get infected and other disturbing details through audiovisual media, including social media (Landoni et al. 2022).

Children are constantly exposing to news related to the epidemic, so direct conversations with children about these issues can reduce their anxiety and avoid panic. In the case of self-isolation at home, parents are often the closest and best source of help for children. Close and open communication with children is the key to identify any physical and psychological problems and to comfort children in long-term isolation. With the help of the right approach to upbringing, it is possible to strengthen family bonds and satisfy the psychological needs of the child (Chen et al. 2022; Lawson et al. 2020; Griffith et al. 2022 Tang et al. 2021).

Elder people

The perception that the elderly and those with serious co-morbidities are particularly vulnerable to worse outcomes from COVID-19 can cause significant fear among older adults. Other psychological effects can include anxiety, irritability, and feeling overly stressed or angry. Elderly people with cognitive decline can become much more anxious, agitated and socially withdrawn, so their special needs require special attention (Doraiswamy et al. 2020; Lloyd-Sherlock et al. 2020).

Female gender and older age are established demographic risk factors associated with mental health impairment in a pandemic setting (Sepúlveda-Loyola et al. 2020). Risk of infection, risk of poverty, and poor housing conditions are contributing factors for older people.

Medical professionals

Challenges faced by clinicians worldwide include high mortality in the patients they care for, high demands for medical care, and extreme physical and emotional stress (Sorbello et al. 2020).

Healthcare practitioners have been particularly affected by the COVID-19 pandemic and are under more stress than many other professional groups. This is due to several factors, including increased risk of infection, fear of infecting others and being isolated from their families, overtime work, difficult working conditions with long shifts, being a direct witness of suffering and death of patients (Manchia et al. 2022; Bozdağ and Ergun 2021). Healthcare workers, who carry the greatest burden today, are at greatest risk of burnout, a state of depleted psychological resources. Burnout is associated with susceptibility to depression and anxiety, sedatives abuse, increased risk of medical errors, and poor clinical decision-making. Indeed, they are exposed to high levels of stress due to long working hours without sufficient rest, as well as the lack of adequate personal protective equipment in most countries that have been heavily affected by COVID-19. In addition, doctors and nurses who are on the front lines of caring for patients with coronavirus are likely to be among the most affected in mental health and psychosocial well-being (Heath et al. 2020; Liang et al. 2020).

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Public

The mass fear of COVID-19, rightly called "corona phobia" (Asmundson and Taylor. 2020), is likely caused by the uncertain nature and unpredictable course of the disease, intolerance of uncertainty, perceived risk of infection, etc., and may generate negative psychological reactions, including maladaptive behaviors , emotional distress and avoidance of ordinary people (Usher et al. 2020).

During disease outbreaks, news of the first death, an increase in the number of new cases, and extensive media attention can heighten people's fears, frustrations, helplessness, and anxiety about the situation. This leads to inappropriate health-promoting and help-seeking behavior in a concerned public, which can lead to conflicts between clinicians and patients. Such situation can be detrimental to epidemic control programs and hinder social stability (Lindert et al. 2020). An over-anxious public may worry about shortages of emergency and essential services related to quarantine, and this unrealistic panic may lead to false feelings about stocking up on daily necessities or resources (such as hand sanitizer, medicine, face masks, or even toilet paper). The level of psychological stress is influenced by the sheer volume of information coming through social media, the availability and provision of basic and medical resources, and the effectiveness of local health care systems (Wang et al. 2021). Prolonged quarantine causes the unavailability of public services and the collapse of many industries, leading to a negative impact on local and national economic stability (Bueno-Notivol et al. 2021). Thus, a huge number of people are experiencing financial losses or are on the verge of unemployment, which exacerbates the negative emotions of these individuals during the COVID-19 pandemic.

Conclusion

COVID-19 is a serious and life-threatening disease. During a global pandemic, it is very important for society to continue to advocate for the interests of those who are particularly vulnerable; those dealing with this pandemic, with all the stress and uncertainty surrounding it. Mitigating the dangerous mental health impact of COVID-19 is an international public health priority.

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Conflict of interest

None**.**

Consent to publication

All authors read and approved the final version of the manuscript. All authors agreed publishing of this manuscript.

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Життя в умовах пандемії: соціальна ізоляція та психічне здоров'я

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Анотація: нова коронавірусна хвороба 2019 року (COVID-2019) охопила світ страхом, тривогою та збентеженням, і вона поширюється так само швидко, як і вірус. Окрім негативних наслідків зараження COVID-19 для здоров'я, впровадження суворого карантину також вплинуло на світову економіку. Як наслідок, зростає занепокоєння, що пандемія завдала шкоди психічному здоров'ю населення в цілому. Страх, занепокоєння та стрес є нормальною реакцією на уявні чи реальні загрози, а також у час, коли ми стикаємося з невизначеністю чи невідомістю. Тож це нормально та зрозуміло, що люди відчувають страх у контексті пандемії COVID-19. До страху заразитися вірусом під час такої пандемії, як COVID-19, додаються значні зміни в нашому повсякденному житті, оскільки наші пересування обмежені на підтримку зусиль зі стримування та уповільнення поширення вірусу. Оскільки пандемія COVID-19 і карантинні заходи тривають, зростає інтерес до довгострокових наслідків для психічного здоров'я. У цій статті ми прагнемо переглянути та узагальнити результати різноманітних досліджень, які вивчали психосоціологічні наслідки пандемії та її вплив на психічне благополуччя населення в цілому.

Ключові слова: COVID-19, пандемія, карантин, пацієнти, психічне здоров'я.

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Application of physical therapy methods for patients after stroke with spasticity in the early period

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Abstract: *acute cerebrovascular accident is the leading cause of disability. Stroke ranks 4th among diseases that lead to death or disability. The consequences of stroke include neurological disorders, motor disorders (plegia, hemiparesis, paresis, muscle spasticity), loss of sensation, pelvic dysfunction, loss of coordination and balance, high risk of falls, and impaired ability to move independently and perform daily activities. To achieve optimal independence, stroke patients need qualified rehabilitation care as part of a multidisciplinary team. Evidence-based medicine, treatment, and rehabilitation interventions have improved significantly in the acute and early periods for stroke patients. However, in the late period, today, more than half of patients remain limited in their daily activities and have movement disorders that significantly affect their quality of life and independence. Description of the objective. To substantiate the use of evidence-based medicine methods in physical therapy to restore motor function in patients after stroke in the early period. Materials and methods. From October to December 2021, 20 patients with spasticity, aged 47-85 years, who had suffered an ischemic and hemorrhagic stroke, took part in the examination and rehabilitation activities at Kyiv City Clinical Hospital № 6, Palliative Care Department, for a period of 3 weeks to 1 month. Voluntary consent for examination, treatment, and rehabilitation was obtained from all patients and their caregivers. The diagnostic methods used were computed tomography, magnetic resonance imaging, and, if necessary, laboratory tests. Tests and scales for physical therapy were used to determine functional impairment in stroke patients with muscle spasticity: Rankin Scale, Riverbed Mobility Index, Pain Score, Modified Ashworth Scale, Degree of Arm and Hand Recovery; Degree of Leg and Foot Recovery. Results. After analyzing the methods of evidence-based medicine on the topic of the problem, we have confirmation that in the early period, recovery rates are high. However, in the late period after a stroke, the onset of muscle spasticity significantly limits the motor capabilities of patients and complicates the recovery process. In the late period, the effectiveness of methods to overcome spasticity has not been fully developed, and attention is not focused on the complications that arise and accompany them throughout the recovery period. The appearance of muscle spasticity significantly limits the motor capabilities*

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of patients, affects the psycho-emotional state of a person, and causes pain, which prevents the full use of the affected limb. Muscle spasticity inhibits and complicates the restoration of motor function in the long term. Conclusions. The study confirms the high effectiveness of the proposed methods of evidence-based medicine in reducing pain and increasing the range of motion in the shoulder, elbow, and wrist joints in the early period in patients after stroke. As for the late period, this issue remains incomplete and requires further study. In the palliative care unit of Kyiv City Clinical Hospital № 6, an individual multidisciplinary approach to patients after stroke was used, which contributed to the achievement of the goals. It can be stated that evidence-based medicine methods for the acute and early period have a positive effect on patient independence, and improve cognitive function and motor activity of the affected limbs.

Keywords: compensation, diagnosis, treatment, physical activity, rehabilitation.

Introduction

According to WHO statistics, stroke kills about 5 million people worldwide every year. Approximately 70 – 80% of stroke survivors, of which 20 – 30% are dependent on outside help, have a motor and cognitive disabilities. A stroke is a vascular disease that occurs when a blood vessel in the brain blocks or ruptures, thus stopping normal blood flow to the brain. Part of the brain does not receive enough oxygen due to insufficient blood supply caused by blockage or damage due to bleeding. The consequences of a stroke depend on which part of the brain it occurs in and how large the area of damage is. Patients who survive a stroke often face disability, which affects their independent daily life (Martin-Saez and James 2021).

Risk factors for stroke are:

- hypertensive heart disease;
- ischemic heart disease;
- atrial fibrillation;
- myocardial infarction;
- cardiac circulatory failure;
- diabetes mellitus;
- overweight;
- insufficient physical activity;
- constant stress (Lou, Carstensen, & Nielsen, 2017).

The consequences of an acute cerebrovascular accident affect the cognitive, psycho-emotional, and physical functioning of individuals (Bernhardt et al., 2017).

Patients have the following consequences: paresis, hemiparesis, hemiplegia; spasticity; aphasia; swallowing disorders; apraxia; spatial visual disturbances; gait, balance, and coordination disorders; posture changes; pain in paretic limbs; depression; development of contractures; low level of independence in everyday activities (Kuliński & Pasieka, 2021).

It is proved that the use of physical therapy, and ergotherapy in the acute period after stroke, reduce the risk of complications and helps to restore impaired functions, prepares patients for verticalization and the acquisition of the necessary skills to be independent in everyday activities (Chippala & Sharma, 2016).

Activity and participation of patients after stroke is an important elements of the rehabilitation path. It is used as a means of prevention and rehabilitation and has many benefits that affect the cognitive, psychosocial, and physical conditions of patients (Saunders, 2020).

Studies have shown that stroke survivors have limited functional activity and participation and lead sedentary lifestyles (Fini, Holland, & Bernhardt, 2017).

Current research emphasizes the need to increase physical activity and improve the active lifestyle of patients after stroke (Moore et al., 2018). The planning of rehabilitation interventions, as a result of achievements, can vary and are targeted at factors that the patient chooses. Factors include individual, environmental and social needs, which can positively or negatively influence the participation of patients after a stroke (Stretton, Mudge, & McPherson, 2017).

Aim

To determine the effectiveness of evidence-based physical therapy methods to restore motor function in patients after stroke with spasticity in the early period.

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Materials and methods

A course of physical therapy was conducted for patients after a stroke with the consequences of muscle spasticity from October to December 2021, in the Palliative Care Unit at Kyiv City Clinical Hospital № 6. The duration of stay in the institution is from 1 to 3 months. The treatment and rehabilitation activities involved 20 people aged 47-85 years, divided into two groups: the main group – 10 people, and the control group – 10 people. All of them had suffered ischemic and hemorrhagic strokes for a period of 3 weeks to 1 month. All patients had muscle spasticity of paretic limbs. There were no contraindications at the time of treatment and rehabilitation in both group. Patients and caregivers voluntarily consented to examination, treatment, and rehabilitation interventions.

Patients after stroke underwent diagnostic examinations: computerized and magnetic resonance imaging. Ultrasound of the cerebral vessels of the neck, cerebral angiography, echocardiography, and laboratory methods was also performed as needed.

Scales and tests are used to examine and determine the patient's functional status in physical therapy and occupational therapy. During the initial, intermediate, and final examination, the effectiveness of treatment and rehabilitation measures is determined and compared. When patients were admitted to the palliative care unit, the physical therapist used the Rankin Scale from 0-5 points for the main and control groups to understand the severity of the stroke and assess the degree of disability. The Rivermead Mobility Index allowed identifying motor activity in the patient's daily life: 0 points – the inability to perform an arbitrary movement independently, the highest score of 15 – the ability to run 10 meters independently. Measurement of the severity of spastic muscles on the Ashworth scale from 0 – 5 points. Determination of the degree of pain from 1 – 7 points, 1 point – constant severe pain, with shoulder pathology, 7 points – shoulder pain and no prognostic indicators. The degree of recovery of the leg and foot was from 1 to 7 points, and the degree of recovery of the arm and hand was assessed from 1 to 7 points, where the highest score was motor activity and the ability to use the limb in everyday activities.

An occupational therapist for the main and control groups determined the degree of functional independence of patients using the Barthel Activities of Daily Living Index scale, with a total score of 100. The score from 0 to 20 points is complete dependence; from 21 to 60 points – is pronounced dependence; from 61 to 90 points – is moderate dependence; from 91 to 99 points – is slight dependence in the patient's daily activities.

The Montreal Cognitive Scale was used to assess the following cognitive impairments: concentration, executive functions, attention, memory, abstract thinking, counting, orientation in time and space, and constructive visual skills. A score of 26 to 30 points indicates a favorable cognitive status. Shoulder pain was assessed from 1 to 7 points, where the highest score has no pain and prognostic indicators.

Most often, patients after a stroke suffer from shoulder pain, which impairs the range of motion, affects the functional state of paretic limbs, and affects the appearance of muscle contractures. All this worsens balance and coordination, impedes independence in everyday activities, limits motor function, and complicates the rehabilitation process.

For the main group, a physical therapist and an occupational therapist conducted sessions 3 to 4 times a day, from 30 minutes to 1 hour, throughout the treatment and rehabilitation process. Evidence-based medicine methods were also used. During the first month, the sessions were held 2-3 times a day for 30 minutes to 1 hour:

- Positioning every 1.5 hours.
- Mobility in bed and within the ward for 30 minutes a day.
- Verticalization from 10 to 30 minutes, depending on the patient's functional status, and no contraindications.
- Active and passive therapeutic exercises from 30 minutes to 1 hour.
- Restoration of walking skills, focusing on the patient's condition, rapid fatigue from 20 to 30 minutes.

The occupational therapist conducted classes for maximum independence in everyday activities from 30 minutes to 1 hour.

In the second month, the sessions were held 3 to 4 times a day, and the patient used:

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- Coordination and balance exercises from 30 to 45 minutes.
- Restoration of walking skills, focusing on the patient's condition, from 20 to 45 minutes.
- Proprioceptive neuromuscular facilitation combined with stretching exercises, from 30 to 45 minutes.

In the third month, 4 times a day, physical therapy and ergotherapy sessions were conducted, from 30 minutes to 1 hour. Stretching exercises were performed for the affected arm and leg, combined with proprioceptive neuromuscular facilitation. Corrected gait, and continued to perform exercises to improve balance and coordination twice a day, from 45 minutes to 1 hour.

A physical therapist and an occupational therapist in the control group worked with patients for the first month, 1-2 times a day, from 30 minutes to 1 hour. The standard program was followed:

- Physiotherapy: stimulating therapy on the affected limbs for 15-20 minutes a day;
- Passive and active exercises for 30 minutes;
- Verticalization and skills to restore walking 20 – 30 minutes;
- Mechanotherapy 15 – 20 minutes;
- Selection of mobility aids.

For the second placement, classes were held 2 times a day from 30 minutes to 1 hour:

- Passive and active exercises for 30 minutes;
- Restoration of walking skills from 30 minutes to 1 hour.
- Mechanotherapy for up to 30 minutes.
- Exercises for balance.

In the third month, classes were conducted similarly, 2 times a day, up to 1 hour. All the previously listed methods of physical therapy.

To achieve the set goals and specific needs of patients, the practicing physical therapist and occupational therapist of the main and control groups of patients with spasticity in the early period used evidence-based medicine methods with a variety of available tools.

The object of the study: patients after stroke with muscle spasticity 20 people, aged 47 – 85 years in Kyiv City Clinical Hospital №6, Palliative Care Department. A multidisciplinary team was created under the supervision of the attending physician: Neurologist, Psychologist, Speech Therapist, Physical Therapist, Occupational Therapist, Massage Therapist, Ward Nurse, and Junior Nurse. With the voluntary consent of relatives and the patient, upon admission to the department, examinations were carried out, selection of medicines, and methods of evidence-based medicine were also used.

Results

Physical therapist and occupational therapist on admission to the department: assessed the functional status, based on the request and needs of patients, and developed an individual rehabilitation program.

The multidisciplinary team together with the patient discussed short-term and long-term goals built in a Smart format. Each member, within his competence, plans an individual program for the patient for the day. To achieve the goals, they use evidence-based medicine methods and tasks that the patient performs to successfully achieve the result. After all, rehabilitation does not end in the hospital or in the department, recovery continues until the patient is satisfied with his functional state.

For the main group, evidence-based methods were used 2-3 times a day, from 30 minutes to 1 hour:

Positioning is carried out every 1.5 – 2 hours, putting the limbs in the correct position for the body. It helped to reduce any muscle pain, discomfort, and stiffness due to the stroke. Prevention of pressure ulcers and pathological positions.

Mobility in bed and within the ward. Physical therapists conducted training sessions for a safe change of body position.

Functional training – allowed patients to perform tasks in real-time, in a real-life situation (getting up from a chair, walking, and climbing stairs).

Balance and gait training. The physical therapist used various training methods that polished the ability to maintain body balance and improve coordination of movement. Gait training included activities that helped the person to learn and improve the stereotype of walking.

The occupational therapist selected various types of aids: a 4-support stick, walker, and orthosis for the upper or lower limb, for comfortable and safe movement. Training of indepen-

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dence skills in everyday activities and conducting classes with the cognitive state of the patient.

CIMT therapy, restricted-induced movement therapy. By limiting the movement of the healthy arm, the patient does not help the affected upper limb. It requires maximal use of the affected arm or hand to perform everyday tasks to regain control of the upper limb.

As the goals are achieved, the needs of the patients change, and the physical and occupational therapist can apply new rehabilitation techniques to help achieve maximum functionality.

With the control group, the physical therapist and occupational therapist worked from 30 minutes to 1 hour, 1 – 2 times a day, using:

Positioning – used to prevent pressure ulcers, pneumonia, and incorrect body position;

Passive mechanotherapy to prevent contractures in the joints of the affected limbs;

Gradual verticalization, transferring patients to a sitting position, then standing;

Selection of auxiliary means for movement;

Orthotics for the upper limb, during the restoration of walking skills;

Occupational therapist conducted classes to restore self-care skills;

Passive or active exercises for gross and fine motor skills were used.

At the beginning of the study in the control and intervention groups, there were no significant differences in the test examinations and scales. The general characteristics of the control and intervention groups are presented in Table 1. Patients of both groups at admission had a low initial level of functional capacity and independence in everyday activities.

Comparative Pie Chart 1. shows the tests and scales of the treatment and control groups for 3 months of treatment and rehabilitation activities.

At the initial physical therapy examination, the main and control groups had the same rates – 4%. In the first week of intervention, the main group

Table 1. Comparative characteristics of the main and control groups, examination of patients in physical therapy

Tests and scales for Physical Therapy	Primary examination		1 week		2 week		3 week		4 week		2 month		3 month	
	M	C	M	C	M	C	M	C	M	C	M	C	M	C
Barthel index 100 points	20	20	25	20	30	25	40	30	50	35	55	35	60	40
Scale Rankin from 0 - 5 degree	4	4	4	4	4	4	3	4	3	4	3	3	3	3
Degree of pain	2	2	2	2	3	2	4	2	5	2	5	3	5	3
Ashworth scale from 0 – 5 degree	4	4	4	4	3	4	3	4	3	4	2	4	2	4
Index of mobility of Rivermead	3	3	3	3	4	3	5	4	6	4	7	4	8	5
The degree of hand recovery	1	1	1	1	1	1	2	1	2	1	3	2	4	2
The degree of recovery of the hand	1	1	1	1	1	1	2	1	3	2	3	2	4	2
Degree of leg recovery	3	3	3	3	3	3	4	3	4	3	5	3	5	3
The degree of recovery of the foot	2	2	2	2	2	2	3	2	4	3	5	3	5	3

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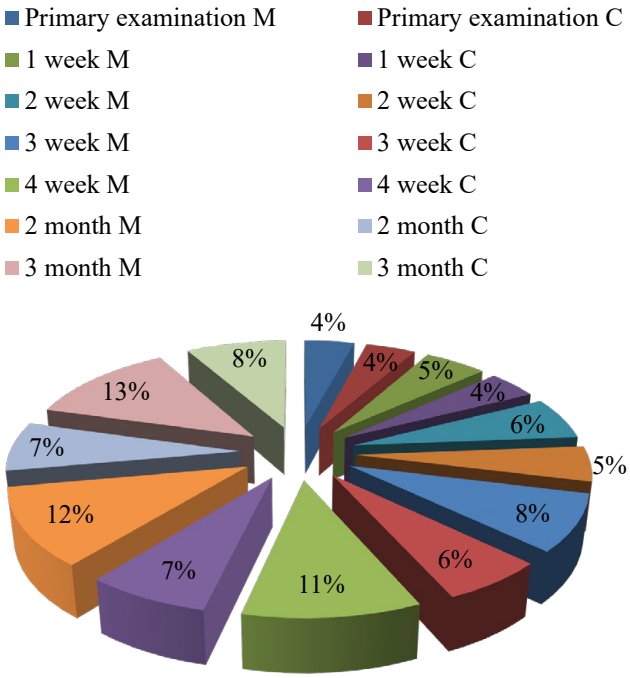
1. Pie chart showing the results of the intervention and control groups for 3 months



has a 1% increase in the results of medical and rehabilitation measures. In the second week, the control group showed a 1% decrease, while the main group showed a 6% decrease. In the third week, the main group – was 8%, and the control group – was 6%, 2% less. In the fourth week, the control group had a result of 7%, and the intervention group had a result of 11%, which is significantly higher. The next month, the functional dynamics of the main group was 12%, while the control group showed no significant changes. Having carried out the final examination, we got a result of 13% in the main group, and 8% in the control group. We assume that the control group did not have a sufficient number of physical therapy sessions and did not follow the recommendations of evidence-based medicine, which has an effective impact on the recovery of patients after stroke with spasticity in the early period.

After the treatment and rehabilitation measures, from 1 to 3 months in the main group, the final examination showed that the Barthel Index, Rankin Scale, Ashworth Scale, Degree of pain, and Degree of recovery of the arm, hand, leg, and foot showed positive dynamics. Patients improved balance, and coordination; discomfort, stiffness of spastic muscles, and pain syndrome decreased; active movements in the affected limbs appeared, which increases the level and quality of life of people after stroke.

And vice versa, the representatives of the control group on similar tests and scales, the final results are not high.

Discussion

At the beginning of treatment and rehabilitation measures, in the anamnesis and examinations conducted in the groups, there were no significant differences. Patients of the main and control groups had a low level of functional capacity, respectively, and a low level of motor activity.

Control examinations were conducted every week and, if possible, for 2, or 3 months.

At the final examination of physical therapy and occupational therapy, significant changes in the dynamics of the functional state of patients in the main group were determined. In the control group, the results were minor changes.

Statistica 8 software was used to collect statistical data. Table 2 shows the average indicators of patients after the stroke of the control and main groups, after treatment and rehabilitation measures in the Palliative Department.

Table 2. Comparative analysis of the main and control group examinations

Tests and scales for Physical Therapy	The main group	Control group
Barthel index	40 %	29 %
Rankine scale	3,42 %	3,71 %
Dagree of pain	3,71 %	2,28 %
Ashworth scale	3 %	4 %
Index of mobility of Rivermead	5,14 %	3,71 %
The degree of hand recovery	2 %	1,28 %
The degree of recovery of the hand	2,14 %	1,42 %
Degree of leg recovery	3,85 %	3 %
The degree of recovery of the foot	3,28 %	2,42 %

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According to the Barthel Index, the main group has a score of 40%, compared to a low score of 29% of the control group. The positive dynamics of the Rankin Scale increased in the main group for 3 weeks, and the indicator of the control group changed only for 2 months of treatment and rehabilitation measures, compared to the main group is significantly behind. The degree of pain according to the results of recent studies, the main group has a degree – 5, which significantly improves the functional state of the hand, and the control group – 3 degrees.

According to the Ashworth scale, the final result, in the main group, muscle spasticity decreased to 2 points, which can not be said about the control group, without significant changes – 4 points. According to Rivermead, the main group prevails in the difference by 1.43%.

The degree of hand recovery in the main group is 2% in the control group – 1.28%. The degree of recovery of the hand in the main group is 4 degrees (2.14%), and in the control group, there was no significant difference in degree 2 (1.42%), without significant changes.

The final result in the main group was the degree of recovery of leg 5 (3.85%), and in the control group – degree 3 (3%). Regarding the degree of recovery of the foot, the main group of 3.28% resulted in a degree 5, and the control group has a rate of 2.42% with a degree 3 final result of staying in the department.

Particularly noteworthy is a more pronounced increase in the final results in patients of the main group compared to the control group. Summarizing the above, the reason, in our opinion, lies in the insufficient number of classes and methods of physical therapy used to achieve the goals and maximize the recovery of lost motor functions of patients in the early period after stroke.

The results obtained indicate that the most effective training is carried out from 2 to 4 times a day, from 30 minutes to 1 hour, depending on the patient's condition. We have selected effective and scientifically based methods that contribute to the achievement of the set goals and maximize the recovery of patients after stroke with spasticity in the early period.

Conclusion

The article highlights the data confirming the effectiveness of evidence-based medicine in the physical therapy of patients after stroke with spasticity in the early period. This is provided that consistent guidelines are followed, physical therapy methods are used appropriately, and the number of sessions performed is measured over time. The use of evidence-based medicine can reduce the disability of patients after early spasticity stroke, gain independence and improve the patient's functional status.

Further work is needed to determine the proposed methods for the restoration of motor functions of patients after a stroke with muscle spasticity in the late period to speed up the rehabilitation process and reduce the negative consequences that occur in the late period. It often turns out that the methods used in the early period are ineffective in the late period. This leads to the adaptation of patients to the consequences and defects after stroke. Worsening the functional state of patients after stroke increases the duration of motor function recovery.

In the future, our goal is to review evidence-based medicine and late-phase examination methods for stroke patients with spasticity.

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Conflict of interest

There is no potential conflict of interest in any form.

Consent to publication

The authors took consent from patients and guardians related to this manuscript, all of whom gave their consent for publication.

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Застосування методів фізичної терапії для пацієнтів після інсульту зі спастичністю у ранньому періоді

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Анотація: гостре порушення мозкового кровообігу головна причина інвалідизації. Інсульт посідає 4 місце серед хвороб, що спричиняють смерть або інвалідність. Наслідками інсульту є неврологічні розлади, рухові (плегія, геміпарез, парез, спастичність м'язів), втрата чутливості; дисфункції тазових органів; втрата координації та рівноваги, високий ризик падінь, перепона до здатності самостійного пересування та здійснення повсякденної діяльності. Для набуття оптимальної незалежності пацієнтам після інсульту потрібна кваліфікована реабілітаційна допомога у складі мультидисциплінарної команди. Доказова медицина, лікування та реабілітацій-

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ні заходи, суттєво поліпшені у гострому та ранньому періоді для пацієнтів після інсульту. Але у пізньому періоді, на сьогоднішній день, більша половина пацієнтів, залишаються обмеженими у побутових діях та мають рухові порушення, це значно впливає на якість життя та незалежність. Опис мети. Обґрунтувати застосування методів доказової медицини у фізичній терапії для відновлення рухової функції пацієнтів після інсульту у ранньому періоді. Матеріали та методи. У Київській міській клінічній лікарні № 6, Відділення паліативної допомоги, з жовтня по грудень 2021 рік, у обстеженні та реабілітаційних заходах взяли участь 20 пацієнтів зі спастичністю, віком від 47 – 85 років, які перенесли ішемічний та геморагічний інсульт, строком від 3 тижнів до 1 місяця. У всіх пацієнтів та опікунів брали добровільну згоду на обстеження, лікування та реабілітаційні заходи. Для діагностичних методів: використовували комп'ютерну томографію, магнітно-резонансну томографію, за потреби здійснювались лабораторні методи обстеження. Для визначення функціональних порушень пацієнтів після інсульту з м'язовою спастичністю були використанні тести та шкали по фізичній терапії: шкала Ренкіна, Індекс мобільності Рівермід, Ступінь болю, Модифікована шкала Ашворд, Ступінь відновлення руки та кисті; Ступінь відновлення ноги та стопи. Результати. Проведений аналіз методів доказової медицини за темою проблематики, маємо підтвердження, що в ранньому періоді високі показники відновлення. Але у пізньому періоді після інсульту поява м'язової спастичності значно обмежує рухові можливості пацієнтів та ускладнює процес відновлення. Не до кінця розгорнуте питання на рахунок ефективних методів подолання спастичності у пізньому періоді, не акцентовано увагу на ускладненнях, що виникають у пізньому періоді. Поява м'язової спастичності значно обмежує рухові можливості пацієнтів, впливає на психоемоційний стан людини, з'являються больові відчуття, які заважають належно використовувати уражену кінцівку. М'язова спастичність гальмує та ускладнює відновлення рухової функції в пізньому періоді. Висновки. Проведене обстеження підтверджує високу ефективність запропонованих методів доказової медицини у зменшенні больового синдрому та збільшенні амплітуди рухів у плечовому, ліктьовому та променево-зап'ястковому суглобах у ранньому періоді пацієнтів після інсульту. На рахунок пізнього періоду, питання залишається незавершеним, і потребує подальшого розгляду. У Київській міській клінічній лікарні №6, Відділення Паліативної допомоги, використовували індивідуальний мультидисциплінарний підхід для пацієнтів після інсульту, що сприяло досягненню поставлених цілей. Можемо стверджувати, що методи доказової медицини для гострого та раннього періоду мають позитивний вплив на самостійність та незалежність пацієнтів, також покращує когнітивну функцію та рухову активність уражених кінцівок.

Ключові слова: діагностика лікування, компенсація, структурна функція, пошкодження головного мозку, реабілітація, фізична активність

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Five discoveries of Volodymyr Betz. Part one. Betz and the islands of entorhinal cortex

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Abstract: *in the series of publications, which this article opens, we consider five fundamental neuromorphological observations of our compatriot, the classic of world neuroscience, Volodymr Betz. For four of them, we demonstrate the status of discoveries for the first time, for the other one — the giant pyramidal neurons of the motor cortex — despite its widespread and long-standing recognition, we reveal the limitations of modern knowledge and ideas. Two of the mentioned observations — giant fusiform, or spindle-shaped neurons of the cingulate and insular cortex and islands of the entorhinal cortex — are currently known only to a narrow circle of specialists; to the others two, islands of Calleja and signs of the columnar cortex organization, we pay attention for the first time. In this, the initial part of the series, exposing modern apprehensions about the structure and functions of the entorhinal cortex, we demonstrate the weight of Betz's pioneering observation of extraordinary neuron clusters, which are nowadays known as entorhinal islands, and prove the fact of recognizing his historical priority in the description of these amazing brain structures.*

Key words: history of medicine, neurosciences, entorhinal cortex, grid cells, memory, episodic, time perception, alzheimer disease.

Introduction

Higher mental functions, including memory, consciousness and the inner world, the sense of time and error-free spatial navigation, are among the most attractive, if not obsessive, topics of human cognition. The last century revealed some details of the arrangement of the material apparatus, which assists the realization of these psyche functions. In the core of this machinery is a small part of the brain - the entorhinal cortex. The study of its structure and function is now quite intensive, probably not least due to the fact that it is also present in lower mammals and is therefore available for all modern tools of experimental neurophysiology. So, at the moment, it is difficult to imagine a neuroscientist who has not seen at least one work devoted to the entorhinal cortex during his professional career. This area of the brain became famous in 2014, because it was for the study of the neurons of the entorhinal cortex that the Nobel Prize was awarded that year. And also the entorhinal cortex is the debut scene of

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Alzheimer's disease.

It so happened that our compatriot, who, as is known, was well-informed and sympathetic to the history of his own people, made a large-scale addition to the study of entorhinal piece of cortex. Historiographic investigations have always been an important segment of the scientific process, since, in addition to issues of honor and respect (without which the development of science, unfortunately, is unthinkable), they reveal the very drama of knowledge in all its unsightly.

It is probably symbolic and appropriate that this material comes out precisely at this difficult time for Ukraine; a time not only and not so much of survival, but also, for the majority - of the second birth or even the metamorphosis of the Ukrainian people. It is at such moments that the examples of success are superimportant. And here is an example of world-class success is Volodymyr Betz.

In this work, we sought to fully reveal the depth and providential significance of his observations regarding the microstructure of the entorhinal cortex, observations, that are recognized, as it turned out, in the neurobiological environment. And for the first time to demonstrate his own preparations of this brain area, which became the basis of his published morphological descriptions and generalizations.

Aim

To demonstrate the Betz priority of in the discovery of entorhinal islands, to determine the importance and relevance of this discovery.

Materials and methods

To determine the relevance and degree of study of entorhinal islands, we used the method of searching and summarizing scientific information. Scientific articles in specialized periodicals, available in the PubMed database, in network electronic catalogs and in the funds of the National Scientific Medical Library of Ukraine, as well as thematic scientific publications in book format, available on the Internet or on market Internet services among the assortment of printed publications, were selected as the subject of the search. When selecting the material, the principles of actuality, reliability, objectivity, informational unity and relevance were taken into account. We used the historical method (*including the chronological approach*) to find out the carrier of priority in the discovery of the entorhinal islands.

From the point of view of the methodology of the scientific process, when working on the material of the article, we used routine methods — analysis, synthesis, abstraction, analogy, comparison, as well as a systematic approach.

Also, using the method of subject morphological search based on given cytoarchitectonic criteria among the collection of Betz neurohistological preparations, which is kept at the Department of Descriptive and Clinical Anatomy of the Bogomolets National Medical University, we found the temporal lobe pole preparations, where entorhinal islands were identified. Photofixation and scaling of histological images of the relevant areas was performed in the Neuropathomorphology Department electron microscopy laboratory of the State Institution «Romodanov Neurosurgery Institute (National Academy of Medical Sciences of Ukraine)» on an Axiophot optical microscope (Opton, Germany), using a Canon 600 digital camera (Canon Inc., Taiwan), computer analyzer CAI-01ABH (Selmi, Ukraine), software «Kappa opto-electronics GmbH» (Germany) and a object-micrometer. Delicate optimization of images in order to achieve equivalence of their color characteristics carried out with MS Power Point tools on a personal computer.

1.1. Brain Navigation System

The Nobel Prize of 2014 confirmed significance of the mammals' navigation system characteristics. At this time, a significant number of brain cells have been described, the activity of which correlates with the realization of this function certain aspects (*Tab. 1*). Perhaps it currently includes neurons whose unique status in providing certain nuance of navigation will be disproved over time. However, it is important that huge proportion of these cells was detected exactly in the entorhinal cortex. So, let's dwell on the peculiarities of this small area of the brain arrangement.

1.2. Entorhinal Cortex

The term "*entorhinal cortex*" was suggested by Korbinian Brodmann (*R. Insausti & Amaral, 2012*), probably, because this region (*Brodman's areas 28 and 34*) in a human is located more medially, more interiorly from the rhinal sulcus and perirhinal cortex (*fig. 1*). In primates it is local-

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Table 1. Currently Known Neurons of the Mammals' Brain Navigation System

Type of the cells	Localization in the brain	The organism for which the presence of these cells has been established	Main references
grid cells	medial entorhinal cortex (MEC), particularly its II layer, and the parasubiculum	rodents, probably human	*Hafting, Fyhn, Molden, M.B. Moser and E.I. Moser, 2005; Fyhn, Hafting, Treves, M.B. Moser and E.I. Moser, 2007; Yartsev, Witter and Ulanovsky, 2011; Killian, Jutras and Buffalo, 2012; reviewed by: E.I. Moser, M.B. Moser and McNaughton, 2017, and Tukker et al., 2022*
place cell	CA1 *(Cornu Ammonis, field 1)* and CA3 field of the hippocampus	rodents	*O'Keefe and Dostrovsky, 1971; reviewed by: E.I. Moser et al., 2017*
head direction cells *(including pure azimuth cells and pure pitch cells in a bat)*	MEC, presubiculum, postsubiculum, anterodorsal thalamic nucleus, lateral mammillary nucleus, dorsal tegmental nucleus	rodents, bats, primates	*Taube, Muller and Ranck Jr, 1990 a, b; Mizumori and Williams, 1993; L.L. Chen, Lin, Green, Barnes and McNaughton, 1994; Taube, 1995; Stackman and Taube, 1998; Sargolini et al., 2006; Giocomo et al., 2014; Finkelstein et al., 2015; Shinder and Taube, 2019; Angelaki and Laurens, 2020; reviewed by Tukker et al., 2022*
angular head velocity cells	list of the brain locations of these cells is less numerous than that for ordinary head direction cells	rodents	*reviewed by Taube, 2009*
conjunctive cells	MEC	rats	*reviewed by Tukker et al., 2022*
boundary cells, border cells	presubiculum, parasubiculum, the II, III and V layers of the entorhinal cortex	rodents	*Savelli, Yoganarasimha and Knierim, 2008; Solstad, Boccara, Kropff, M.B. Moser and E.I. Moser, 2008; Tang et al., 2014; Tang et al., 2015; reviewed by Tukker et al., 2022*
path cells	entorhinal cortex	human	*Jacobs, Kahana, Ekstrom, Mollison and Fried, 2010*
cue cells	MEC	mice	*Kinkhabwala, Gu, Aronov and Tank, 2020*
object-vector cells	MEC	mice	*Høydal, Skytøen, Andersson, M.B. Moser and E.I. Moser, 2019; reviewed by Tukker et al., 2022*

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speed cells, as well as the angular and linear speed cells	*speed cells* — MEC, field CA1 and CA3 of the hippocampus; at least some of them belong to the place cells and the grid cells; *angular and linear speed cells* — MEC, presubiculum, parasubiculum	rodents	*C. Sun et al., 2015; Kropff, Carmichael, M.B. Moser and E.I. Moser, 2015, and Spalla, Treves and Boccara, 2022; reviewed by Tukker et al., 2022*
time cells	CA1 and CA3 fields of the hippocampus, probably, MEC *(Salz et al., 2016)* and lateral entorhinal cortex (LEC; *Tsao et al., 2018; Rolls and Mills, 2019)*	rodents	*Salz et al., 2016; Tsao et al., 2018; reviewed by Rolls and Mills, 2019*
spatial view cells	in primates — fields CA1 and CA3 of the hippocampus, parahippocampal gyrus, presubiculum	primates, human, probably rodents	*Robertson, Rolls and Georges-François, 1998; reviewed by Rolls, 2021*
egocentric bearing cells	medial temporal cortex, particularly parahippocampal cortex	human and other mammals	*Kunz et al., 2021*
allocentric bearing to a landmark neurons	in a macaque -— parietal cortex *(Brodman's area 7a)* and posterior cingulate cortex	primates, probably human, rodents	*reviewed by Rolls, 2021*
movement cells	posterior parietal cortex	rodents	*Rochefort, Lefort and Rondi-Reig, 2013, based on Whitlock et al., 2012*
whole body motion cells	hippocampus, subiculum	primates, possibly human, rodents	*reviewed by Rolls, 2021*
goal-direction cells, goal-distance cells	CA1 field of hippocampus	bat	*Sarel, Finkelstein, Las and Ulanovsky, 2017*
3D border cells, 3D head-direction cells, 3D grid cells	presubiculum *(3D head-direction cells),* MEC *(3D border cells, 3D head-direction cells, 3D grid cells)*	bat	*Finkelstein et al., 2015; Ginosar et al., 2021*
navigation cells of subiculum: axis-tuned cells, barrier-related cells, boundary vector cells, multiplexed place cells	subiculum	rat	*reviewed by N. Matsumoto, Kitanishi and Mizuseki, 2019*
social place cell	field CA1 of hippocampus	rat, bat	*Danjo, Toyoizumi and Fujisawa, 2018; Omer, Maimon, Las and Ulanovsky, 2018*

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ized on the ventromedial surface of the temporal lobe anterior part, bordering with periamygdaloid cortex, presubiculum and parasubiculum, perirhinal cortex and the rest of the parahippocampal gyrus cortex (*Kobro-Flatmoen & Witter, 2019*). It contains 6 layers, but refers to the transitional cortex — periarchicortex (*Stephan, 1975*). The total number of neurons of the entorhinal area in a human hemisphere makes up 7–8•10^6 (*R. Insausti & Amaral, 2012; Naumann et al., 2016*).

Two main parts of the entorhinal cortex are distinguished: in rodents — medial (*medial entorhinal cortex, MEC*) and lateral (*lateral entorhinal cortex, LEC*), in a human — posteromedial (*p*MEC) and anterolateral (a*LEC*) (*R. Insausti & Amaral, 2012; Kobro-Flatmoen & Witter, 2019*). Traditionally, the MEC and pMEC, LEC and aLEC are considered homologous (*Navarro Schroder, Haak, Zaragoza Jimenez, Beckmann & Doeller, 2015; Ohara et al., 2021, and many other works*).

The II layer of the entorhinal cortex is the most interesting from many points of view. Within the MEC borders it contains two types of neurons — stellate and pyramidal (*reviewed by Witter, Doan, Jacobsen, Nilssen & Ohara, 2017; Tukker et al., 2022*). The ***pyramidal ones*** are predominantly excitatory, expressing calbindin or wolframin (*wolfram syndome protein 1*); they represent 30–40 % of all MEC type II neurons, preferentially projected on the CA1-neurons, demonstrate a clear dependence of activity on a θ-rhythm, and receive cholinergic inputs (*reviewed by Naumann, Preston-Ferrer, Brecht, & Burgalossi, 2018*). The ***stellate neurons*** are the excitatory ones, express Reelin, represent up to 50–60 % of all MEC layer II neurons, and being a basic source of the perforant fibers which make synapses with the granule cells of the dentate gyrus (*reviewed by Naumann et al., 2018*). The LEC layer II also contains two basic neuron phenotypes (*Witter, Doan, et al., 2017*) — *Reelin*-positive (*analogues of the MEC layer II stellate neurons*) and calbindin-positive ones (*analogues of the MEC layer II pyramidal neurons*).

The entorhinal cortex afferents come from the perirhinal, piriform, cingulate, insular and orbitofrontal cortex, from other regions of parahippocampal cortex and from the superior temporal gyrus cortex (*Van Hoesen, Pandya & Butters, 1972; R. Insausti, Amaral & Cowan, 1987; R. Insausti & Amaral, 2008, 2012; Witter & Amaral, 2021*), as well as the medial part of the septal complex (*Jacob, Poucet, Liberge, Save & Sargolini, 2014*) and, probably, from the amygdaloid complex, basal forebrain, thalamus, **supramammillary nucleus**, ventral tegmental area, raphe nuclei and from the locus coeruleus (*R. Insausti & Amaral, 2012*).

The main efferents of the entorhinal cortex make a perforant path, which mainly consists of the layer II and III neuron axons (*Xu, Y. Sun, Holmes & López, 2016; Witter, Kleven & Kobro Flatmoen, 2017*). At that, the *Reelin*-positive stellate glutamatergic neurons of layer II project into the dentate gyrus, hippocampal field CA3 and CA2 (*Naumann et al., 2018; Matsumoto et al., 2019; Nilssen, Doan, Nigro, Ohara & Witter, 2019*), while the calbindin-positive pyramidal glutamatergic neurons of layer II project into the field CA1 and subiculum (*R. Insausti & Amaral, 2012; Nilssen et al., 2019*), producing the so-called temporo-ammonic pathway (*Witter, Kleven et al., 2017*). It was for the glutamatergic synapses of the perforant path axons with the dentate gyrus granule cell dendrites of the rabbit, that the long-term potentiation was described (*Lømo, 1966; Bliss &* Lømo, 1973) — which is one of the most probable electro-physiological correlates of memory and learning (*Abraham, Jones & Glanzman, 2019; Bliss & Collingridge, 2019; Joshi, Patel, Rehan & Kuppa, 2019; Dringenberg, 2020*).

It is obvious that the connections of the entorhinal cortex are wider than those listed (*Ohara et al., 2019, 2021; Guthman et al., 2020; Hu, C.H. Chen, S.Q. Chen & Ding, 2020; Meier, Q. Wang, Ji Ganachaud & Burkhalter, 2021; Huang, Rolls, Hsu, Feng & Lin, 2021; Raithel & Gottfried, 2021; Syversen et al., 2021*) and cover distal cortex areas, e.g., primary somatosensory cortex (*C. Wang et al., 2020*) and *area prostriata* (*Hu et al., 2020*).

A, B і **E** (*Kobro-Flatmoen et al., 2021, fig. 1 A, B, C*) — schematic image of the human entorhinal cortex localization in the left brain hemisphere (**A**), and the corresponding temporal lobe 3D-fragment with the designation of this region main formations on a photomicrograph of a transverse histological section stained with thionin (**E**), the original of which was taken by the authors from fig. 24.8 of R. Insausti and Amaral (*2012*) with minimal changes.

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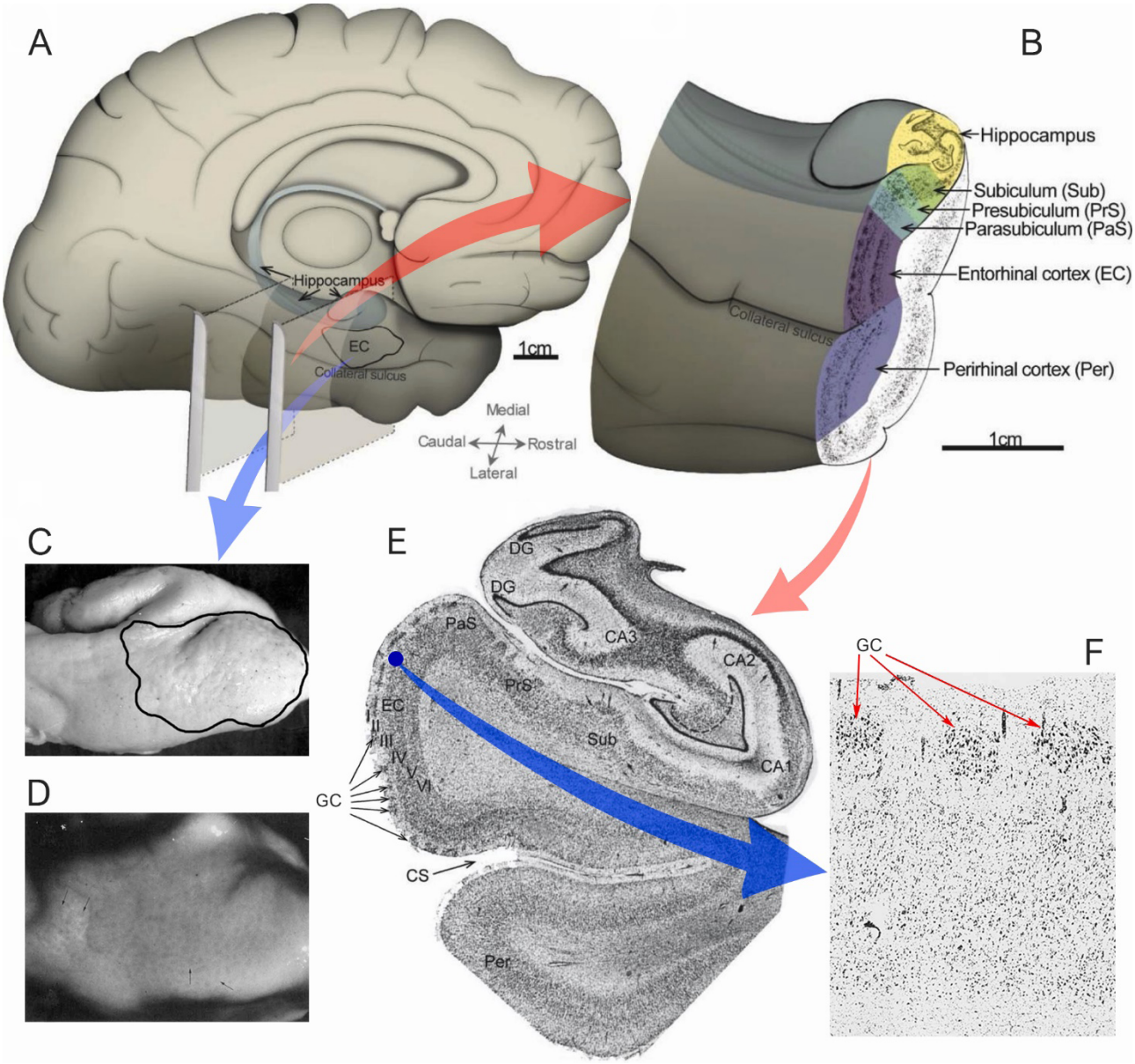

Fig. 1. Human entorhinal cortex and its main morphological peculiarities according to various authors. Scheme-collage.

C (*Simic et al., 2005, fig. 1 C*) — entorhinal tuberosity; unfixed fragment of an adult left temporal lobe (*woman, 59 years old, cause of death — liver cirrhosis*); the delineation of the entorhinal area with a black line was carried out by the authors on the basis of the «*verrucae areae entorhinalis*» localization (*the conventional designations in the original drawing were removed by us — V.M.*).

D (*Hevner & Wong-Riley, 1992, fig. 3 A*) — "*leopard*" appearance of the unstained and uncuted human entorhinal cortex surface; dark spots correspond to the entorhinal islands visible through the surface of the cortex (*notations in the original drawing were removed by us — V.M.*); the reticular complex of white strips of the brain substance between the dark spots was called the *substantia reticularis alba of Arnold*.

F (*Beall & Lewis, 1992; fig. 4 A*) — Nissl-stained transverse histological section through the human entorhinal cortex (*male, 48 years old, cause of death — complications of atherosclerosis*); scale bar is given in the original.

Symbols not deciphered in the figure: **GC** — *glomerula corticalia*; layers of the entorhinal cortex are marked with Roman numerals in Figure 1 E.

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1.3. Clusters of Entorhinal Cortex

The most interesting characteristic of the entorhinal cortex is its modular composition, which is manifested through clusters of the layer II neurons, or by clusterization of layer II neuronal population. Two types of clusters have been described: the MEC/pMEC contains the so-called *patches* (*cell patches*), with the small pyramidal neurons, while the LEC/aLEC contains the so-called *islands*, *nests* or *glomeruli* (*fig. 1 E, F*), filled basically with the stellate neurons. This islands in humans have a macroscopic counterpart — *tubercles* (*eminences, elevations*), also known as *bumps*, or *warts* (*verrucae*) of the entorhinal cortex surface (*fig. 1 C; see further*).

1.3.1. Islands

The islands of the LEC/aLEC layer II, or **entorhinal islands** are detected already by ordinary neurohistological staining (*Braak, 1972; fig. 1 E, F*). Analogous structures are visualized when identifying the expression of various enzymes, proteins and peptides (*Solodkin & van Hoesen, 1996; Mikkonen, Soininen & Pitkänen, 1997*). Some authors state, that the majority of the human entorhinal islands contain stellate cells, surrounded with a parvalbumine-positive neuropil (*Beall & Lewis, 1992; Hevner & Wong-Riley, 1992*). The diameter of an entorhinal island of the human aLEC is ~0.5–1 mm, and the mean distance between them is 369 ± 162 μm (*Solodkin & Van Hoesen, 1996*). An average number of neurons in one island of the left and right human hemisphere is, respectively, ~$4.7 \cdot 10^5$ and ~$4.1 \cdot 10^5$ (*Simic et al., 2005*). The entorhinal cortex of the human left hemisphere contains ~121 macroscopic islands analogues — the entorhinal tubercles, the right one — ~111, which overall makes — ~232 (*Simic et al., 2005*).

1.3.2. Patches

The MEC/pMEC layer II contains immunohistochemically detectable clusters of pyramidal neurons, which are named **entorhinal patches**. Detection of these patches using ordinary light-optic examination methods is almost impossible for rodents and dogs (*Woźnicka, Malinowska & Kosmal, 2006*), though, quite real for a human and primates (*Beall & Lewis, 1992, fig. 5 A, 6 A*). Beside pyramidal neurons, the patches contain other neurons types (*Ray et al., 2014; Naumann et al., 2016*); in particular, the human patches contain also stellate neurons (*Naumann et al., 2016*). The total number and average diameter of an entorhinal patches in one rat brain hemisphere are, respectively, 69 ± 17 units and 145 ± 41 μm, in a one human hemisphere — 115 ± 16 units and 532 ± 197 μm. The average number of calbindin-positive neurons in an entorhinal patch of a rat is 111 ± 42 cells, that of a human — 837 ± 84 cells (*reviewed by Naumann et al., 2016*). On the tangential section, the patches make hexagonal, rectangular and geometrically irregular structures, which in a human are divided in such proportion: ~45 %, ~35 % and ~20 %, respectively, or, by other calculations, — ~50 %, ~30 % and ~20 % (*reviewed by Naumann et al., 2016*).

1.3.3. Tangential Localization of Islands and Patches

Entorhinal islands and patches do not overlap in space (*Naumann et al., 2016, fig. 8 A*). Sporadic observations in human and other higher mammals (*Ramon y Cajal, 1988, work of 1901–1902, p. 301, fig. 15; Beall & Lewis, 1992, fig. 5 A, 6 A; Suzuki & Porteros, 2002, fig. 6 B, fig. 8*) evidence about opportunity of both clusters identification within one optical field, and besides, when the human islands and patches take the same tangential position, in some places it produces an impression of various depth of their occurrence (*Naumann et al., 2016; fig. 8 A*). Such assumption is confirmed by the earlier data, received for the entorhinal cortex of the human and apes (*Beall & Lewis, 1992, fig. 5 A, 6 A; Suzuki & Porteros, 2002, fig. 6 B, fig. 8*).

1.3.4. Patches and Islands in Other Areas of the Cortex

It is well known, that the tangential clusters of neurons, similar with the entorhinal patches, are characteristic for other various cortex regions, the list of which is given in many works (*see Horton & Adams, 2005; Rockland, 2021; Tukker et al., 2022*). What is less thoroughly studied, is the cortical prevalence of clasterization, characterizing layer II of the LEC/aLEC. At present, such type of clasterization in mammals has been also described for the uncal cortex, subiculum, presubiculum and parasubiculum (*Hevner & Wong-Riley, 1992; Heinsen et al., 1994; von Economo, 2009,*

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p. 150–169; R. Insausti & Amaral, 2012; Ding, 2013; R. Insausti, Muñoz-López, A.M. Insausti & Artacho-Pérula, 2017), as well as for many other areas of the cerebral cortex of those mammalian species that are not used in experimental medicine (*Hof & van der Gucht, 2009; Butti & Hof, 2010; Butti et al., 2014; Raghanti et al., 2015; Raghanti et al., 2019*) — hump-backed whale (*Megaptera novaeangliae*), fin whale (*Balaenoptera physalus*), minke whale (*Balaenoptera acutorostrata*), beluga whale (*Delphinapterus leucas*), bottlenose dolphin (*Tursiops truncatus*), Florida manatee (*Trichechus manatus latirostris*), Atlantic walrus (*Odobenus rosmarus rosmarus*), river hippopotamus (*Hippopotamus amphibius*), pigmy hippopotamus (*Hexaprotodon liberiensis*), Western bongo (*Tragelaphus eurycerus*), white-tailed deer (*Odocoileus virginianus*), domesticated pig (*Sus scrofa domesticus*), and a horse (*Equus ferus caballus*).

1.4. Entorhinal Patches and Grid Cells

The most thoroughly studied functional type of the MEC neurons are the grid cells (*Hafting et al., 2005*), for the discovery of which E.I. Moser and M.B. Moser were awarded the Nobel Prize in physiology and medicine in 2014. A peculiar trait of these neurons is their maximum firing rate when the animals is moving through the special plane points — nodes of the grid formed by the apices of imaginary regular triangles assembled into hexagonal figures. In this way, each grid cell possesses its own map of the fiducial locomotion plane points (*Hafting et al., 2005*), which is quite flexible (*Fyhn et al., 2007; Krupic, Bauza, Burton, Barry & O'Keefe, 2015; Ismakov, Barak, Jeffery, Derdikman, 2017; Krupic, Bauza, Burton, O'Keefe, 2018*), and that which may deform due to the memorized goal representation (*Boccara, Nardin, Stella, O'Neill & Csicsvari, 2019*), considering the target-related reward information (*W. Wang & W. Wang, 2021*) and being represented in various scales (*reviewed by: E.I. Moser et al., 2017*). The prevalent position of the grid cells is in the MEC layer II (*reviewed by: Tukker et al., 2022*). Nowadays, it is possible to state, though with some precautions, about the existence of similar mechanism metrification of neighbourhood in human (*Doeller, Barry, & Burgess, 2010; Bellmund, Deuker, Navarro Schröder, & Doeller, 2016; Horner, Bisby, Zotow, Bush, & Burgess, 2016; Constantinescu, O'Reilly, & Behrens, 2016; Nau, Navarro Schröder, Bellmund, & Doeller, 2018; Julian, Keinath, Frazzetta, & Epstein, 2018; D. Chen et al., 2018; Maidenbaum, Miller, Stein & Jacobs, 2018; Staudigl et al., 2018; He & Brown, 2019; Kim & Maguire, 2019; Bellmund et al., 2020; W. Wang & W. Wang, 2021*).

The data about the morphological and immunohistochemical phenotype of the grid cells are sparse. It is admitted, that the grid cells account for 18 % of the MEC neurons, border cells — 9 %, head direction cells — 1 %, and the non-classified space-dependent cells — 68 % (*Diehl, Hon, Leutgeb & Leutgeb, 2017*). According to Miao, Cao, M.B. Moser and E.I. Moser (*2017*), among all identified grid cells in the mice, 94 % were identified in the MEC, and slight portion — in presubiculum. At that, 33 % of the grid cells were in layer II of the MEC (*~9 % of the layer neurons*), 31 % — in layer III (*~6 % of the layer neurons*), and 36 % — between the layers (*Miao et al., 2017*). Overall, the proportion of the grid cells among all MEC neurons makes up 10–20 % (*Naumann et al., 2018*), that one among the pyramidal neurons — 19% (*Tang et al., 2014*), and among the stellate neurons — about 3–25 % (*Tang et al., 2014; Rowland et al., 2018*).

Currently, the mechanism of formation of the typical spatial-preferential grid cell activity is unidentified (*Witter, Doan, et al., 2017; Naumann et al., 2018; Tukker et al., 2022*), the evidence about contribution of the stellate and pyramidal neurons of the MEC layer II in the formation of the grid cell specific activity is fragmental (*Naumann et al., 2018*), and the mechanisms of interdependence of the various navigation system cell are shrouded in darkness (*E.I. Moser et al., 2017; Rowland et al., 2018; Angelaki & Laurens, 2020; Tukker et al., 2022*), and the role of visual and other types of information for the peculiar grid cell activity is the subject of hypotheses (*Connor & Knierim, 2017; Campbell & Giocomo, 2018; Jacob, Capitano, Poucet, Save, & Sargolini, 2019; Jayakumar et al., 2019; Moon, Gauthier, Park, Faivre & Blanke, 2022; Waaga et al., 2022*). Although, there exists a considerable number of models, aimed to answer this questions (*Finkel-*

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stein et al., 2015; Igarashi, 2016; E.I. Moser et al., 2017; Naumann et al., 2018; Widloski, Marder & Fiete, 2018; Kang & Balasubramanian, 2019; Mosheiff & Burak, 2019; Park, Jang, Kim & Kwag, 2019; Rodríguez-Domínguez & Caplan, 2019; Spalla, Dubreuil, Rosay, Monasson, & Treves, 2019; Agmon & Burak, 2020; D'Albis & Kempter, 2020; Ekstrom, Harootonian & Huffman, 2020; Vinepinsky, Perchik, & Segev, 2020; Waniek, 2020; Krishna et al., 2021; Rueckemann, Sosa, Giocomo & Buffalo, 2021; T. Wang, Yang, Z. Wang, Zhang & W. Wang, 2021; Tukker et al., 2022 and many others). This situation is caused by impossibility of comparing various phenotype brain cells characteristics: functional, morphological and immunohistochemical ones (*Hardcastle, Ganguli & Giocomo, 2017; Naumann et al., 2018*). Modern studies gradually help us cope with this methodological difficulty; so, the most probable is the toroidal functional network topology of the MEC cells population (*Gardner et al., 2022*).

Another key issue of the brain navigation system physiology is the correlation of the tangential, often hexagonal distribution of the entorhinal cortex layer II modular structures with the ability to hexagonally mapping of the planar neighbourhood by the located here grid cells (*Naumann et al., 2018*). The search for an answer to this question has not yet been successful yet (*Igarashi, 2016; Gu et al., 2018; Naumann et al., 2018*). It is important to note, that the tangentially clustered in patches pyramidal neurons of the MEC layer II may play a significant role in the grid cell activity formation (*Naumann et al., 2016*). Simultaneously, tangential clustering of the MEC grid cells, if present, is different (*Naumann et al., 2018; Gu et al., 2018; Obenhaus et al., 2022*).

1.5. Functions of the LEC/aLEC

The entorhinal islands function remains unidentified.

The paraentorhinal projections of calbindin-positive neurons of the LEC layer II, and, probably, LEC itself, are wider than those of the analogous cells of the MEC layer II and MEC itself (*Ohara et al., 2019*). The LEC receives significant convergent inputs from the perirhinal cortex and postrhinal cortex to all main neurons of the II layer, which allows this part of the brain to take into account continuous changes in the behavioral environment (*Doan, Lagartos-Donate, Nilssen, Ohara & Witter, 2019*), e.g., changes in the elemental composition of the environment (*Tsao, M.B. Moser & E.I. Moser, 2013*). Regarding this, it is important that the LEC is directly associated with the olfactory bulb and piriform cortex (*Igarashi et al., 2012; Liu, 2020*), the neuronal networks of the LEC layer II are involved in the processing of olfactory information (*Bitzenhofer, Westeinde, Zhang & Isaacson, 2022*), and the LEC altogether participates in odor-context associations (*Persson et al., 2022*). Probably, due to this, certain LEC neurons are preferentially activated in the case of animal close location to a new, limited in space, object (*Deshmukh & Knierim, 2011; Tsao, M.B. Moser & E.I. Moser, 2013*). Oscillations with a frequency of 20–40 Hz, which are the electrophysiological equivalent of the functional connection of the LEC and hippocampal field CA1 during the engramming of certain specific information (*Igarashi, Lu, Colgin, Moser & Moser, 2014; Igarashi, 2015*), can be generated precisely with the participation of the olfactory bulb and piriform cortex (*reviewed Igarashi, 2016*). Finally, modulation or mediation by the LEC of cortical γ-oscillations associated with the θ-rhythm is an important condition for memorizing or reproducing spatially-connoted information (*Luo et al., 2022*).

Nilssen et al. (*2018*), and Nilssen et al. (*2019*) suggest that the LEC may contain similar to the MEC neuronal network and cells with similar to the grid cells spatial-preference activity, which provide metrification of the LEC-specific object-dependent information about environment. Witter, Doan et al. (2017) consider that the LEC provides connection of the hippocampus with the anterior parts of the cortex, mediating access to the information about movement contextual changes, including information about transformation of the environment.

The LEC/aLEC is a key node of the episodic (*Bellmund, Polti, & Doeller, 2020, Vandrey et al., 2020; Takehara-Nishiuchi, 2022*) and social (*Dang et al., 2022; Lopez-Rojas, de Solis, Leroy, Kandel, & Siegelbaum, 2022*) memory, provides fast information reproduction under similar context (*Pilkiw, Jarovi & Takehara-Nishiuchi, 2022*),

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participates in detecting familiarity for events (*Mahnke, Atucha, Pina-Fernàndez, Kitsukawa & Sauvage, 2021*), in time association of the stimuli which are applied in a certain sequence (*Yu, Yu, Choi & Takehara-Nishiuchi, 2021*), in engramming and reproduction of the temporal information, summarized in the LEC according to the acquired behavioral experience (*Tsao et al., 2018; Bellmund, Deuker & Doeller, 2019; Bellmund, Polti, & Doeller, 2020*), and finaly, in producing the space-time map of the experienced events (*Deuker, Bellmund, Navarro Schröder & Doeller, 2016; Bellmund et al., 2019; Montchal, Reagh & Yassa, 2019; Bellmund, Polti, & Doeller, 2020*). The LEC may also play a role in the mechanisms of fear memory (*East Jr., Brady & Quinn, 2021*) and neuropathic pain syndrome (*Guida et al., 2022*), in the formation of spatial correlates of feeding behavior (*Azevedo et al., 2019*) and, together with the anterior cingulate cortex — participate in the motivation sphere function and in the network reinforcement correlates formation (*Ionov et al., 2021*).

With all this, it turns out that synapses of LEC axons with newly formed dentate gyrus granule cells acquire the ability to form long-term potentiation not immediately, but after several months (*Vyleta & Snyder, 2021*) and, most interestingly, LEC has a significant, but still poorly studied effect on the motor system (*Ionov, Pushinskaya, Gorev & Frenkel, 2020; Ionov, Pushinskaya, Gorev, Frenkel & Severtsev, 2021*).

1.6. Functions of the Entorhinal Cortex in General

1.6.1. Space

The representation of "spatiality" in the sphere of consciousness is provided with the participation of a number of brain areas — the orbitofrontal cortex, medial prefrontal cortex, dorsolateral prefrontal cortex, cortex of the inferior parietal lobule, posterior cingulate cortex, medial temporal cortex, entorhinal cortex, hippocampus, anterior thalamus, claustrum, and cerebellum (*Rochefort et al., 2013; Bareš et al., 2019; Cona & Scarpazza, 2018; Schafer & Schiller, 2018; O'Mara & Aggleton, 2019*).

To date, a number of indirect evidences have been obtained for the participation of the hexagonal metrification system (*Doeller et al., 2010; Bellmund et al., 2016; Horner et al., 2016; D. Chen et al., 2018; Maidenbaum et al., 2018; Staudigl et al., 2018; He & Brown, 2019; Bellmund et al., 2020; W. Wang & W. Wang, 2021*) and the entorhinal cortex (*D. Chen et al., 2018; Maidenbaum et al., 2018; Moon et al., 2022*) in the internal, subjective representation of a person's neighbourhood, at that taking into account the target related reward (*W. Wang & W. Wang, 2021*), as well as in subjective conceptual (*Constantinescu et al., 2016*) and social metrification (*Kaplan & Friston, 2019*). However, network mechanisms of the locomotor navigational entorhinal-hippocampal system engagement into these higher psychic functions are still staying unexplained (*Ekstrom et al., 2020; Raithel & Gottfried, 2021*).

The role of each of the two entorhinal cortex part in the space metrification by the subject is ambiguous. According to the common opinion (*reviewed by C. Wang et al., 2018*), LEC/aLEC provides into the hippocampal networks information about the arrangement of the environment in the egocentric coordinates of the observer (*i.e. idiothetic information*), while, the MEC/pMEC provides information about the location of the observer in space in allocentric coordinates built on the relationships between the elements of the environment (*i.e. allothetic information*), as well as about the current motor activity and its target. Nevertheless, the role of the LEC even in the context of this scheme seems broader (*Kuruvilla, Wilson & Ainge, 2020*), both parts of the entorhinal cortex are involved in the processing of allocentric information (*Shine, Valdés-Herrera, Tempelmann & Wolbers, 2019*), and the MEK, in turn, plays a key role in both types of navigational metrification (*Save & Sargolini, 2017*). In general, some authors (*Connor & Knierim, 2017*) tend to consider MEC as the basis of exactly idiothetic navigational metrification (*see also Campbell & Giocomo, 2018*), and LEK — as allothetic (*see Vandrey, Duncan & Ainge, 2021*). Somewhat similar conclusions can be drawn based on the data of X. Chen, Vieweg and Wolbers (*2019*).

In the context of another paradigm, information about the object (*what?*) is processed by the LEC, information about the place (*where?*) — by the MEK (*Connor & Knierim, 2017; Nilssen et al., 2019; Fernández-Ruiz et al., 2021*), though

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the information processing networks for these two features (*ventral and dorsal stream, respectively*) appeared to be less segregated than it had been assumed before (*Huang et al., 2021*). Naumann et al. (*2018*) state that the aLEC networks are preferentially activated in response to the demonstration of object images, while the pMEC networks — to the images of rooms and locations. According to other data (*Peng et al., 2018*), the human aLEC participates in processing of the object-associated information, pMEC — visually-associated information. There is also evidence that accurate information about the observer's position in space is formed due to LEC on the base of the data about location of the environment objects (*Vandrey et al., 2021*). And at the same time, other data indicate that navigation based on the close to the animal positional determinants does not require function of MEC and LEC at all, and navigation based on distant positional determinants is carried out with the participation of MEC (*Poitreau et al., 2021*).

1.6.2. Time

Field CA1 of the hippocampus of the mammals, and, probably, the MEC (*Salz et al., 2016*) contains neurons, whose "rosary" of individual activity bursts can represent time segments of different scales — seconds, minutes, and days (*Eichenbaum, 2017; Mau et al., 2018*). Their activity significantly depends on the MEC function (*Eichenbaum, 2017*), and the MEC, in a whole, plays significant role in memorizing (*Vo et al., 2021*) and exact reproduction (*Dias, Ferreira & Remondes, 2021*) of temporal intervals.

In its turn, temporal information about engrammed behavioral episodes can also be extracted from the LEC neurons network activity, at that in various scale — from seconds to hours (Tsao et al., 2018), possibly, even days (Bellmund, Deuker & Doeller, 2019). The LEC neurons, function of which is considerable for the engramming of temporal information, possess the property to slowly reduce activity after a sharp or gradual its increase (*ramp-like activity; Tsao et al., 2018*), which allows to obtain within the set of this cells, chains of their sequential firing, similar to the time cell chains (*Rolls & Mills, 2019*). In the same way, temporal information can be obtained through analysis of activity of the set of macaque anterior and posterior entorhinal cortex neurons (*Bright et al., 2020*).

The shaping of the spatio-temporal map of the experienced events (*Deuker et al., 2016*), exact representation and reproduction of their temporal structure (*Bellmund et al., 2019; Montchal et al., 2019*) are performed under the leading aLEC participation. Though, mechanisms of, for example, mnestic reconstruction of the events temporal sequence remain unknown (*Bellmund, Deuker, Montijn & Doeller, 2022*).

1.6.3. Speed

The results of a number of early and recent studies (*C. Sun et al., 2015; Kropff et al., 2015; Hinman, Brandon, Climer, Chapman & Hasselmo, 2016; Ye, Witter, Moser & Moser, 2018; reviewed Tukker et al., 2022*) testify to the existence of brain neurons, activity of which closely correlates with the value of an animal linear speed — the so-called speed cells. Unlike population of such cells in hippocampus, the MEC speed cells are a rather distinct functional group (*Kropff et al., 2015*). Some MEC cells whose activity correlates with an animal movement speed are parvalbumin-positive, inhibitory neurons that project into the hippocampus (*reviewed Tukker et al., 2022*). However, in general, the composition of the MEC speed cell population and its relation to other populations of the navigation system neurons currently remain unknown (*see Tukker et al., 2022*).

1.6.4. Memory

The memory function is provided with key participation by the entorhinal-hippocampal complex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial prefrontal cortex, inferior and lateral frontal cortex parts, inferior and lateral parietal cortex parts, structures of the fornix, nucleus basalis of Meynert, amygdaloid complex, hypothalamus, nucleus accumbens, and, possible, some thalamic nuclei and the pedunculopontine nucleus (*reviewed by Khan, D'Agostino, Calnan, Lee & Aronson, 2019*).

The entorhinal-hippocampal complex is well known for its participation in the engramming of current information (*Kelley, Evans & Kelley, 2018; Rolls, 2018*), at that, not only spatial (*Suthana et al., 2012*), but also integral one, i.e. whole episodes, with their temporal, spatial, so-

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cial and other attributes (*Sugar & Moser, 2019; Bellmund, Polti, & Doeller, 2020*). As mentioned before, LEC/aLEC is regarded as one of the nodes of episodic (*Bellmund, Polti, & Doeller, 2020; Takehara-Nishiuchi, 2022*) and temporal (*Deuker et al., 2016; Tsao et al., 2018; Bellmund et al., 2019; Montchal et al., 2019; Bellmund, Polti, & Doeller, 2020*) memory. The entorhinal cortex also plays significant role in engramming of the affective-emotional information, particularly, under participation of the pyramidal and stellate neurons of the MEC layer II (*Kitamura, 2017*).

It should be mentioned also that the entorhinal-hippocampal complex participates in transformation of the primarily engrammed information into the semantically linked, conceptual, and therefore long-term retained information (*Dandolo & Schwabe, 2018; see also Sekeres, Winocur & Moscovitch, 2018*).

1.7. Entorhinal Cortex and Alzheimer's disease

The role of the entorhinal cortex, LEC in particular, in brain pathology has been most substantially studied regarding the Alzheimer's disease (*Kobro-Flatmoen et al., 2021; Olajide, Suvanto & Chapman, 2021; Tran, Speck, Gallagher & Bakker, 2022*), but it is not limit with this disease only (*e.g., see Braden & Riecken, 2019*). For a long time, the most significant decrease in neuron number under the Alzheimer was revealed only in the hippocampus, particularly, in field CA1, then — also in the hilus of the dentate gyrus, in the subiculum, and in the layers II and V of the entorhinal cortex (*Beall & Lewis, 1992; Solodkin & van Hoesen, 1996; van Hoesen, Augustinack, Dierking, Redman & Thangavel, 2000; R. Insausti & Amaral, 2012*) and in the perirhinal cortex (*van Hoesen et al., 2000*). A decrease in the entorhinal cortex volume under the Alzheimer's disease is also revealed by the life-time MRI studies (*Wisse et al., 2014*), and its key role in the disorder pathogenesis is confirmed by the comparative regional analysis of the genetic expression in the cerebral cortex (*Gryglewski et al., 2022*).

In a human, with aging, the area of the entorhinal tuberosity and average number of neurons in ordinary island/protuberance significantly decreases, and entorhinal cortex layer III neurons are the first to demonstrate senile accumulation of pathological neurofilament aggregates (*Simic et al., 2005*), at that in the elderly persons with absent cognitive disorders the MRI-detected entorhinal cortex atrophy correlates with presence of the β-amyloid accumulations (*Nosheny et al., 2019*). The human entorhinal cortex can also accumulate the τ-protein neurofibrillary tangles even in the pre-clinical phase of Alzheimer's disease (*Llamas-Rodríguez et al., 2022*), though for some variants of this pathology, accumulation of the τ-protein in typical brain regions is not pathognomonic (*Singleton et al., 2021*).

A significant vulnerability of the entorhinal cortex layer II neurons was proven in the model of Alzheimer's disease (*Yang et al., 2018*), and rapid age-related disturbances of this entorhinal cortex layer projection were described in intact animals (*Amani et al., 2021*). There is an assumption that the LEC neurons are affected under the Alzheimer's disease retrogradely, due to the action of the certain dentate gyrus pathological factors (*Young, 2020*). A number of studies reveal significant age-related decline in persistent firing ability of the LEC layer III pyramidal neurons, which cause deficits in temporary associative memory and learning (*Lin, Sherathiya, Oh & Disterhoft, 2020; Lin, Oh & Disterhoft, 2022*).

And yet, the conclusion about Alzheimer's disease-dependent reduction in the entorhinal cortex neuronal population is called into question by the available, albeit far from complete data on the age-related dynamics of this neuron population in relatively intact individuals.

Thus, Heinsen et al. (*1994*) state a negative correlation between the number of the entorhinal cortex layer II neurons of each hemisphere and the individual's age, so that when comparing the averaged data for persons aged 20 and 85 years, they note the loss of up to 27 % of the neurons of the considered layer. Simic et al. (*2005*) define this index for the age sample of 32–83 years at the level of 44 %. Kordower et al. (*2001*) registered loss of 64 % of the entorhinal cortex layer II neurons, in patients of 80–97 years old, under mild cognitive deficits, while under the Alzheimer's disease the value was 58 %. Price et al. (*2001, as cited in R. Insausti & Amaral, 2012*) state the 0.7 % annual age decrease of the entorhinal cortex neurons population in people with mild,

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preclinical Alzheimer's disease, at that the 1.2 % level of decrease was revealed for layer II neuronal population. According to R. Insausti, A.M. Insausti, Sobreviela, Salinas and Martínez-Peñuela (*1998*), as cited in R. Insausti and Amaral (*2012*), age-related decrease of the entorhinal cortex area in the interval 12–110 years reached 4 %. While, Gómez-Isla et al. (*1996*) did not detect the left entorhinal cortex layer II neuron loss in individuals with no signs of dementia during the age range from 60 to 89 years, at all.

1.8. Betz Cortical Glomeruli

1.8.1. Glomerula corticalia

A neuromorphological description, presented below, is nowadays the first cytoarchitectonic evidence about the entorhinal cortex modular organization, i.e. existence of entorhinal islands: «*The end of the Ammon gyrus the entire end of the temporal lobe (polus temporalis) have the peculiarity that in them the pyramids of the third layer, in addition to their own place, is also placed directly under the first layer. Here they are arranged quite peculiarly in large round heaps, located at a distance from one another. The pyramidal cells of these heaps are arranged in a variety of directions to each other, directions, which are similar with the directions of the rows of threads in a ball, so I want to name them glomeruli of the cortex (glomerula corticalia).*». This is a part of the paper by Volodymyr Betz, completed by him on November 15, 1880, and published in Russian in 1882 (*translation — ours, with maximum observance of the author's vocabulary and style peculiarities*). The Russian-language version of this article is almost identical to the world-famous German version of 1881 (*fig. 2*). Here is quote from the relevant part: "*Das Ende der Ammonswindung und das ganze Ende des Schläfenlappens (Polus temporalis) besitzen die Eigentümlichkeit, dass in ihnen die Pyramidenzellen der dritten Schicht auch noch unmittelbar unter der ersten Schicht anzutreffen sind. Hier lagern sie sich ganz eigentümlich in Form grofser, runder Haufen, die durch bedeutende Zwischenräume von einander geschieden sind. Die Pyramidenzellen dieser Haufen selbst sind ganz eigentümlich gegen einander gerichtet und erinnern an Garnknäule, weshalb ich sie „Glomeruli corticales" benannt habe.*" (*Betz, 1881, N. 12, p. 211*). In the same work, we also find another, hitherto unnoticed by commentators, fragment, which reinforces Betz' priority in description of the entorhinal cortex modular organization: «*The Ammon gyrus of this brain* [referring to the brain of Mottè, or Motey, who suffered from idiocy — V.M.] *represents a very strongly developed substantia reticularis alba, which, especially on the inferior part of the gyrus, represents the appearance of the fish caviar grains located next to each other.*» (*Betz, 1882; translation is ours, with maximum observance of the author's style — V.M.*). The German version is identical: "*Die Ammonswindung dieses Gehirns hat eine sehr stark entwickelte Substantia reticularis alba, welche namentlich an dem unteren Teile der Windung das Aussehen von dicht neben einander gelagerten Fischlaichkörnern hat.*" (*Betz, 1881, N. 13, p. 232*). The fact that the author is fully aware of the unordinarity of his own cytoarchitectonic observation is demonstrated by a fragment from the introductory part of the article, which states the following: «*Regarding the peculiar structure specificity following cortex parts are differentiated: the anterior central gyrus* [precentral gyrus — V.M.]*, cingulate gyrus (gyrus cinguli), Ammon gyrus, third frontal* [gyrus — V.M.]*, paracentral lobule, lingual lobule (gyrus lingualis), terminal lobule (lobulus extremus) and* ***the end of the temporal lobe (polus temporalis)****.*» (*Betz, 1882; translation is ours, with maximum observance of the author's style; highlighting is ours — V.M.*). The German version is almost identical: «*Ganz besonders charakteristisch ist der Bau folgender Rinde bezirke: der vorderen Central windung, der bogenförmigen Windung (Gyrus cinguli), der Ammonswindung, der dritten Stirnwindung, des Lobulus paracentralis, des Gyrus lingualis, des Lobulus extremus und* ***das untere*** *Ende des Polus temporalis.*» (*Betz, 1881, N. 11, p. 195; the Russian and German versions differ by the word we highlighted, the meaning of which is 'the lower'*). After difficult searches, we managed to find among Betz's collection of preparations precisely those that, in our opinion, contain the morphological material described in the above quotations (*fig. 3–5*).

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Wöchentlich erscheinen 1—2 Bogen; am Schlusse des Jahrgangs Titel, Namen- und Sachregister. **Centralblatt** für die **medicinischen Wissenschaften.** Preis des Jahrganges 20 Mark; zu beziehen durch alle Buchhandlungen und Postanstalten.

Redigirt von Dr. H. Kronecker, Professor in Berlin, und Dr. H. Senator, Professor in Berlin.

1881. 19. März. No. 11.

Inhalt: Betz, Feinere Structur der menschlichen Gehirnrinde (Orig.-Mitt.). — Eng, Tabes und Syphilis (Orig.-Mitt.). Wölfler, Entwickelung und Bau der Schilddrüse und Kropfbildung. — Simanowsky, Einfluss der Reizung der Gallenblase und Nieren auf das Herz. — Finkler, Respiration bei Inanition. — Galtier; Larbet, Uebertragung des Rotzes und der Stomatitis ulcerosa. — Holl, Aetiologie des angeborenen Plattfusses. — Herxheimer, Mycosis tracheae. — Langenbuyen, Syphilitische Pharynxstenosen. — Bille, Fremdkörper in Speiseröhre und Magen. — Oerecke, Locale Gehirnerkrankungen. Krause, Frühzeitige menschliche Embryonen. — Döhnoff, Einfluss der Jahreszeiten auf Lebenserscheinungen. — Wurtz, Papain. — Schrötter, Operation von Kehlkopfpolypen. — Sasseki, Künstliche Hypertrophie und Dilatation des Herzens. — Mank, Poliomyelitis anterior acuta adultorum. — Dubrino, Pityriasis maculata et circinnata.

Ueber die feinere Structur der Gehirnrinde des Menschen.

Vorläufige Mittheilung von Prof. W. Betz in Kiew.

(Dem Andenken von Paul Broca, Prof. der med. Facultät zu Paris, gewidmet.)

Der bahnbrechende [illegible] von Fritsch und Hitzig, dass die Gehirnrinde des Hundes durch [illegible] Reizung erregbar sei, hat eine Reihe von Untersuchungen an [illegible] Tiere, namentlich des Affen, hervorgerufen, welche noch anderer [illegible]keit der Voraussetzung eines Gebundenseins bestimmter in Richtig- Thätigkeiten an bestimmten Gehirnrindenbezirken nachweisen. Der Untersuchungen Ferrier's an der Hirnrinde höherer Affenarten haben ferner gezeigt, dass es auch Rindengebiete giebt, welche in einem bestimmten Verhältniss zu den einzelnen Sinnen, zum Sehen, Hören, Riechen, Schmecken und Tasten, stehen.

Aber weder die Untersuchungen von Fritsch und Hitzig, noch die von Ferrier, hatten bisher in dem anatomischen Bau der Gehirnrinde eine Stütze finden können.

Im Juni 1874 wurde von mir eine Arbeit veröffentlicht über die Gehirnrinde der Tiere, der Affen und namentlich des Menschen, worin ich nachwies, dass an den Stellen, die den motorischen Centren von Fritsch und Hitzig entsprechen, ganz eigenthümliche, bis dahin von Niemandem beobachtete Nervenzellen vorhanden sind,

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Wöchentlich erscheinen 1—2 Bogen; am Schlusse des Jahrgangs Titel, Namen- und Sachregister. **Centralblatt** für die **medicinischen Wissenschaften.** Preis des Jahrganges 20 Mark; zu beziehen durch alle Buchhandlungen und Postanstalten.

Redigirt von Dr. H. Kronecker, Professor in Berlin, und Dr. H. Senator, Professor in Berlin.

1881. 19. März. No. 12.

Inhalt: Betz, Feinere Structur der menschlichen Gehirnrinde (Orig.-Mitt. Forts.). — Eng, Tabes und Syphilis (Orig.-Mitt. Schluss). Ohmus, Absterben der Muskeln und Nerven. — Durchbel; Salomon, Entstehung von Hypoxanthin aus Eiweisskörpern. — Wolff, Hasenscharten-Operation. — Estelle, Eiweisstoffe im Urin. — Meschede, Epilepsie mit Zwangsbewegungen und Zwangsvorstellungen. — Baiberg, Schreckl ähmung. — Freudenberger, Conchinin. Königstein; Leber, Canalis Schlemmii. — Ellenberger, Galoppbewegung der Pferde. — Dogiel, Einfluss der Musik auf den Kreislauf. — Danilewski, Krystallisirtes Spaltungsproduct der Eiweisskörper. — Lappter, Gehirnerweichung durch Mikrokokken-Infection bei puerperaler Pyämie. — G. Fischer, Trepanation des Darmbeins beim Beckenabscess. — C. Weil, Rhinolith. — Anders, Resorcin bei Magenleiden. — Stuching, Katalepsie.

Ueber die feinere Structur der Gehirnrinde des Menschen.

Vorläufige Mittheilung von Prof. W. Betz in Kiew.

(Dem Andenken von Paul Broca, Prof. der med. Facultät zu Paris, gewidmet.)

(Fortsetzung.)

Die vordere Centralwindung, von der oberen Grenze des unteren Drittels beginnend, bietet in der Richtung nach oben folgende Eigenthümlichkeiten: Vor allen Dingen treten in ihr, oberhalb der fünften Schicht, vereinzelt oder paarweise, grosse Zellen auf, die durch grosse Zwischenräume von einander geschieden sind; mehr nach oben sind diese Zellen zu 3, 4 in Nestern gruppirt, deren Entfernung von einander immer geringer wird. Noch mehr oberhalb werden diese Nester bereits aus einer grösseren Menge Zellen gebildet (nicht weniger als aus 4, manchmal aus 5—7); zugleich geben sie aus ihrem früheren Aufenthaltsorte (oberhalb der fünften Schicht) in die dritte Schicht über, wo sie sich in Form einer geschlossenen Reihe lagern; dabei sind sie auch vereinzelt in der zweiten, ebenso wohl wie in der vierten und oberhalb der fünften Schicht anzutreffen. In der Nähe des Lobulus paracentralis löst sich diese Reihe wieder in Nester auf und im Lobulus paracentralis selbst lagern sich diese Zellen bald schichtenweise über einander, bald in Nestern, die verschieden gruppirt sind. Je näher diesem Lobulus, desto

XIX. Jahrgang. 14

Wöchentlich erscheinen 1—2 Bogen; am Schlusse des Jahrgangs Titel, Namen- und Sachregister. **Centralblatt** für die **medicinischen Wissenschaften.** Preis des Jahrganges 20 Mark; zu beziehen durch alle Buchhandlungen und Postanstalten.

Redigirt von Dr. H. Kronecker, Professor in Berlin, und Dr. H. Senator, Professor in Berlin.

1881. 26. März. No. 13.

Inhalt: Elsenberg, Veränderungen der Speicheldrüsen bei Wutkrankheit (Orig.-Mitt.). — Aufrecht, Syphilis-Mikrokokken (Orig.-Mitt.). — Arnstein, Albuminöse Degeneration (Orig.-Mitt.). — Betz, Feinere Structur der menschlichen Gehirnrinde (Orig.-Mitt. Schluss). Stilling, Centrale Endigungen des N. opticus. — Franck und Pitres, Bewegungen durch Reizung des Grosshirns. — Zadek; v. Basch, Messung des Blutdrucks am Menschen. — Cash, Magen und Paukreas bei Fettverdauung. — v. Recklinghausen, Verbrennungswärme organischer Verbindungen. — Popoff; Czokor, Folgen der Unterbindung der Ureteren und der Nierenarterien. — Beigelbaum, Unterbindung des Vas deferens. — Beigbs Adams, Hämoglobin- und Eiweiss-Ausscheidung in der Niere. — Pooley, Taubheit durch Thrombose des Hirnsinus. — Ganghofner, Stenosirende Entzündung der Luftwege. — Bacinsky, Pneumonie und Pleuritis bei Kindern. — Nicati und Richaud, Biliäre Lebercirrhose. — Strempell, Spastische Spinalparalysen und Pseudoparalysen. — Kroener, Heilung des Lichen ruber exsudativus durch Arsen. — Runge; Credé sen.; Schultze, Behandlung der Nachgeburt. Deutschmann, Quellen des Humor aqueus. — E. u. H. Salkowski, Skatolbildende Substanz. — Erdmann, Wasserfreier Milchzucker. — Bäyer, Beziehungen der Zimmtsäure zur Indigogruppe. — Pasteur, Milzbrand-Infection. — Marvaud, Plötzlicher Tod bei Typhus. — Malassez und Terrillon, Epididymitis bei Entzündung des Vas deferens. — K. Schultze, Fibroma molluscum am Kopf. — Bruns, Resection des Kehlkopfs bei Stenose. — Leber, Klinisch-ophthalmologische Miscellen. — Maden, Kehlkopfstenose durch scrophulöse Drüsen. — Schnitzler, Exstirpation eines Kehlkopfpolypen. — Kingston Fowler, Katarrh bei acutem Rheumatismus. — Fruhbach, Mitbewegung von Kehlkopf und Zunge mit dem Herzen in Folge Traumas. — Riegel, Pneumothorax. — Putnam, Parästhesie der Finger. — Schiller, Katalepsie mit Sprachreflexen. — Schapter, Athetose und uncoordinirte Bewegungen. — Neumann, Heilbarkeit des Prurigo bei Kindern. — Ludwig u. Mautner, Nachweis der Blausäure. Eulenburg, Bemerkung über die locale Anästhesirung des Kehlkopfs durch subcutane Morphium-Injection.

Anatomische Veränderungen der Speicheldrüsen bei Wutkrankheit der Hunde und Menschen.

Vorläufige Mittheilung von Dr. A. Elsenberg, Assistenten am pathologischen Institut der Warschauer Universität.

Obwohl die inficirende Eigenschaft des Speichels bei Lyssa wohl bekannt ist, giebt es bisher keine positiven Befunde über Veränderungen der Speicheldrüsen bei von dieser Krankheit ergriffenen Tieren. Es wird wohl angegeben, dass die Drüsen im hyperämischen Zustande sich befinden, doch widerspricht Bruckmüller auch dieser Angabe. — Einiges Licht wirft auf diese Frage die Beobachtung von Nepveu

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Fig. 2. Three consecutive March issues of the German scientific and medical periodical "Centralblatt für die medicinischen Wissenschaften" ("Central journal for the medical sciences", Berlin) in which Betz's article (*1881*) was printed in three parts. In the first two numbers (*N. 11 and N. 12*) the relevant parts of Betz's work are placed first, in the third of the considered numbers (*N. 13*) the final part of Betz's work is placed fourth. Source of the electronic file of the edition number binder for 1881: https://archive.org/details/bub_gb_acADAAAAYAAJ/page/192/mode/2up

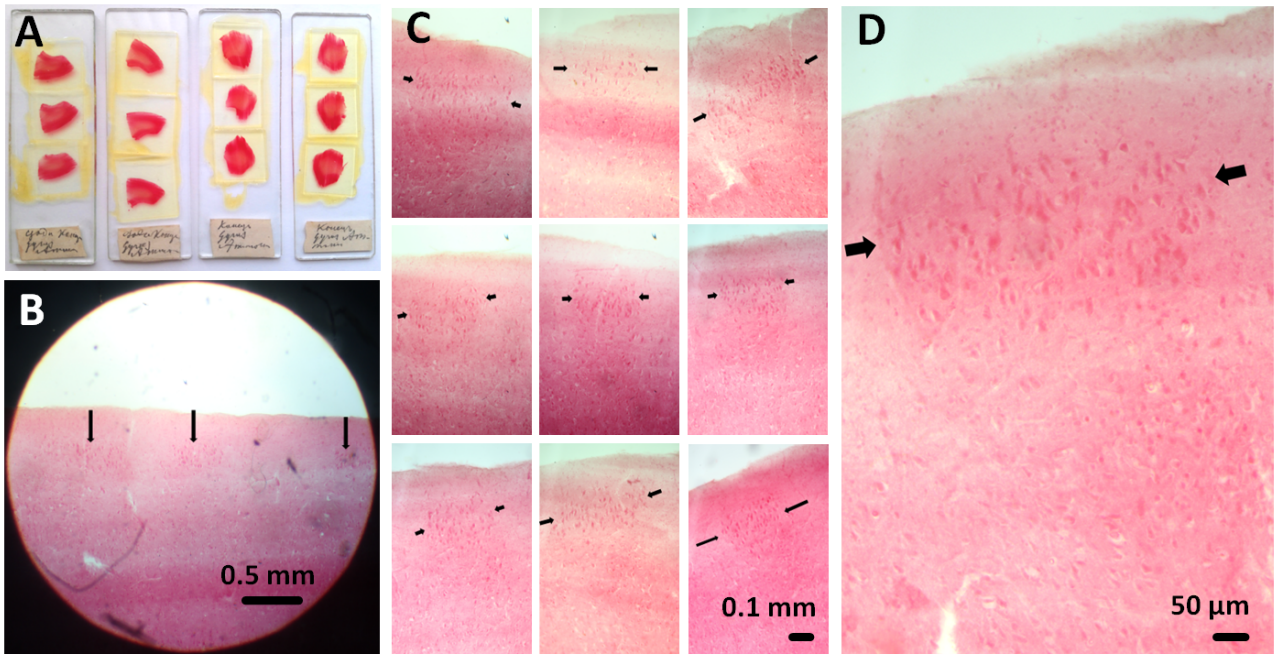

Fig. 3. *Glomerula corticalia* on Betz's authentic preparations.

A — four histological preparations with the carmine-stained «*end of Ammon's gyrus*» sections. Betz's own handwritten inscriptions: on the two preparations located on the left — «*posteriorly [from] the End of gyrus Amm[onis]*», on the two preparations located on the right — «*End of the*

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gyrus Amm[onis]»; the inflexion of the word «*Amm[onis]*» in both cases is illegible. The wording of these signatures exactly corresponds to the vocabulary of the above-cited place of the article by Betz (*1882*), where the islands of the entorhinal cortex, i.e. *glomerula corticalia*, were first described. This leaves no doubt that the source of this description was at least these four preparations from Betz's collection given here.

B — view of a typical part of the cortex histological section, available on one of the four Betz's preparations we examined; arrows indicate entorhinal islands.

C, **D** — variants of the entorhinal islands, which we found on the same four Betz's preparations, at different magnifications (*the boundaries of the islands are marked horizontally with black arrows*)

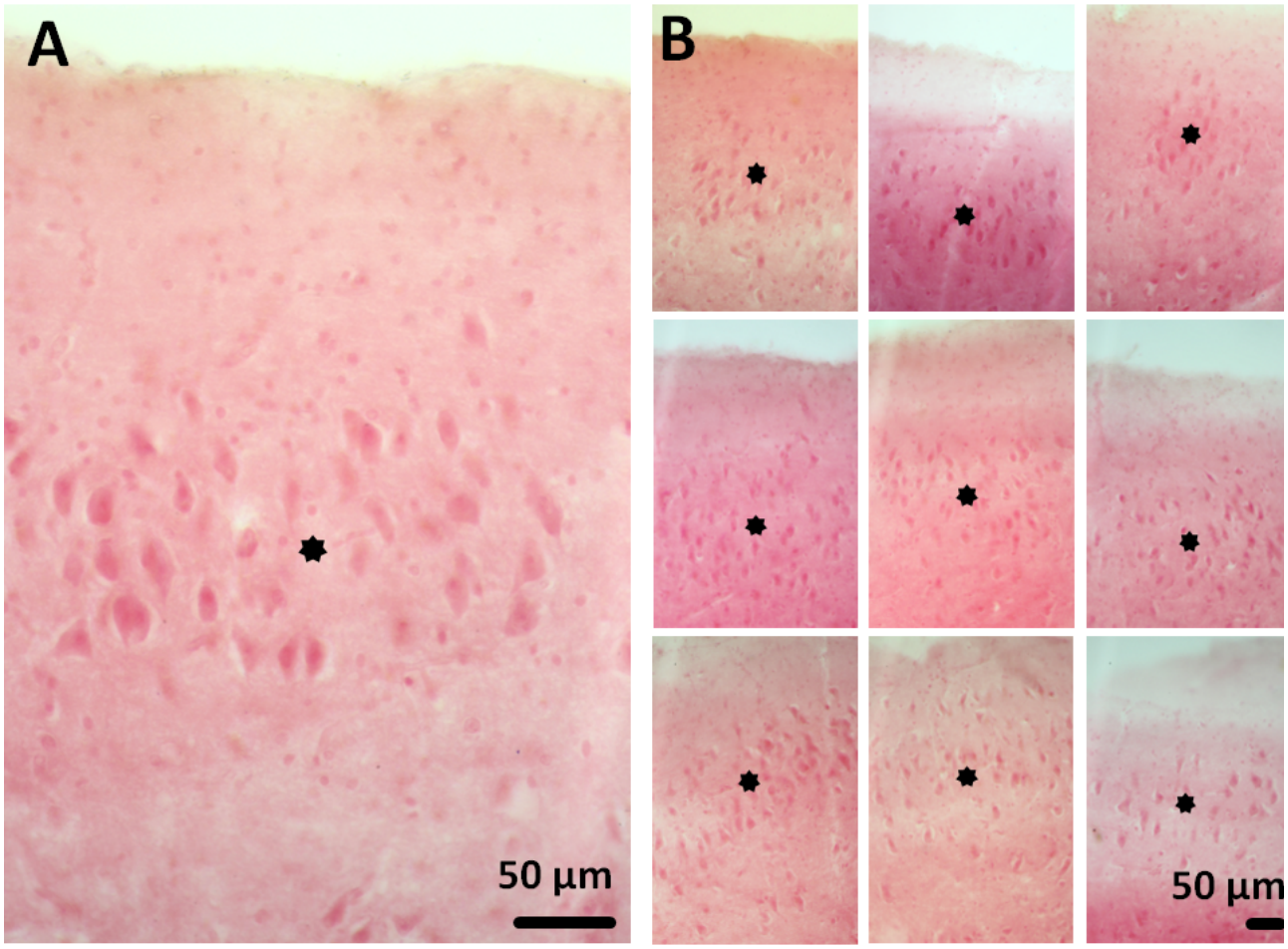

Fig. 4. Variants of the entorhinal islands, which we found on the Betz's preparations (*fig. 3 A*), at different magnifications (**A**, **B**). Carmine-staining. In each photomicrograph, the conventional center of the entorhinal island is marked with a black asteriks

Betz's priority regarding the description of the Ammon's horn cortex cytoarchitectonics has been recognized by Ramon y Cajal (*1988, work of 1901–1902, p. 294–295*): «*The structure of the hippocampal gyrus in man and that of the piriform lobule in animals have been little studied. In general, the authors have distinguished in the hippocampal gyrus two regions or segments: the subiculum, or portion adjacent to Ammon's horn, recognizable by showing a plexiform layer furrowed by thick bundles of white matter; and the principal portion, distant from [Ammon's] horn, in which an organization almost identical to that of the other [cerebral] gyri has been supposed. However, some authors, among whom* ***we must cite Betz****, Obersteiner, Dejerine, Hammarberg, and especially Calleja and Kölliker, have recognized some structural peculiarities exclusive to*

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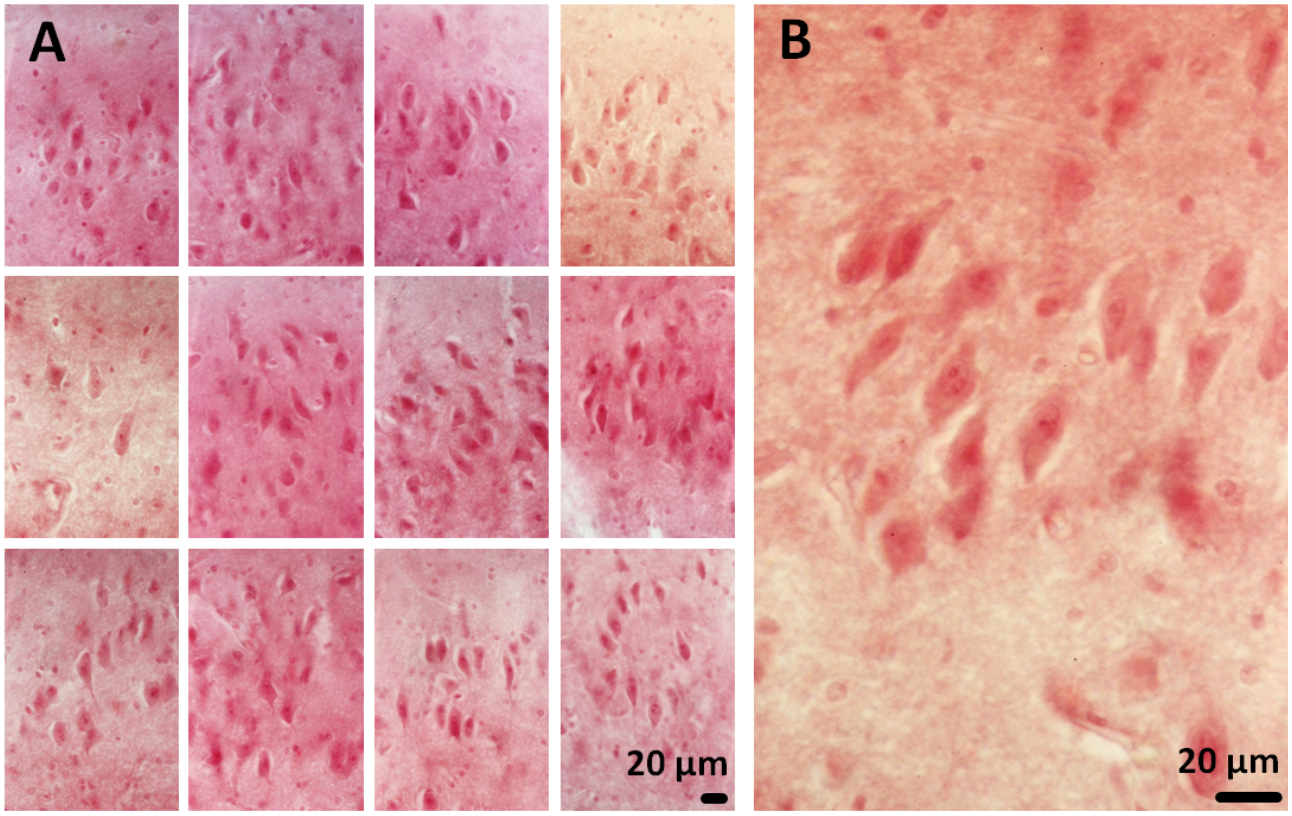

Fig. 5. Variants of the entorhinal islands, which we found on the Betz's preparations (*fig. 3 A*), under strong magnification (**A**, **B**). Carmine-staining. The neuronal composition of the islands and even the cytological features of neuronal somata are well visualized (**B**)

the piriform lobule and hippocampal gyrus. One of the typical features of the cortex of the subiculum is the presence, at the level of the small pyramids, of pleiades of cells separated by ascending bundles of white matter ***which were alredy recognized by Betz,[9] who named them cortical glomeruli****. For his part, Obersteiner,[10] who studied also the structure of the subiculum ... [A]t the level of second layer, he also observed the* ***cellular accumulations of Betz****, as well as the bundles of white matter that separate them; ... One neurologist who dedicated more attention to the theme we are dealing with, exploring equally all the regions of the hippocampal gyrus with method of Nissl, was Hammarberg.[13] ...* ***In agreement with Betz and Obersteiner, he observed the small islands of the second layer and the ascending white bundles****.*" (*highlighting is ours — V.M.*).

This evidence of Ramon y Cajal is well known to specialist. Thus, Amaral, R. Insausti and Cowan (*1987*) write: «*According to Ramon and Cajal ('01, '02), Hammarberg (1895) provided the first comprehensive study of the laminar organization of the entorhinal cortex, although Betz (1881), Obersteiner (1888), and Calleja (1893) had earlier described some aspects of its structural organization.*». R. Insausti, Tuñón, Sobreviela, A.M. Insausti and Gonzalo (*1995*) in a special final part of the article, referring, most likely, to the same work of S. Ramon y Cajal, give a number of early reports on the microscopic structure of the entorhinal cortex, the first three authors in which are the analogous: Betz, Obersteiner, Calleja, and Hammanberg.

Amaral et al. (*1987*) before the brief exposition of the entorhinal cortex research history note that the thorough study of the issue were made by Stephan (*1975*) and Haug (*1976*). A close look at both of these works reveals details of the Betz's role reception in the discovery of the entorhinal islands. Thus, Haug (*1976*), describing the cytoarchitectonic features of the rat parahippocampal cortex, associates the beginning of this brain part structure study with Ramon y Cajal. Instead,

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Stephan (1975) presents an original vision of a historical series of personalities who contributed most significantly to the human entorhinal cortex microstructure study. This list looks as follows (*references to relevant primary sources are given in Stephan's cited work*): Campbell (*1905*), Brodmann (*1909*), C. Vogt and O. Vogt (*1919*), von Economo and Koskinas (*1925*), Rose (*1927*), Sgonina (*1938*), and Braak (*1972*). Unexpected absence of Ramon y Cajal and Lorente de No in these list, without a doubt, is obvious to the author himself; he notes that the contribution of both morphologists is described by him separately, in point 8.11.5. Among the listed works, the author emphasizes evidence of Campbell (*1905*): he, according to Stephan (*1975, p. 666*), describes the notable near-surface clusters of the entorhinal cortex cells — «*Er gibt aber eine Beschreibung und eine sehr schone Illustration der Zell- und Faserarchitektonik von einer Gegend, die er als «as near as possible the central point of the lobule» — gemeint ist sicherlich der Gyrus parahippocampalis — beschreibt (Campbell, 1905, Plate XVII). Er gliedert die Rinde in sechs Schichten. An Besonderheiten hebt er die großen Fasermassen im Stratum moleculare hervor, und die* ***bemerkenswerten Zellnester an der Oberflache des Zellbandes****, die im Faserbild durch besondere Faserarmut auffallen. Die Molekularschicht ist ungewohnlich breit.*» (*highlighting is ours — V.M.*). Dwelling on this morphological peculiarity, Stephan (*1975, p. 666*) casually notes that the II layer of the entorhinal cortex contains two types of nests — those which consist of polymorphic giant cells and those that contain significant number of small pyramidal cells: «*Die zweite Schicht enthalt zwei Typen von Zellnestern. Einmal solche aus «polymorphen Riesenzellen» (CAJAL) und solche aus kleinen Pyramidenzellen*[483]*). Die großen Zellen haben beim Menschen einen mittleren Durchmesser von 28 mkm und sind bevorzugt sternformig. Der Kern ist klein und liegt im Zentrum des Zellkörpers. Die kleinzelligen Nester enthalten viele sehr kleine Zellen.*». At this point the author gives a key for us footnote (*at number 483*), in which he states that the cellular nests mentioned, besides Ramon y Cajal, according to Campbell, are described also by Hammarberg and Flechsig; however, Stephan continues, according to von Economo and Koskinas, "*Betz may have been the first to describe the 'glomeruli corticales' of the 'Ammon gyrus anterior part and the temporal pole'*": «*Diese charakteristischen Zellnester sind neben CAJAL auch von HAMMARBERG und FLECHSIG beschrieben worden (CAMPBELL, 1905, S. 179). Nach ECONOMO u. KOSKINAS (1925) hat möglicherweise BETZ die «glomeruli corticales» des «vorderen Teils der Ammonswindung und des Temporalpols» erstmals beschrieben.*» (*H. Stephan, 1975, p. 666, footnote 483*). The phraseological and lexical closeness of Betz's indirect quotation given by Stephan (*1975*) with the relevant fragment of its Russian and German counterpart (*see above*) leaves no doubt that von Economo and Koskinas considered Betz to be probably the first to testify the existence of entorhinal cortex layer II neurons clusters, naming them "*glomeruli of the cortex*".

Knowing all this, it is not difficult to guess where the term "*entorhinal glomeruli*" appeared and was used throughout the 20th century in the literature devoted to the microstructure of the entorhinal cortex. For example, in the English reprint of von Economo's work, it is the term "*glomeruli*" is used to denote the islands of the entorhinal and adjacent areas of the cortex (*von Economo, 2009, p. 150–169*). Unfortunately, in the cited reprint of von Economo's work has not preserved information about the etymology of the term, which, as just mentioned, according to Stephan (*1975*), was present in the 1925 edition. Altschul (*1933*), although with reservations, uses the same lexeme for description of the island structures of the mammalian presubiculum. Solodkin and van Hoesen (*1996*), referring to a number of sources, call the entorhinal islands «*concentric patches that create the impression of glomeruli*». A similar historical name of the entorhinal islands is also mentioned by Simic et al. (*2005*).

It should be noted that the tradition of calling the entorhinal glomeruli as islands (*and islets*) dates back to Ramon y Cajal, in any case, in his work devoted to the olfactory cortex of humans and mammals, such terms (*islands, islets*) in relation to the structures under consideration are found everywhere (*Ramon y Cajal, 1988, work of 1901–1902, pp. 295-315*). Solodkin and van Hoesen (*1996*) once used the term "*clumps*" to

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denote entorhinal islands, R. Insausti et al. (*2017*) call the clusters of the II layer of the presubiculum in this way. Finally, there is precedent for using the term "*nests*" (van Hoesen et al., 2000) to refer to entorhinal islands.

We also note that van Hoesen et al. (*2000*), citing the work of Bielschowsky (*1928*) in the context of history of the Alzheimer's disease pathomorphological signs elucidation, evidence to his use of the term "*islands of Cajal*" in relation to the cell clusters of the subiculum outer layer. van Hoesen et al. (*2000*) immediately correct Bielschowsky, recalling that Ramon y Cajal described such peculiarity of cytoarchitectonic precisely in relation to the entorhinal cortex, and the co-inclusion of the subiculum in its boundaries is doubtful. However, in our opinion, a completely different circumstance is doubtful in this situation — the use of the eponym in relation to the cell clusters of the entorhinal cortex outer layer without taking into account Betz's pioneering observation.

1.8.2. Entorhinal Tuberosity and *Substantia Reticularis Alba*

As it was mentioned before, the layer II neuronal glomeruli, or islands represent a unique differential sign of the entorhinal cortex, which has a macroscopic correlate (*Solodkin & van Hoesen, 1996, p. 620; van Hoesen et al., 2000,* p. *259; Simic et al., 2005, p. 911*): in the intermediate and caudal regions of the entorhinal cortex, they form the tuberosity of the surface (*fig. 1 C*), described as a collection of "*verrucae hippocampi*" (*R. Insausti et al., 1995*), or "*warts*" (*R. Insausti et al., 1995; R. Insausti & Amaral, 2012*), "*bumps*" (*R. Insausti et al., 1995*) or even "*wart-like bumps*" (*Witter, Doan, et al., 2017*). Most likely, the grayish spots often visible to the naked eye are associated with the "*verrucae hippocampi*" — areas where the entorhinal islands can be seen through the surface of the cortex (*Hevner & Wong-Riley, 1992, p. 455 and fig. 3*).

In our opinion, the emergence of the term "*verrucae*" of the human parahippocampal gyrus anterior part is most comprehensively described by van Hoesen et al. (*2000*). According to them, Retzius (*1896*) commented on this morphological peculiarity of the anterior medial temporal region surface, comparing it to the skin surface of some amphibians. Klingler (*1948*), as noted by van Hoesen et al. (*2000*), subsequently generalized, detailed and deepened the observations of Retzius. The priority of Retzius in the description of entorhinal tuberosity, i.e. entorhinal *verrucae* is also recognized by other authors (*Simic et al., 2005; Witter, Doan et al. 2017*). However, in both quoted versions of Betz' work (*1881, 1882*), completed by him on 15th November 1880, we find an earlier and, in our opinion, an accurate and exquisite description of this morphological phenomenon: «*The Ammon gyrus of this brain* [referring to the brain of Motey, who suffered from idiocy — V.M.] *represents a very strongly developed substantia reticularis alba, which,* ***especially on the inferior part of the gyrus, represents the appearance of the fish caviar grains located next to each other***.» (*Betz, 1882; translation — ours, with maximum observance of the author's style; highlighting is ours — V.M.*).

Also notable in this quote is Betz's mention of another macroscopic feature of the entorhinal region. When examining the surface of the intact human entorhinal cortex between the dark spots, which correspond to the visible through the thin surface entorhinal islands, one can observe the white matter (*R. Insausti & Amaral, 2012; fig. 1 D*), which probably contains associative fibers from other areas of the cortex (*van Hoesen et al., 2000*). This macroscopic feature was first described, according to van Hoesen et al. (*2000*), in the work of Arnold (*1851*), so that it is now known as the *substantia reticularis alba* of Arnold. «*At the transition of gyrus cinguli to gyrus ammonii ... a white layer of longitudinal fibers of gyrus cinguli passes on the surface of the entire gyrus above it and, gradually increasing, forms the so-called white granular substance of the ammon's horn (substantia reticularis alba) and, finally, wraps into the creature of the ammon's horn, where it is described by Meinert under the incorrect name of a granular leaf (Kernblatt) in the form of a white nonthrough septum.*» (*Betz, 1882; translation — ours, with maximum observance of the author's style, V.M.*). The German version is very similar: "*An der Uebergnngsstelle des Gyrus cinguli in den Gyrus Ammonii ... und die weifse Schicht der Längsfasern des Gyrus cinguli verläuft längs der Oberfläche des Ammon-*

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shorns und bildet, immer gröfser werdend, die sog. weifse Kernsubstanz desselben (Substantia reticularis alba); dann biegt sie in die Substanz des Ammonshorns, selbst um, wo sie als weifse unvollkommene Scheidewand von Meinert unter dem unrichtigen Namen „Kernblatt» beschrieben wurde." (*Betz, 1881, N. 12, p. 210*).

1.8.3. Entorhinal Cortex Clusters as the first Evidence of Modular Brain Organization

One of the most widespread current concepts of neurobiology is the idea of a neural networks modular organization. There is an opinion (*Naumann et al., 2018*) that the entorhinal cortex neuronal composition clustering is perhaps the first historical evidence in its favor. However, the formulation of this idea is difficult to imagine outside the neurohistological context, as evidenced by at least the history of the cortical column concept. Therefore, the appeal of Naumann et al. (*2018*) to the macroscopic observations of Arnold (*1838*) and Retzius (*1896*) as the first evidence in favor of the modular organization of the brain is doubtful. Instead, Betz's observations discussed above, together with other neurohistological non-ordinarities described by him, which we will describe in one of the following publications, can be confidently considered the first arguments in favor of this currently widespread neurobiological concept.

Conclusion

Having reviewed modern notion about the structure and functions of the entorhinal cortex, we can affirm the unique and fundamental significance of Betz's pioneering observation regarding layer II neuronal islands of this cortex part, named by him "*glomerula corticalia*". There is no doubt that in the foreseeable future we will obtain information about entorhinal islands neurons' function, the reason and meaning of these cells such clustering. However, today, a leading role of Volodymyr Betz in this cytoarchitectonic phenomenon discovery is already evident.

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Анотація: у серії публікацій, котру відкриває ця стаття, ми розглядаємо п'ять фундаментальних нейроморфологічних спостережень нашого співвітчизника, класика світової нейронауки Володимра Беца. Для чотирьох із них ми вперше демонструємо статус відкриттів, для іншого одного — гігантських пірамідних нейронів рухової кори — попри повсюдне і давнє його визнання, розкриваємо обмеженість сучасних знань і уявлень. Два із згаданих спостережень — гігантські веретеноподібні нейрони поясної й острівцевої кори і острови енторінальної кори — наданий час відомі лише вузькому колу фахівців; на решту два, острови Калеха і ознаки колонкової організації кори — ми звертаємо увагу вперше. У цій, початковій частині циклу, розкриваючи сучасні уявлення про будову і функції енторінальної кори, ми демонструємо вагу першоспостереження Бецом непересічних нейронних кластерів, відомих зараз як енторінальні острови, доводимо факт визнання його історичного пріоритету у описанні цих дивовижних структур мозку.

Ключові слова: історія медицини, нейронауки, енторінальна кора, клітини решітки, епізодична пам'ять, сприйняття часу, хвороба Альцгеймера.

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Improvement of enteral nutrition technologies in patients with a severe course of acute pancreatitis

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Abstract: *in the case of severe acute pancreatitis, the early start of enteral nutrition (24-72 hours from the moment of hospitalization) by means of nasogastric or nasojejunal administration of the mixture is considered appropriate, which is associated with a 24% decrease in the frequency of infectious complications and a 32% decrease in mortality. However, 30.5-65.7% of patients may develop intolerance to this type of nutritional support. The aim of the study was to improve the results of treatment of patients with severe acute pancreatitis by improving enteral nutrition technologies. There were 101 patients with severe acute pancreatitis took part in the study, who were divided into the main group, where enteral nutrition was carried out according to the improved protocol - 34 patients, comparison group No. 1, where standard nasogastric nutrition was carried out - 34 patients, and comparison group No. 2, where standard EN – 33 patients. The effectiveness of enteral nutrition in the studied groups was evaluated by analyzing and comparing biochemical indicators of blood serum, frequency of intolerance to nutritional support, infected local complications, mortality, duration of multiple organ failure and stay of patients in the hospital. When using the proposed protocol of enteral nutrition in patients with a severe course of acute pancreatitis, 14 days after the start of treatment, a significant difference was obtained between the content of albumin, creatinine, cholesterol and K+ blood serum ($p<0.05$) between patients of the main group and the comparison groups, as well as the content of Na+ in blood serum ($p<0.05$) between patients of the main group and the group of standard nasogastric tube feeding. Application of the proposed protocol of enteral nutrition significantly reduces the frequency of intolerance of nutritional support in the first 7 days of treatment by 23.6% ($\chi2=5.7$, 95% CI 4.41-41.56, $p=0.01$) compared to the control group patients, where standard nasogastric tube feeding is used, by 21.5% ($\chi2=4.87$, 95% CI 2.34-39.48, $p=0.02$) compared to the group of standard enteral tube feeding, as well as the duration of multiple organ failure from 12.2±1.7 days to 10.5±1.9 days in comparison with the group of patients where standard nasogastric tube feeding was used ($p=0.0002$) and from 11.5±1.9 days to 10.5±1.9 days compared to the group of standard enteral tube feeding ($p=0.03$). The use of the proposed technology of enteral nutrition in patients with a severe course of acute pancreatitis improves treatment results by reducing the duration of multiple organ failure and the frequency of intolerance to this type of nutritional support.*

Key words: acute pancreatitis, enteral nutrition, intestinal absorption, nutritional support, treatment.

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Introduction

Acute pancreatitis (AP) is a common disease that accounts for 5-10% of urgent pathologies of the abdominal cavity (Petrov et al., 2019). Particularly dangerous is the severe course of the disease, which is accompanied by the progression of hypermetabolism and hypercatabolism syndromes, a high risk of complications (up to 50%) and fatalities (40-70%) (Purschke et al., 2022). Timely application of nutritional support in this category of patients prevents the development of catabolic processes, leads to a decrease in inflammatory processes and improves treatment results. According to modern protocols of nutritional support in patients with AP with mild and moderate severity of the disease, fasting during the first 2–3 days is recommended, followed by oral fractional consumption of water (1–1.5 l/day), polymeric isocaloric isonitrogenous nutritional mixtures in an increasing volume (100 ml 6 times a day on the 1st day, 150 ml 6 times a day on the 2nd day) under the control of serum amylase level and a gradual transition to a gentle medical diet (Lakananurak et al., 2020). With a severe course of AP, early start of enteral nutrition (EN) (24-72 h from the moment of hospitalization) by nasogastric or nasojejunal administration of the mixture is considered appropriate, which is associated with a 24% decrease in the frequency of infectious complications and a 32% decrease in mortality (Arvanitakis et al., 2020). Polymeric, semi-elemental and elemental food mixtures are used for introduction into the enteral probe at the rate of 250 kcal/day, with a further increase to 1800 kcal/day for one week and constant monitoring of intra-abdominal pressure. However, according to literature data, when using EN in 30.5-65.7% of cases, intolerance to the latter may occur in the form of nausea, vomiting, abdominal distension, diarrhea, increased intra-abdominal pressure, which are reasons for stopping enteral nutritional support (Fan et al., 2021).

Aim

Improving the results of treatment of patients with severe acute pancreatitis by improving the technologies of enteral nutrition.

Materials and methods

There were 101 patients with AP who were hospitalized at the clinic of the Department of Surgery #2 of Bogomolets National Medical University in the period from 2012 to 2022 and was approved by the Ethics Committee of Bogomolets National Medical University (December 15, 2011, protocol # 5). All patients signed informed consent for participation in the study and/or treatment at the clinic. The study included patients with a severe course of the disease (according to the classification of AP Atlanta 2012), who received EN. Prediction and assessment of the severity of the course of HP was carried out using the APACHE II scale (severe course -8 points and more). Exclusion criteria were chronic somatic diseases in the decompensation phase, the patient's refusal to participate in the study. Prediction and assessment of the severity of the course of AP was carried out using the APACHE II scale (severe course - 8 points and more). Exclusion criteria were chronic somatic diseases in the decompensation phase, the patient's refusal to participate in the study.

Depending on the specifics of the selected treatment tactics, the patients were divided into three groups: the main group, where EN was performed according to the improved protocol - 34 patients, comparison group No. 1, where standard nasogastric nutrition was performed - 34 patients, and comparison group No. 2, where standard EN was performed – 33 patients. Comprehensive conservative treatment of patients was carried out in intensive care and intensive care units in accordance with international treatment protocols. The improvement of the EN protocol was preceded by studies that were devoted to the study of the timing of the recovery of intestinal absorption, as one of the main criteria for the initiation of EN in patients with AP, the comparison of the effectiveness and safety of nasogastric administration of feeding mixtures, and the improvement of methods of preventing intestinal complications in patients with this pathology (Kolosovych and Hanol, 2022). Based on the results of the research, the use of a 3% solution of potassium iodide was proposed in order to determine the recovery of intestinal absorption as an indicator of the onset of EN in patients with severe AP (it was established that in most patients the recovery of intestinal absorption occurs only 48 hours after the start of treatment), it was proved, that naso-

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gastric feeding is an effective and safe method of introducing mixtures and can be considered as an alternative to enteral tube feeding, and the use of antiflatulents in the composition of the mixture was also proposed in order to reduce the frequency of EN intolerance. The local protocol for enteral nutrition in patients with severe AP developed in the clinic was based on own research and recommendations of the European Society of Clinical Nutrition and Metabolism (ESPEN) (Cañamares-Orbís et al., 2022) and included the following provisions:

in patients with a severe course of AP, EN is preferred compared to parenteral, while it should be started 48 hours after the start of treatment with a preliminary determination of the state of recovery of intestinal absorption by using a test with a 3% solution of potassium iodide;

contraindications to the start of EN are uncontrolled shock, hypoxemia, acidosis, gastrointestinal bleeding from the upper parts of the digestive tract, secretion of stagnant gastric contents in the amount of >500 ml/6 h, ischemic damage to the small intestine, intestinal obstruction, abdominal compartment syndrome;

EN should be started with nasogastric administration of the mixture, and in case of complications, use nasojejunal administration;

with an increase in intra-abdominal pressure >15 mm Hg. preference is given to nasojejunal administration of feeding mixtures at a rate of 20 ml/h, and with intra-abdominal pressure >20 mm Hg. EN should be stopped and parenteral nutrition should be started;

nutrition begins with drip administration of a glucose-electrolyte solution through a probe at a rate of 100 ml/hour, followed by control after 2 hours by the method of passive or active aspiration for 15 minutes. If the volume of the residual liquid exceeds 100 ml - the probe is used for decompression and injection of the solution in the lavage mode in the previous time mode. In the presence of a smaller amount of residual fluid - the volume of infusion increases by 50% with further monitoring every 3-4 hours;

on the second day of therapy, the introduction into the probe of a 20% solution of an oligomeric (elemental or semi-elemental) mixture for EN in the volume of up to 300 ml/day (1 kcal in 1 ml) with the introduction of simethicone emulsion in a dose of 2 ml (80 mg) is additionally prescribed 3- 5 times a day;

in the absence of complications associated with the use of oligomeric mixtures, their number increases by 2 times the next day (the rate of administration does not change). In case of complications, the rate of introduction of the mixture should be reduced by 2 times. In case of persistent intestinal dyspepsia, it is necessary to temporarily (for 12-24 hours) return to the introduction of only glucose-electrolyte solution;

starting from the third day, ⅔ of the injected volume can be polymer mixtures, while the amount of nutritional support for patients for 5–6 days should be 20–25 kcal/kg and protein 1–1.2 g/kg per day (nitrogen-conserving effect in the first three days, it is achieved by parenteral administration of 150 g/day of 10% glucose solution and 25-50 g/day of lipids in the form of 10-20% fat emulsions), in case of persistent hyperglycemia over 10 mmol/l, specialized polymer mixtures should be used;

removal of probes and transition to oral fractional use of mixtures for EN by the sipping method (more often it is 6-7 days), as well as the subsequent transition to a gentle medical diet is possible in the absence of signs of gastroduodenostasis, enteropathy and amylasemia, elimination of endotoxicosis phenomena, stabilization of the patient's condition, presence of appetite, preservation of swallowing function.

The general characteristics of the patients in the studied groups are presented in the table. 1.

Patients of the three groups did not differ significantly in terms of age, sex, etiology, and prognostic indicators (sum of points on the APACHE II scale) of the severity of the course of the disease at the time of hospitalization. The frequency of surgical interventions in the main group and the group of standard nasogastric tube feeding was the same and amounted to 73.5% (25 patients), in the group of standard enteral tube feeding, surgical interventions were performed in 26 (78.9%) patients.

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Table 1. Characteristics of patients in the studied groups

Demographic data		Main group (n=34)	Group of standard nasogastric tube feeding (n=34)	Group of standard enteral tube feeding (n=33)
Age (year)		52,0±9,5	51,6±5,7#	50,8±7,3#
Sex	**Male**	19 (55,9%)	19 (55,9%)#	19 (57,6%)#
	Female	15 (44,1%)	15 (44,1%)#	14 (42,4%)#
Etiological factors:	**alcoholic**	19 (55,9%)	19 (55,9%)#	19 (57,6%)#
	biliary	11 (32,4%)	11 (32,4%)#	10 (30,3%)#
	idiopathic	4 (11,8%)	4 (11,8%)#	4 (12,1%)#
The sum of points on the APACHE II scale at the time of hospitalization		13,5±3,1	13,2±1,9#	12,9±2,7#

Note: # - p>0.05 when compared with the main group.

Evaluation of the effectiveness of EN in the studied groups was carried out by analyzing biochemical indicators of blood serum 7 and 14 days after the start of treatment, namely, the content of total protein, albumin, total bilirubin, creatinine, glucose, cholesterol, C-reactive protein, Na+ and K+ serum was determined of blood. We also analyzed the frequency of complications that were associated with EN and were manifested by increased pain in the epigastric area, projection of the small and/or large intestine, the occurrence of vomiting, regurgitation, diarrhea in the first 24 hours and 7 days after the use of EN, compared intra-abdominal pressure, frequency of infected local complications during the course of AP, mortality, duration of multiple organ failure, and hospital stay of patients.

Statistical analysis was performed using the programs Statistica 10 (Serial Number: STA999K347150-W) and MEDCALC® (Internet resource with open access, https://www.medcalc.org/calc/).

Results

To evaluate the effectiveness of EN, a comparative analysis of biochemical indicators of blood serum in patients in the studied groups was carried out. The evaluation of the indicated indicators was carried out before the start of EN use (Table 2), after 7 days (Table 3) and after 14 days after its start (Table 4).

No significant difference was found in the analysis of biochemical indicators of blood serum at the time of treatment initiation in the studied groups (p>0.05).

Table 2. Initial biochemical indicators of blood serum in the studied groups

Laboratory indicators	Rate	Main group (n=34)	Group of standard nasogastric tube feeding (n=34)	Group of standard enteral tube feeding (n=33)	F	P
Total serum protein, g/l	65-85	47,4±2,5	47,4±2,0	47,8±1,9	0,40	0,75
Serum albumin, g/l	35-50	27,4±1,1	27,3±0,8	27,7±1,1	0,91	0,43
Total bilirubin, μmol/l	3,4-20,8	38,5±13,1	39,9±13,5	37,5±13,5	0,19	0,89
Creatinine, μmol/l	62-115	152,3±13,0	152,7±9,4	151,0±12,7	0,28	0,83
Glucose, mmol/l	3,5-5,5	8,2±2,1	8,9±2,4	8,0±1,9	2,06	0,10
C-reactive protein, mg/l	0,8-8	69,2±20,6	69,8±28,6	70,6±26,4	0,03	0,99
Serum cholesterol, mmol/l	2,9-5,17	5,0±0,6	5,3±0,7	5,0±0,6	2,0	0,12
Na+ serum, mmol/l	130-149	136,9±7,5	137,1±8,1	136,6±7,6	0,95	0,42
K+ serum, mmol/l	3,5-5,4	3,4±0,1	3,4±0,2	3,4±0,1	0,62	0,59

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Table 3. Dynamics of biochemical parameters of blood serum in the studied groups 7 days after the use of enteral nutrition

Laboratory indicators	Rate	Main group (n=34)	Group of standard nasogastric tube feeding (n=34)	Group of standard enteral tube feeding (n=33)
Total serum protein, g/l	65-85	52,9±1,6	50,7±2,4*	51,7±2,6
Serum albumin, g/l	35-50	29,8±1,3	28,3±1,1*	28,8±1,6*
Total bilirubin, μmol/l	3,4-20,8	27,7±7,5	29,8±6,5	26,8±7,1
Creatinine, μmol/l	62-115	137,9±16,5	146,9±13,7*	141,0±12,4
Glucose, mmol/l	3,5-5,5	6,1±0,7	6,2±0,9	6,2±0,6
C-reactive protein, mg/l	0,8-8	105,5±49,7	109,6±51,4	103,5±60,7
Serum cholesterol, mmol/l	2,9-5,17	4,6±0,3	4,1±0,7*	4,3±0,4*
Na+ serum, mmol/l	130-149	140,9±3,1	140,1±4,8	140,5±5,2
K+ serum, mmol/l	3,5-5,4	3,9±0,2	3,7±0,2*	3,7±0,1*

*Note: * - p<0.05 when compared with the main group.*

When analyzing the results after 7 days from the moment of application of EN, a significant difference was obtained in the content of albumin, cholesterol and K+ blood serum (p<0.05) between the patients of the main group and the comparison groups, as well as the content of total protein and creatinine (p<0, 05) between patients of the main group and the group of standard nasogastric tube feeding.

When analyzing the results after 14 days from the moment of application of EN, a significant difference was obtained between the content of albumin, creatinine, cholesterol and K+ in the blood serum (p<0.05) between patients of the main group and the comparison groups, as well as the content of Na+ in the blood serum (p< 0.05) between patients of the main group and the group of standard nasogastric tube feeding.

A comparative analysis of the frequency of intolerance to EN in patients of the main group and the group of standard nasogastric tube feeding on the first day after the use of EN was performed (41.2% and 58.8%, respectively ($\chi 2$=2.07, 95% CI -5.87 -38.55, p=0.15), the main group

Table 4. Dynamics of biochemical parameters of blood serum in the studied groups 14 days after the use of enteral nutrition

Laboratory indicators	Rate	Main group (n=34)	Group of standard nasogastric tube feeding (n=34)	Group of standard enteral tube feeding (n=33)
Total serum protein, g/l	65-85	58,4±3,8	56,3±3,7	56,7±3,6
Serum albumin, g/l	35-50	32,7±1,8	30,1±1,2*	30,6±1,6*
Total bilirubin, μmol/l	3,4-20,8	21,1±2,1	23,4±2,7	22,4±4,8
Creatinine, μmol/l	62-115	107,9±10,8	127,9±14,7*	119,9±12,1*
Glucose, mmol/l	3,5-5,5	5,4±0,3	5,6±0,6	5,5±0,8
C-reactive protein, mg/l	0,8-8	101,6±54,5	121,5±56,2	116,6±77,6
C-reactive protein, mg/l	2,9-5,17	4,7±0,4	4,0±0,5*	4,0±0,4*
Na+ serum, mmol/l	130-149	142,2±1,8	140,7±2,7*	141,3±2,5
K+ serum, mmol/l	3,5-5,4	4,1±0,2	3,9±0,2*	3,9±0,1*

*Note: * - p<0.05 when compared with the main group.*

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and the group of standard enteral tube feeding (41.2% and 51.5%, respectively ($\chi2$=0.7, 95% CI -12.96-32.09, p=0.4), and after 7 days: 8.8% and 32.6%, respectively ($\chi2$=5.7, 95% CI 4.41-41.56, p=0.01) and 8.8 % and 30.3%, respectively ($\chi2$=4.87, 95% CI 2.34-39.48, p=0.02). When comparing the intra-abdominal pressure in patients of the main group and the group of standard nasogastric tube feeding on the first day from the moment of application of EN, this indicator was 10.6±2.9 and 11±2.9 mm Hg. (p=0.57), in the main group and the group of standard enteral tube feeding 10.6±2.9 and 10.9±3.1 mm Hg. (p=0.57) respectively; after 7 days – 10.3±2.4 and 11.8±2.8 mm Hg. (p=0.02), 10.3±2.4 and 11.4±1.9 mm Hg. (p=0.04) respectively; after 14 days – 9.3±2.0 and 10.1±2.2 mm Hg. (p=0.12), 9.3±2.0 and 10.2±1.9 mm Hg. (p=0.06) respectively. The frequency of developing infected local complications of the course of AP in the main group and the group of standard nasogastric tube feeding was also analyzed (32.4% and 35.3%, respectively ($\chi2$=0.063, 95% CI -18.85-24.28, p=0, 8), in the main group and the group of standard enteral tube feeding (32.4% and 33.3%, respectively ($\chi2$=0.006, 95% CI -20.70-22.48, p=0.9), duration of multiple organ failure (10.5±1.9 [8-16] days and 12.2±1.7 [8-16] days, respectively (p=0.0002), as well as 10.5±1.9 [8-16] days and 11.5±1.9 [6-16] days, respectively (p=0.03)), duration of hospital stay (50.7±28.8 [23-124] days and 55.5±30.5 [27-124] days, respectively (p=0.5), as well as 50.7±28.8 [23-124] days and 54.9±32.6 [20-119] days, respectively (p=0.5)) and fatal cases (11.8% and 14.7%, respectively) ($\chi2$=0.123, 95% CI -14.10-19.88, p=0.7), as well as 11.8% and 12.1%, respectively ($\chi2$=0.001, 95% CI -16.25-17.07, p=0, 9)).

Discussion

EN is an important component of complex therapy in patients with a severe course of AP. The issues of the time of onset and the method of introduction of the food mixture into the gastrointestinal tract remain debatable, which is associated with the opinion of the need for «pancreatic rest» in the early period of the disease and the high frequency of development of intolerance to EN (Li et al., 2019). At the same time, there are studies that prove the safety and absence of a reliable difference in the frequency of complications when using the nasogastric or nasojejunal method of introducing a mixture for nutrition in patients with AP (Jabłońska et al., 2021). We have improved the EN protocol in patients with a severe course of AP, which is based on the determination of the timing of restoration of intestinal absorption as one of the main criteria for the initiation of enteral tube feeding in patients of this category, the use of antiflutal agents to prevent the development of intestinal complications in EN, and the safety of nasogastric administration of mixtures for enteral food. According to the results of our study, 14 days after the start of treatment, when using the proposed EN protocol in patients with a severe course of AP, a significant difference was obtained between the content of albumin, creatinine, cholesterol and K+ blood serum (p<0.05) between patients of the main group and comparison groups, as well as the content of Na+ in blood serum (p<0.05) between patients of the main group and the group of standard nasogastric tube feeding. It has also been proven that the use of the proposed protocol of nutritional support significantly reduces the frequency of EN intolerance in the first 7 days of treatment by 23.6% ($\chi2$=5.7, 95% CI 4.41-41.56, p=0.01) in compared with the group of patients where standard nasogastric tube feeding is used, by 21.5% ($\chi2$=4.87, 95% CI 2.34-39.48, p=0.02) compared with the group of standard enteral tube feeding, as well as the duration of multiple organ failure from 12.2±1.7 days to 10.5±1.9 days in comparison with the group of patients where standard nasogastric tube feeding was used (p=0.0002) and from 11.5±1, 9 days to 10.5±1.9 days compared to the group of standard enteral tube feeding (p=0.03).

Conclusions

Determination of the terms of restoration of intestinal absorption is one of the main criteria for the initiation of enteral nutrition in patients with severe acute pancreatitis.

Application of the proposed protocol of enteral nutrition significantly reduces the frequency of intolerance of nutritional support in the first 7 days of treatment by 23.6% ($\chi2$=5.7, 95% CI 4.41-41.56, p=0.01) compared to the control group patients, where standard nasogastric tube feeding is used, by 21.5% ($\chi2$=4.87, 95% CI 2.34-39.48, p=0.02) compared to the group of standard enteral tube feeding.

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There is no significant difference between the frequency of local infectious complications, the duration of multiple organ failure, the duration of hospital stay, and deaths when comparing nasogastric and enteral feeding mixtures in patients with severe acute pancreatitis.

The use of the proposed protocol of enteral nutrition in patients with severe acute pancreatitis leads to a decrease in the duration of multiple organ failure from 12.2±1.7 days to 10.5±1.9 days in comparison with the group of patients who used standard nasogastric tube feeding (p= 0.0002) and from 11.5±1.9 days to 10.5±1.9 days in comparison with the group of standard enteral tube feeding (p=0.03).

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Conflict of interests

Authors have no conflict of interest to declare.

Consent for publication

All authors have read and approved the final version of this manuscript. All authors agreed to publish this manuscript.

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Удосконалення технологій ентерального харчування у хворих з тяжким перебігом гострого панкреатиту

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Анотація: при тяжкому перебігу гострого панкреатиту доцільним вважається ранній початок ентерального харчування (24-72 год від моменту госпіталізації) шляхом назогастрального або назоеюнального введення суміші, що асоціюється зі зниженням частоти інфекційних ускладнень на 24% та смертності на 32%. Однак, у 30,5-65,7% пацієнтів може виникати непереносимість даного виду нутритивної підтримки. Метою дослідження було покращення результатів лікування хворих на тяжкий гострий панкреатит шляхом удосконалення технологій ентерального харчування. В дослідженні приймали участь 101 хворий на тяжкий гострий панкреатит, що були розділені на основна групу, де проводилось ентеральне харчування за удосконаленим протоколом – 34 пацієнти, група порівняння №1, де проводилось стандартне назогастральне харчування – 34 пацієнти та група порівняння №2, де проводилось стандартне ЕХ – 33 пацієнти. Оцінку ефективності ентерального харчування в досліджуваних групах проводили шляхом аналізу та порівняння біохімічних показників сироватки крові, частоти виникнення непереносимості нутритивної підримки, інфекованих локальних ускладнень, летальності, тривалості поліорганної недостатності та перебування пацієнтів в стаціонарі. При використанні запропонованого протоколу ентерального харчування у хворих з тяжким перебігом гострого панкреатиту через 14 діб з моменту початку лікування було отримано достовірну різницю між вмістом альбуміну, креатиніну, холестерину та К+ сироватки крові ($p<0,05$) між пацієнтами основної групи та груп порівняння, а також вмістом Na+ сироватки крові ($p<0,05$) між пацієнтами основної групи та групи стандартного назогастрального зондового харчування. Застосування запропонованого протоколу ентерального харчування достовірно зменшує частоту виникнення непереносимості нутритивної підтримки в перші 7 діб лікування на 23,6% ($\chi2=5,7$, 95% ДІ 4,41-41,56, $p=0,01$) в порівнянні з групою хворих, де застосовується стандартне назогастральне зондове харчування, на 21,5% ($\chi2=4,87$, 95% ДІ 2,34-39,48, $p=0,02$) в порівнянні з групою стандартного ентерального зондового харчування, а також тривалості поліорганної недостатності з 12,2±1,7 діб до 10,5±1,9 діб в порівнянні з групою хворих, де застосовувалось стандартне назогастральне зондове харчування ($p=0,0002$) та з 11,5±1,9 діб до 10,5±1,9 діб в порівнянні з групою стандартного ентерального зондового харчування ($p=0,03$). Використання запропонованої технології ентерального харчування у хворих з тяжким перебігом гострого панкреатиту покращує результати лікування шляхом зменшення тривалості поліорганної недостатності та частоти виникнення непереносимості даного виду нутритивної підтримки.

Ключові слова: гострий панкреатит, ентеральне харчування, кишкова абсорбція, нутритивна підтримка, лікування.

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Prognostic Factors for Parasagital Meningiomas Recurrence

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Abstract: *the study is relevant due to high prevalence of this type of pathology. Meningiomas account for 18% to 34% of all primary brain tumors. Parasagital meningiomas occur in 24.3% to 38.6% of cases. Despite their predominantly benign nature, parasagital meningiomas are more likely to recur/continue growing than meningiomas in other areas (18% to 40%). The key purpose of the study was to analyze the prognostic factors of parasagital meningiomas recurrence/continued growth, which will eventually improve surgical treatment outcomes. We conducted a retrospective and prospective analysis of 199 parasagital meningioma patients who were treated in Mechnikov Dnipropetrovsk Regional Clinical Hospital, Dnipropetrovsk Regional Council, from 2000 to 2021 inclusive. This article is based on a comparative analysis of the results of examination and surgical treatment and further analysis of pathohistological conclusion in two study groups. The first group included 180 (90.5%) patients with no recurrence/continued growth and second group included 19 (9.5%) patients with detected postoperative parasagital meningioma (PM) recurrence/continued growth. The selected patients were analyzed for demographic data (gender, age); computed tomography and magnetic resonance brain imaging results before and after adding an intravenous contrast (in terms of key characteristics); angiographic studies data (computed tomography angiography/ selective digital subtraction cerebral angiography); surgical radicality; pathohistological conclusions; recurrence-free period duration (one to 20 years after the surgery). In the follow-up period, 19 (9.5%) patients had PM recurrence/continued growth. In the first year after the surgery, only 2 of those patients had continued PM growth; within 5 years (60 months), 12 patients; within 10 years, 17 patients; the percentage of no- recurrence patients, based on censored data (recurrence-free survival), was 99.0% (95% CI, 97,6-100), 93,1% (95% CI, 89.3-96.9). and 87.5% (95% CI, 81.6-93.4) in the above follow-up periods. The actual median time to recurrence in our study was 44.1 (25.7; 85.4) months. It means that the majority (12 of 19 patients; 63.2%) of continued PM growth was detected within 5 years after the surgery. The last case of PM recurrence was diagnosed after 13 years (154.5 months) of the follow-up. Thus, recurrence-free 5- and 10-year survival in PM patients is as follows: in case of total tumor removal (Simpson I), 96.0% and 85.5%, respectively; in case of non-radical removal (Simpson II-V), 88.9% ($p<0.05$) and 81.9% ($p<0.05$), respectively. At the same time, non-radical surgery in type I-II SSS invasion by the PM reduces 5- and 10-year recurrence-free survival to 86.6% ($p<0.01$) and 78.3% ($p<0.01$), respectively; in case of tumor size of up to 54 mm, the indicators are 95.5% and 91.4%; with tumor size >54 mm, they are as low as 87.5% ($p<0.001$)*

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and 72.5% (p<0.001); in case of type I-III or V-VI SSS damage according to M. P. Sindou and J. E. Alvernia, 94.0% and 89.1%; and in case of type IV invasion, 66.5% (p<0.01) and 43.5% (p<0.001); in female patients, 95.2% and 88.5%; in male patients, 84.8% (p<0.05) and 73.0% (p<0.01). According to the Cox regression proportional hazards model, the relative risk of tumor recurrence/continued growth increases by: 7.04 times (95% CI, 2.33-21.2) in case of initial PM size >54 mm (p<0.001); 5.57 times (95% CI, 1.27-24.34) in case of non-radical (Simpson II-V) tumor removal during primary intervention (P<0.05); 10.1 times (95% CI, 1.31-78.1) in case of type I-II SSS invasion by the PM or incomplete (Simpson II-V) tumor removal (p<0.05); 3.25 times (95% CI, 1.32-8.02) in male patients (p<0.01); 3.33 times (95% CI, 1.10-10.12) in case of type IV SSS invasion (according to M.P. Sindou and J.E. Alvernia) (p<0.05). Adequate analysis of the results obtained will help the neurosurgeons plan the optimal surgery volume and ensure further postoperative recurrence-free period and improved long-term treatment outcomes.

Keywords: meningioma, prognosis, recurrence, risk factors, superior sagittal sinus, treatment outcome.

Introduction

Meningiomas account for 18% to 34% of all primary brain tumors. Parasagital meningiomas occur in 24.3% to 38.6% of cases. According to existing studies, parasagital meningiomas are more likely to recur/continue growing than meningiomas in other areas (18% to 40%). Low-grade meningiomas are the most common parasagital meningiomas (Behzadmehr et al., 2021, Balik et al., 2020, Cucu et al., 2020). Topographic and anatomical tumor connections with the surrounding intracranial structures is the key problem in trying to prevent the recurrence. Neoplasm location in close proximity to the superior sagittal sinus and the involvement of the sinus and parasagital emissary veins in the pathological process complicate the task of radical (Simpson I), and still safe, surgical removal. (Salah et al., 2019, Cucu et al., 2020). In this regard, the neurosurgeon is faced with a choice: either to attempt a radical (Simpson I) parasagital meningioma resection at the cost of a high risk of severe irreversible intraoperative and postoperative complications or opt to more gentle surgery, maintaining/improving the patient's functional state but, at the same time, exposing the patient to a higher risk of meningioma recurrence/continued growth.

It was found that parasagital meningioma mostly recurs in male patients (up to 70%). Continued tumor growth is more common in patients under 60 (61.5%) vs. patients over 60 (38.5%) (Balik et al., 2020).

According to the literature, the average time to recurrence is 97 months (59 to 135 months) for atypical meningiomas (WHO's grade II). At the same time, 77% of patients had recurrence-free survival in 5 years and 46% in 10 years. However, for benign meningiomas (WHO's grade I) there was no significant difference between 5- and 10-year recurrence-free survival — 98% and 93%, respectively. Based on 7 studies, the WHO's grade I parasagital meningioma recurs, in average, in 11.4% of patients; WHO's grade II, in 25% to 55.1% of patients. Moderate- to low-grade meningiomas (grades II-III) recur in up to 61% of patients (Behzadmehr et al., 2021, Balik et al., 2020).

In case of type II-VI superior sagittal sinus invasion according to M.P. Sindou and J.E. Alvernia, the 2-year recurrence reaches 33.3%; type I invasion according to M.P. Sindou and J.E. Alvernia, 8.3% (in average). In patients with type I-III sinus invasion according to M.P. Sindou and J.E. Alvernia, the risk of recurrence is significantly lower than in patients with more aggressive (type IV-VI) sinus lesion according to M.P. Sindou and J.E.Alvernia: 4.2% vs. 9.4%, respectively. However, there was no significant difference in the recurrence rate between the following groups of patients: type I vs. type II-VI; type I-II vs. type III-IV, and type I-IV vs. type V-VI according to M.P. Sindou and J.E. Alvernia. The risk of recurrence demonstrates insignificant dependence on the meningioma location expressed in a third of the superior sagittal sinus (Behzadmehr et al.,

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2021). However, there are isolated reports that 54% to 70% of all recurrences are in the middle third of the superior sagittal sinus, which is associated with topographic and anatomical characteristics of meningioma in this particular area (Balik et al., 2020).

After radical (Simpson I) removal of parasagital meningioma as low as 1% of patients have any recurrence; after a substantially total removal (Simpson I-II), 12.2%; and after subtotal removal (Simpson III-V), up to 24% (Behzadmehr et al., 2021, Cucu et al., 2020).

Results of imaging studies (computed tomography and magnetic resonance imaging) belong to other prognostic factors of tumor recurrence. Such factors, particularly, include neoplasm volume, which in almost 70% of cases exceed the average value. In some studies, (Nakasu et al., 2020, Siempis et al., 2020, Huang et al. 2019), almost 100% of recurrences had fuzzy edges of meningioma on magnetic resonance imaging, while other researchers reported no such association (Behzadmehr et al., 2021, Balik et al., 2020). In addition, it is reported that the majority of patients (61.5%) with recurrent meningioma experienced severe perifocal brain edema (Nakasu et al., 2020, Siempis et al., 2020).

Such conflicting data is still a subject of debate and raise questions about the role of the identified factors in the re-growth of meningioma. That is why the objective of our study was to determine the prognostic factors for parasagital meningioma recurrence/continued growth based on literature review and analysis of our own clinical experience.

Objective

Improving surgical parasagital meningiomas treatment outcomes by determining prognostic factors for their recurrence/continued growth.

Materials and Methods

We conducted retrospective and prospective analysis of 199 (100%) parasagital meningioma patients who were treated in Mechnikov Dnipropetrovsk Regional Clinical Hospital, Dnipropetrovsk Regional Council, from 2000 to 2021 inclusive.

This article is based on a comparative analysis of the results of examination and surgical treatment and further analysis of pathohistological conclusion in two study groups. The first group included 180 (90.5%) patients with no recurrence/continued growth and second group included 19 (9.5%) patients with detected postoperative parasagital meningioma (PM) recurrence/continued growth.

The selected patients were analyzed for demographic data (gender, age); computed tomography and magnetic resonance brain imaging results before and after adding an intravenous contrast (in terms of key characteristics); angiographic studies data (computed tomography angiography/selective digital subtraction cerebral angiography); surgical radicality; pathohistological conclusions; recurrence-free period duration (one to 20 years after the surgery).

Surgical radicality was identified according to Simpson I-V scale (Gatterbauer et al., 2017). The risk of recurrence was analyzed individually in the category of patients who had radical (Simpson I) parasagital meningioma removal, which is understood as macroscopically total tumor removal with matrix excision, and in the category of patients with non-radical removal (Simpson II-V).

Meningioma malignancy was determined according to the WHO World Health Organization (WHO) classification (Goldbrunner et al., 2016): Grade I = benign meningioma, Grade II = atypical meningioma, Grade III = anaplastic meningioma.

Brain computed tomography (CT) was performed using Optima CT660 | GE Healthcare, which assessed the meningioma's impact on adjacent bone: hyperostosis, bone destruction, extracranial tumor spread.

Brain magnetic resonance imaging (MRI) was performed using Toshiba Excelart Vantage 1.5 T. Key neuroimaging (T2WI, T1WI, DWI, and T1WI modes + intravenous contrast, axial, sagittal, and coronal planes) results included: location relative to the superior sagittal sinus (anterior, middle, posterior thirds); tumor size based on its largest linear size; tumor edges contrast (the edges were considered "clear" when a gap filled with cerebrospinal fluid was seen around the tumor perimeter); brain invasion (described if it was impossible to draw boundaries between the tumor and the surrounding brain tissue); signal intensity

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(hyper-, hypo-, isointensive, homogeneous, heterogeneous); intratumoral inclusions (necrosis, hemorrhage, cysts, calcification); presence and severity of perifocal edema.

Computed tomography angiography was performed using PHILIPS Mx 8000 IDT. Selective subtraction digital cerebral angiography was performed in the Endovascular Center, Mechnikov Dnipropetrovsk Regional Clinical Hospital, Dnipropetrovsk Regional Council, using Innova IGS 540 (GE Healthcare). Ultravist 370 and Visipaque 320 contrast agents were used for angiographic studies. The superior sagittal sinus damage degree was based on M.P. Sindou and J.E. Alvernia classification (types I-VI) (Ricci et al., 2017). The risk of parasagital meningioma recurrence was individually assessed in patients with types I-II, III-IV, and V-VI superior sagittal sinus damage according to M.P. Sindou and J.E.Alvernia.

Meningioma re-growth after its radical (Simpson I) removal was considered as its *recurrence*. Residual tumor growth was called the *continued growth* of a meningioma. This term was also used to describe the transformation of a lower-grade meningioma to a higher-grade meningioma (e.g., from the WHO's grade I to grade II) (Buerki et al., 2018). In our study, tumors that had continued growth included those that underwent Simpson II-V removal.

Postoperatively, all patients were subjected to dynamic monitoring by a neurologist and serial follow-up computed tomography and magnetic resonance imaging. The first follow-up brain magnetic resonance imaging was performed 6 months after the surgery, thereafter it was performed annually (subject to stable neurological status). If existing neurological symptoms worsened or new symptoms were detected, an unscheduled follow-up brain MRI was performed.

Data was processed and analyzed using STATISTICA 10 (StatSoft ® Inc., USA, license no. STA862D175437Q) and SPSS 17.0 (IBM, USA). Based on the law of quantitative data distribution (Shapiro-Wilk test), the following parametric and nonparametric characteristics and comparison methods were used: for normal distribution — arithmetic mean (M), standard deviation (SD), and Student's t score (t); for abnormal distribution — median (Me), interquartile range (LQ; HQ), and Mann-Whitney value (U). Probability of differences in categorical data was estimated using the Pearson chi-square value ($\chi 2$) without Yates chi-square correction. Prognostic significance of various factors for assessing the probability of postoperative tumor recurrence was determined using ROC analysis by determining the point of differentiation of indicator values in the recurrence and no-recurrence groups and calculating the area under ROC curve (AUC) and operational characteristics (sensitivity, specificity). The recurrence-free survival indicators depending on certain factors (predictors) were analyzed using the life tables, Kaplan-Meier curves, and the Cox proportional hazards regression model with the risk ratio (RR) calculated in a 95% confidence interval (95% CI). Differences in survival rates in the early follow-up period were assessed using the Gehan-Wilcoxon Test (GWT); in the entire follow-up period, using the log rank test (LRT). The critical level of statistical significance when testing all hypotheses (P) was assumed to be ≤ 0.05 and the trend was assessed for $p<0.1$.

Results

In the follow-up period, 19 (9.5%) patients had PM recurrence/continued growth. In the first year after the surgery, only 2 of those patients had continued PM growth; within 5 years (60 months), 12 patients; within 10 years, 17 patients; the percentage of no- recurrence patients, based on censored data (recurrence-free survival), was 99.0% (95% CI, 97,6-100), 93,1% (95% CI, 89.3-96.9). and 87.5% (95% CI, 81.6-93.4) in the above follow-up periods. The actual median time to recurrence in our study was 44.1 (25.7; 85.4) months. It means that the majority (12 of 19 patients; 63.2%) of continued PM growth was detected within 5 years after the surgery. The last case of PM recurrence was diagnosed after 13 years (154.5 months) of the follow-up.

A comparative analysis of key characteristics of patients and neoplasms in 2 study groups was used to determine the factors associated with the post-surgery PM recurrence (see Table 1).

As can be seen from Table 1, the first group (no recurrence) was dominated by female patients — 133 (73.9%), the age of patients ranged from 19 to 75 and averaged 53.9±12.1 years. In the second group (recurrence), there were 9 female patients

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Table 1. General characteristics of patients and neoplasms in the study groups

Characteristics		Group 1 (no recurrence) n=180	Group 2 (with recurrences) n=19	Statistical significance of inter-group differences
Gender	Female	133 (73.9%)	9 (47.4%)	χ2=5.91; p=0.015
	Male	47 (26.1%)	10 (52.6%)	
Age, years	18-44	34 (18.9%)	2 (10.5%)	χ2=0.81; p=0.368
	45-59	79 (43.9%)	13 (68.4%)	χ2=4.16; **p=0.041**
	60-75	67 (37.2%)	4 (21.1%)	χ2=1,96; p=0,162
	Average age, M±SD	53.9±12.1	55.8±9.6	t=0.67; p=0.506
Parasagital meningioma location relative to the superior sagittal sinus	Anterior third	56 (31.1%)	5 (26.3%)	χ2=0,19; p=0,666
	Middle third	99 (55.0%)	10 (52.6%)	χ2=0.04; p=0.844
	Posterior third	25 (13.9%)	4 (21.1%)	χ2=0,71; p=0,400
	Left	84 (46.7%)	10 (52.6%)	χ2=0.245; p=0.62
	Right	78 (43.3%)	7 (36.9%)	χ2=0,296; p=0,586
	Bilateral	18 (10.0%)	2 (10.5%)	χ2=0,005; p=0,942
Average size, IU (LQ; HQ) (mm)		48 (35; 60)	60 (55; 75)	U=842.5; **p<0.001**
SSS invasion according to M.P. Sindou and J.E. Alvernia	Type I	112 (62.2%)	12 (63.2%)	χ2=0.006; p=0.936
	Type II	13 (7.2%)	1 (5.3%)	χ2=0,10; p=0,751
	Type III	16 (8.9%)	-	χ2=1.84; p=0.175
	Type IV	10 (5.6%)	4 (21.1%)	χ2=6.31; **p=0.012**
	Type V	11 (6.1%)	1 (5.3%)	χ2=0,02; p=0,883
	Type VI	18 (10.0%)	1 (5.3%)	χ2=0.45; p=0.504
	Category I-II	125 (69.4%)	13 (68.4%)	χ2=0,08; p=0,927
	Category III-IV	26 (14.5%)	4 (21.1%)	χ2=0,59; p=0,444
	Category V-VI	29 (16.1%)	2 (10.5%)	χ2=0.41; p=0.523

(47.4%) and 10 male patients (52.6%), p<0.05 between the groups; average age was 55.8±9.6 (p>0.05). According to the WHO classification by age, the first group's age category of 18 to 44 included 34 (18.9%) patients; age category of 45 to 59 included 79 (43.9%) patients, and age category of 60 to 75 included 67 (37.2%) patients. In the second study group, 2 (10.5%) patients were assigned to the first age category, 13 (68.4%) to the second, and 4 (21.1%) to the third. Despite the absence of significant differences between the groups in terms of average patient's age, patients from the age category of 45 to 59 dominated the recurrence group (p<0.05).

We found no significant association between the PM location relative to the superior sagittal sinus (SSS) and tumor recurrence (p>0.05). In the first group, PM located in the anterior third of the SSS occurred in 56 (31.1%) patients, the middle third in 99 (55.0%) patients, and the posterior third in 25 (13.9%) patients. 84 (46.7%) had meningiomas growing to the left, 78 (43.3%) growing to the right, and 18 (10.0%) had bilateral meningiomas. 5 (26.3%) patients had recurrent meningiomas in the anterior third of the SSS, 10 (52.6%) in the middle third, and 4 (21.1%) in the posterior third. Among them, 10 (52.6%) patients had a tumor node on the left side of the sinus, 7 (36.9%) on the right side, and 2 (10.5%) patients had bilateral tumor spread. Average meningioma size in the second group was 1.3 times higher than in the first group — 60 (55; 75) (mm) vs. 48 (35; 60) (mm), p<0.001.

According to M.P. Sindou and J.E. Alvernia, 112 (62.2%) patients of the first group had type I

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SSS invasion, 13 (7.2%), had type II; 16 (8.9%) had type III, 10 (5.6%) had type IV, 11 (6.1%) had type V, and 18 (10.0%) had type VI. 125 (69.4%) patients were categorized to type I-II according to M.P. Sindou and J.E. Alvernia, 26 (14.5%) to types III-IV, and 29 (16.1%) to type V-VI sinus occlusion. In the recurrence group, parasagital meningiomas invaded the SSS as follows: type I according to M.P. Sindou and J.E. Alvernia, 12 (63.2%) patients; type II, 1 (5.3%); type III, 0 (0%); type IV, 4 (21.1%); type V, 1 (5.3%); type VI, 1 (5.3%). Type I-II category included 13 (68.4%) patients, type III-IV 4 (21.1%) patients, and type V-VI 2 (10.5%) patients. In terms of the SSS invasion by the tumor, the recurrence group had higher frequency of type IV sinus occlusion: 21.1% vs. 5.6% in the no-recurrence group ($p<0.05$).

127 of 180 (70.6%) patients in the first group underwent brain magnetic resonance imaging (MRI) with intravenous contrast added in 88 (69.3%) cases. 73 (57.5%) patients had hyperintensive meningioma, 8 (6.3%) hypointensive, 16 (12.6%) isointensive, and 30 (23.6%) heterogeneous (see Table 2). Perifocal edema was detected in 46 (36.2%) patients, intratumoral necrosis in 37 (29.1%), dural tail in 29 (22.8%), and signs of brain tissue tumor invasion in 9 (7.1%). In the second group, 12 of 19 (63.2%) patients underwent brain MRI with intravenous contrast added in 10 of 12 (83.3%) cases. Hyperintensive meningioma was diagnosed in 7 (58.3%) patients, isointensive in 2 (16.7%), heterogeneous in 3 (25.0%), with no cases of hypointensive PM. Perifocal edema was detected in 5 (41.7%) patients, intratumoral necrosis in 5 (41.7%), and dural tail in 3 (25.0%). 3 (25.0%) patients of the second group had fuzzy meningioma edges and signs of brain tissue tumor invasion, which significantly exceeded the value in the first group (7.1%) with $p<0.05$.

119 (66.1%) patients of the first group underwent brain computed tomography (CT); in 64 (53.8%) cases, intravenous contrast was added. Among the bone manifestations of meningioma, hyperostosis was detected in 27 (22.7%) patients, bone destruction in 21 (17.6%) patients (see Table 2). Similar brain CT scan was performed in 14 (73.7%) patients of the second group; in 50.0% of cases (7 of 14), intravenous contrast was added. Among the bone manifestations of meningioma, hyperostosis was detected in 3 (21.4%) patients and bone destruction in 2 (14.3%) patients.

Study groups comparison in terms of selected brain MRI and CT results (see Table 2) showed no dependence of PM recurrence/continued growth on signs of adjacent bone invasion, T2WI signal intensity, presence of perifocal edema, intratumoral inclusions, or signs of dural tail ($p>0.05$). At the same time, patients with MR signs of brain tumor invasion had significantly higher ($p<0.05$) PM recurrence rate.

Radical (Simpson I) surgical meningioma removal in the first group was achieved in 90 (50.0%) patients (see Table 2). The remaining 90 (50.0%) patients underwent non-radical (Simpson II-V) tumor removal. Among them, 56 (31.1%) patients had Simpson II removal, 14 (7.8%) Simpson III, and 20 (11.1%) Simpson IV. In the second study group, radical surgery was only performed in 2 (10.5%) cases, which is significantly less than in the no-recurrence group ($p=0.001$). The remaining 17 (89.5%) patients underwent non-radical surgery, 11 (57.9%) of which had Simpson II removal, 2 (10.5%) Simpson III, and 4 (21.1%) Simpson IV.

Note that the frequency of continued PM growth was significantly higher after non-radical removal of type I-II SSS invasion neoplasms — 92.3% vs. 43.2% ($p<0.001$) (see Table 3). In SSS type III-IV and V-VI invasion tumors, there was no significant association between continued growth surgical radicality ($p>0.05$). That is, the risk of PM recurrence increases if type I-II SSS invasion tumor is not totally removed.

According to histological examination of removed neoplasm specimens, 169 of 199 PMs (84.9%) were benign (grade I), 14 (7.0%) met the criteria of grade II (atypical meningioma), and 16 (8.1%) grade III (anaplastic meningioma). At the same time, recurrence/continued growth of grade I PMs was detected in 14 (8.3%) patients, grade II in 3 (21.4%), and grade III in 2 (12.5%).

Analysis of histological PM structure in the study groups (see Table 2) showed that among 155 (86.1%) benign meningiomas in the first group, mixed meningiomas were diagnosed in 39 (21.7%) cases, meningoteliomatous in 54

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Table 2. Comparative study groups characteristics in terms of results of diagnostic and histological studies and surgeries

Characteristics		Group 1 (no recurrence)	Group 2 (with recurrences)	Statistical significance of inter-group differences
Magnetic resonance brain imaging (n1=127, n2=12)				
T2WI mode density	Hyperintensive	73 (57.5%)	7 (58.3%)	$\chi2$=0.003; p=0.954
	Hypointensive	8 (6.3%)	-	$\chi2$=0.80; p=0.370
	Isointensive	16 (12.6%)	2 (16.7%)	$\chi2$=0.16; p=0.688
	Heterogeneous	30 (23.6%)	3 (25.0%)	$\chi2$=0.01; p=0.915
Perifocal edema		46 (36.2%)	5 (41.7%)	$\chi2$=0.14; p=0.708
Intrathumoral inclusions		37 (29.1%)	5 (41.7%)	$\chi2$=0.82; p=0.366
Dural tail		29 (22.8%)	3 (25.0%)	$\chi2$=0,03; p=0,865
Brain invasion		9 (7.1%)	3 (25.0%)	$\chi2$=4.46; p=0.035
Computed tomography brain imaging (n1=119, n2=14)				
Hyperostosis		27 (22.7%)	3 (21.4%)	$\chi2$=0.01; p=0.915
Bone destruction		21 (17.6%)	2 (14.3%)	$\chi2$=0.10; p=0.753
Surgical intervention characteristics (n1=180, n2 = 19)				
Surgical radicality according to Simpson grading scale	Simpson I	90 (50.0%)	2 (10.5%)	$\chi2$=10.77; p=0.001
	Simpson II-V	90 (50.0%)	17 (89.5%)	
	Simpson II	56 (31.1%)	11 (57.9%)	$\chi2$=5.52; p=0.019
	Simpson III	14 (7.8%)	2 (10.5%)	$\chi2$=0.18; p=0.675
	Simpson IV	20 (11.1%)	4 (21.1%)	$\chi2$=1.60; p=0.206
	Simpson V	-	-	
Histological neoplasm examination (n1 = 180, n2 = 19)				
Meningioma malignancy and histological type according to the World Health Organization (WHO) classification	Grade I	155 (86.1%)	14 (73.7%)	$\chi2$=2.07; p=0.150
	Mixed	39 (21.7%)	2 (10.5%)	$\chi2$=1.30; p=0.254
	Meningoteliomatous	54 (30.0%)	9 (47.4%)	$\chi2$=2.40; p=0.122
	Fibrous	23 (12.8%)	1 (5.3%)	$\chi2$=0.92; p=0.339
	Transitional	3 (1.7%)	-	$\chi2$=0.32; p=0.571
	Psamomatous	32 (17.8%)	2 (10.5%)	$\chi2$=0.64; p=0.424
	Angiomatous	3 (1.7%)	-	$\chi2$=0.32; p=0.571
	With severe lymphoplasmocytic infiltration	1 (0.6%)	-	$\chi2$=0.11; p=0.745
	Grade II (atypical)	11 (6.1%)	3 (15.8%)	$\chi2$=2.46; p=0.117
	Grade III (anaplastic)	14 (7.8%)	2 (10.5%)	$\chi2$=0.18; p=0.675

Note: n_1 = the number of patients in the study group 1; n_2 = the number of patients in the study group 2

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Table 3. Surgical radicality depending on the SSS invasion by parasagital meningioma in the study groups

Radical meningioma removal	SSS damage according to M.P. Sindou and J.E. Alvernia classification					
	I-II		III-IV		V-VI	
	Group 1 (n=125)	Group 2 (n=13)	Group 1 (n=26)	Group 2 (n=4)	Group 1 (n=29)	Group 2 (n=2)
Simpson I	71 (56.8%)	1 (7.7%)	4 (15.4%)	–	15 (51.7%)	1 (50.0%)
Simpson II-IV	54 (43.2%)	12 (92.3%)	22 (84.6%)	4 (100.0%)	14 (48.3%)	1 (50.0%)
Statistical significance of inter-group differences	$\chi2$=11.38; p<0.001		$\chi2$=0.71; p=0.399		$\chi2$=0.002; p=0.962	

(30.0%), fibrous in 23 (12.8%), transient in 3 (1.7%), psamomatous in 32 (17.8%), angiomatous in 3 (1.7%), and meningiomas with severe lymphoplasmocytic infiltration in one case (0.6%). 11 (6.1%) patients had moderate-grade meningiomas (grade II) and 14 (7.8%) had low-grade meningiomas. In the continued PM growth group, benign meningiomas were detected in 14 (73.7%) patients, including mixed meningiomas in 2 (10.5%) cases, meningoteliomatous meningiomas in 9 (47.4%) cases, fibrous meningioma in 1 (5.3%) case, and psamomatous meningiomas in 2 (10.5%) cases. Grade II (atypical) meningioma was detected in 3 (15.8%) patients and grade III (anaplastic) meningioma in 2 (10.5%).

In general, study groups' indicators comparison in terms of histological PM structure showed insignificant differences (p>0.05), which can be explained by low number of cases of grade II and grade III PMs (14 and 16 cases, respectively) and sufficiency of surgical intervention during primary tumor removal. The first, no-recurrence, group, among 12 patients of moderate- and low-grade PM with type I SSS invasion according to M.P. Sindou and J.E. Alvernia, 7 (58.3%) underwent radical surgery (Simpson I); in the second group, 4 patients with type I sinus occlusion underwent Simpson II surgery (p=0.042 based on χ^2). The above may indicate a low informative value of tumors malignancy to predict the risk of postoperative PM recurrence/continued growth, which requires further research.

Significant differences between the study groups based on comparative analysis allowed determining the factors (predictors) associated with postoperative PM recurrence. In particular, tumor recurrence occurs significantly more often in men than in women (low direct correlation, r=0.17, p=0.015) and in the 45 to 59 age group (low direct correlation, r=0.14, p=0.042). Higher risk of tumor recurrence (r=0.26, p<0.001) is associated with increased tumor size, type IV SSS invasion according to M. P. Sindou and J. E. Alvernia (r=0.18, p=0.012), and Simpson II-V incomplete tumor removal (r=0.23, p=0.001), especially in case of type I-II SSS invasion (r=0.29, p<0.001). According to the MRI, the risk of PM recurrence can be reliably indicated by such neuroimaging sign of meningioma brain invasion as fuzzy tumor edges (low direct correlation, r=0.18, p=0.035). At the same time, in cases of radical tumor removal (Simpson I), recurrence was significantly less common (inverse correlation is low: r=-0,23, p<0,001).

Predictive potential of the above factors for PM recurrence/continued growth was assessed using ROC analysis and Cox proportional hazards regression models. The latter made it possible to assess the predictors impact on the risk of recurrence within 20 years (240 months) of the follow-up, given all primary data, including incomplete (censored) data.

The ROC analysis demonstrated that non-radical (Simpson II-V) PM removal and large tumor sizes have the highest prognostic potential in determining the risk of continued PM growth, especially in type I-II SSS invasion (see Fig. 1, Table 4).

With an initial PM size of >54 mm (area under ROC curve, 0.754 (95% CI, 0.688-0.812)), the rel-

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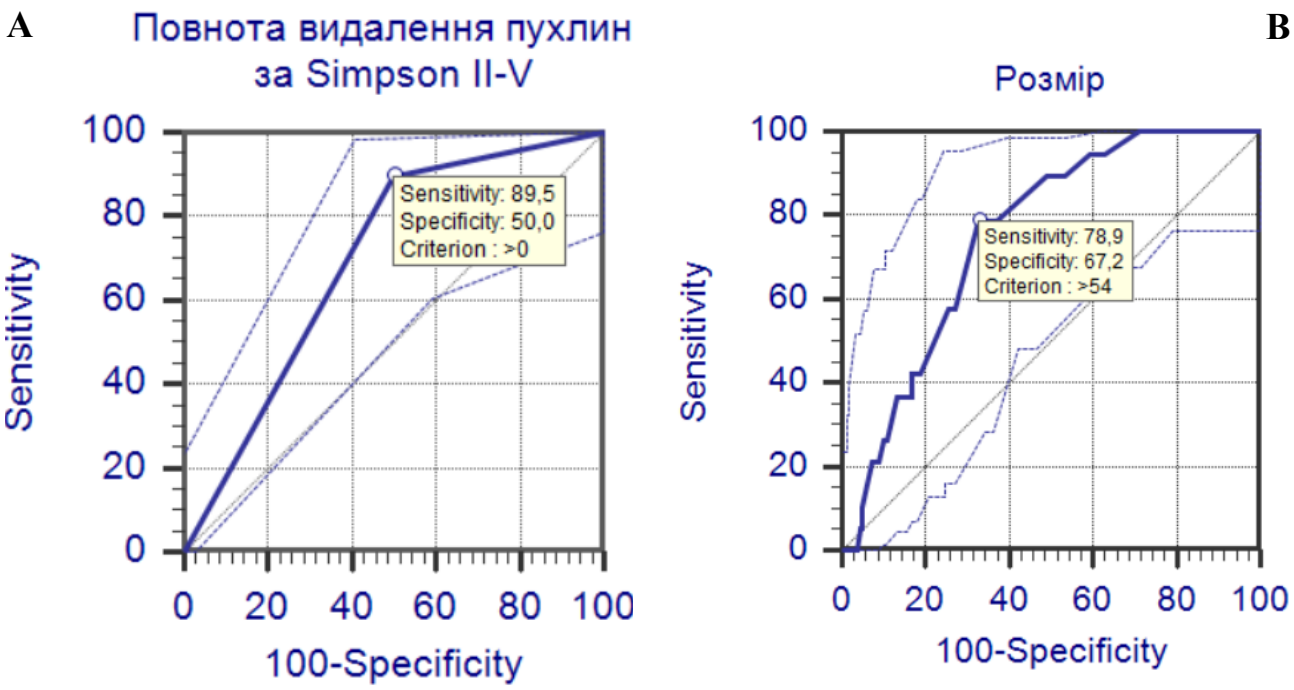

Fig. 1. ROC curves of surgical radicality (A) and PM size (B) in determining the risk of continued PM growth within 20 years of the follow-up

Table 4. Prognostic significance of individual factors associated with postoperative PM recurrence

Indicator	ROC analysis				Cox model	
	Criterion (cut-off threshold)	Area under the ROC curve (AUC, 95% CI)	AUC significance level (p)	Se/Sp (%)	RR (95% CI)	Signif-icance level (p)
Patient's gender	male	0.633 (0.562-0.700)	0.046	52.6/73.9	3.25 (1.32-8.02)	0.01
Age, years	45-59	0.623 (0.551-0.690)	0.087	68.4/56.1	2.27 (0.86-6.01)	0.098
SSS invasion according to M.P. Sindou and J.E. Alvernia classification)	IV	0.577 (0.508-0.647)	0.099	21.1/94.4	3.33 (1.10-10.12)	0.034
MRI sign of brain tissue tumor invasion	Yes	0.590 (0.503-0.672)	0.177	25.0/92.9	3.56 (0.96-13.17)	0.057
Surgical radicality according to Simpson grading scale	II-V	0.697 (0.628-0.760)	0.005	89.5/50.0	5.57 (1.27-24.34)	0.023
Surgical radicality in type I-II SSS invasion by the PM	II-V	0.746 (0.664-0.816)	<0.001	92.3/56.8	10.1 (1.31-78.1)	0.027
Tumor size, mm	>54	0.754 (0.688-0.812)	<0.001	78.9/67.2	7.04 (2.33-21.2)	<0.001

Notes: Se/Sp = criterion sensitivity/specificity; RR = relative risk of PM recurrence or continued growth based on censored data.

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Table 5. Cumulative recurrence-free survival of PM patients depending on prognostically significant factors

Indicator	Criterion (cut-off threshold)	Recurrence-free survival (according to life tables)*		
		after 1 year	after 5 years	after 10 years
Patient's gender	female (n=142)	0/99.6 (98.7-100)	5/95.2 (91.4-99.0)	8/88.5 (81.4-95.5)
	male (n=57)	2/96.4 (91.6-100)	7/84.8 (74.6-95.0)	9/73.0 (58.5-87.5)
SSS invasion according to M.P. Sindou and J.E. Alvernia classification)	I-III, V-VI (n=185)	2/98.9 (97.4-100)	9/94.0 (90.3-97.8)	13/89.1 (83.4-94.9)
	IV (n=14)	0/96.3 (86.2-100)	3/66.5 (41.2-91.8)	4/43.5 (16.8-70.3)
Surgical radicality according to Simpson grading scale	I (n=92)	0/99.5 (97.9-100)	1/96.0 (91.4-100)	2/85.5 (72.5-98.5)
	II-V (n=107)	2/98.1 (95.5-100)	11/88.9 (82.7-95.1)	15/81.9 (73.7-90.2)
Surgical radicality according to Simpson grading scale in type I-II SSS invasion by the PM	I (n=72)	0/99.3 (97.4-100)	1/94.9 (89.2-100)	1/85.1 (71.7-98.4)
	II-V (n=66)	2/97.0 (92.8-100)	8/86.6 (78.3-95.0)	11/78.3 (67.3-89.2)
Tumor size, mm	≤54 (n=125)	1/99.2 (97.6-100)	4/95.5 (91.5-99.4)	4/91.4 (85.2-97.7)
	>54 (n=74)	1/98.6 (95.9-100)	8/87.5 (79.3-95.7)	13/72.5 (59.0-86.0)

*Notes: *Actual number of patients who experienced PM recurrence or continued growth within the specified follow-up period /recurrence-free survival based on the censored data in % (95% CI).*

ative risk of tumor recurrence (according to Cox regression) increased by 7.04 times (95% CI, 2.33-21.2) vs. smaller tumor sizes ($p<0.001$) (see Table 4). Moreover, this criterion has high sensitivity (78.9%) and specificity (67.2%). Non-radical (Simpson II-V) tumor removal during primary intervention increases the risk of unfavorable prognosis by 5.57 times (95% CI, 1.27-24.34); in case of type I-II SSS invasion by the PM, by 10.1 times (95% CI, 1.31-78.1), with high sensitivity indicators (89.5% and 92.3%, respectively).

As for other identified PM recurrence predictors, based on censored data, male gender (BP=3.25) and type IV SSS invasion according to M.P. Sindou and J.E. Alvernia had a statistically significant effect ($p<0.05$) (RR=3.33) (see Table 4). Moreover, the latter criterion has a low sensitivity (21.1%) and high specificity (94.4%). Statistical significance of continued PM growth risk indicators in patients aged 45 to 59 and MRI signs of brain tissue invasion by the tumor met the trend criteria ($p<0.1$).

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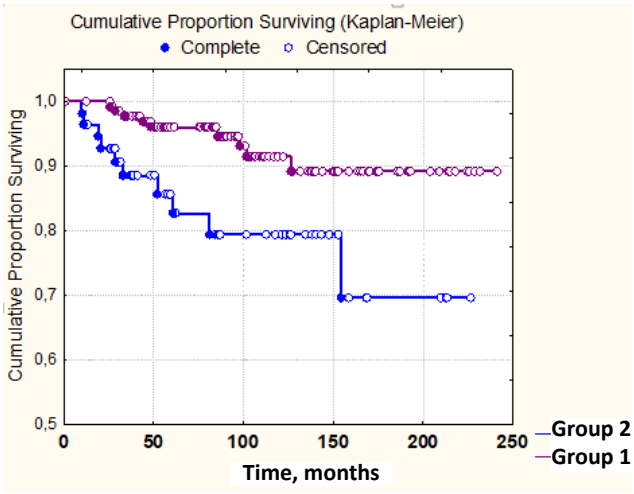
Fig. 2. Cumulative Kaplan-Meier curves for the PM recurrence/continued growth depending on the patient's gender.



Notes: 1. Group 1 = female patients; group 2 = male patients. 2. Statistical significance of inter-group differences according to the GWT criteria: p=0.004, LRT criteria: p=0.009.

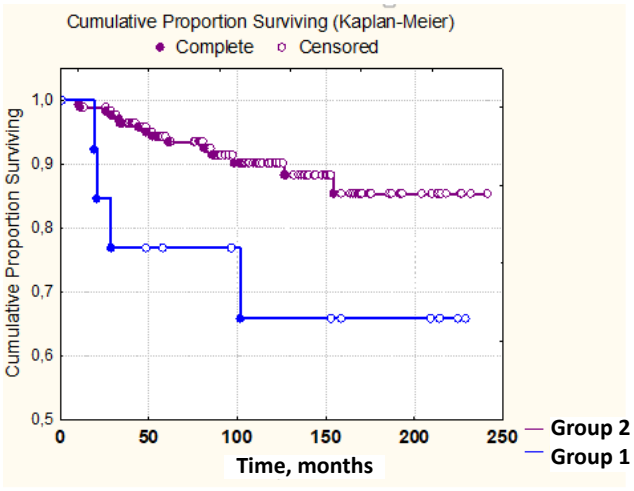
Table 5 and Figs. 2-6 show recurrence-free survival and cumulative Kaplan-Meier curves for PM recurrence/continued growth within 20 years of postoperative follow-up, depending on statistically significant (p<0.05) impact factors.

As can be seen from Figure 2 and Table 5, the longest recurrence-free period was demonstrated by female patients, both in the first (GWT: p=0.004) and during the entire follow-up period (LRT: p=0.009). In the shortest follow-up period (1 year) 2 of 57 male patients sustained a recurrence; within 5 years, 7; and within 10 years, 9. Respectively, 96.4%, 84.8% and 73.0% of male patients remained in the state of remission. Female patients had no recurrences within the first year after the surgery, 5 of 142 patients had recurrences within 5 years, and 8 had continued tumor growth within 10 years. At the same time, the recurrence-free survival in female patients in the same periods were 99.6%, 95.2%, and 88.5%, respectively, which is higher than in male patients by, in average, 3.2% (p>0.05), 10.4% (p<0.05), and 15.5% (p<0.01), respectively.

As can be seen from Fig. 3 and Table 5, patients with types I-III and V-VI SSS lesions according to M.P. Sindou and J. E. Alvernia (group 1) had significantly higher cumulative survival (GWT: p=0.006, LRT: p=0.021) vs. patients with type IV invasion (group 2). Within 5 years of the follow-up, only 9 of 185 patients with type I-III and V-VI SSS lesion had tumor recurrence and 94.0% of patients remained in the state of remission; within 10 years of the follow-up, 13 patients experienced continued PM growth and respective recurrence-free survival was 89.1%. In the type IV SSS damage group, in the above periods, 3-4 of 14 patients had PM recurrence and 66.5% and 43.5% of patients remained in the state of remission, respectively. Therefore, in case of type IV SSS lesion, the 5-year recurrence-free survival of PM patients is 1.4 times lower (p<0.01) and the 10-year survival is 2.0 times lower (p<0.001) than in case of type I-III or V-VI SSS invasion according to M.P. Sindou and J. E. Alvernia.

Comparative analysis of the Kaplan-Meier recurrence-free survival curves depending on the PM primary surgery radicality also showed significant discrepancies between the indicators (GWT: p=0.011, LRT: p=0.014) (see Fig. 4). The total number of patients who had PM recurrence or continued PM growth within 1, 5, and 10 years of the follow-up was, respectively, 0, 1, and 2 of

Fig. 3. Cumulative Kaplan-Meier curves for the PM recurrence/continued growth depending on the SSS damage.



Notes: 1. Group 1: types I-III, and V-VI according to M.P. Sindou and J.E. Alvernia; Group 2: type IV; 2. Statistical significance of inter-group differences according to the GWT criteria: p=0.006; LRT criteria: p=0.021

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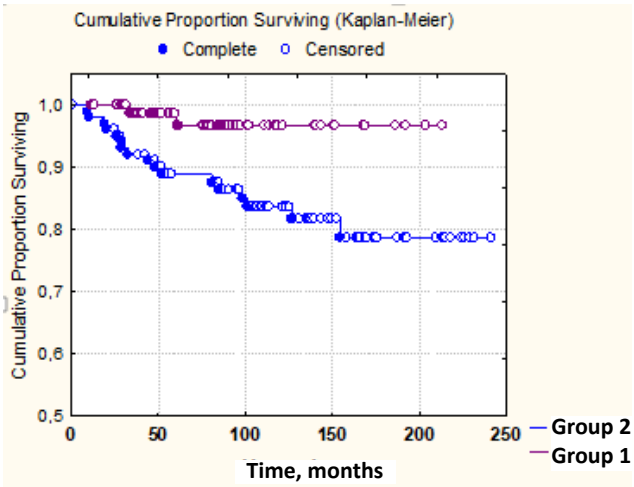
Fig. 4. Cumulative Kaplan-Meier curves for the PM recurrence/continued growth depending on surgical radicality.



Notes: 1. Group 1: Simpson I; group 2: Simpson II. 2. Statistical significance of inter-group differences according to the GWT criteria: p=0.011, LRT criteria: p=0.014.

92 patients who underwent radical (Simpson I) surgery (group 1). At the same time, 99.5%, 96.0%, and 85.5% of the patients remained in the state of remission (see Table 5). Among the 107 patients in the second group, who underwent incomplete (Simpson II-V) tumor removal, 2, 11, and 15 patients had tumor recurrence within 1, 5, and 10years of the follow-up, respectively, and 98.1%, 88.9%, and 81.9% of patients remained in the state of remission, which is less than the first group indicators by 1.4% (p>0.05), 7.1% (p<0.05), and 3.6% (p<0.05).

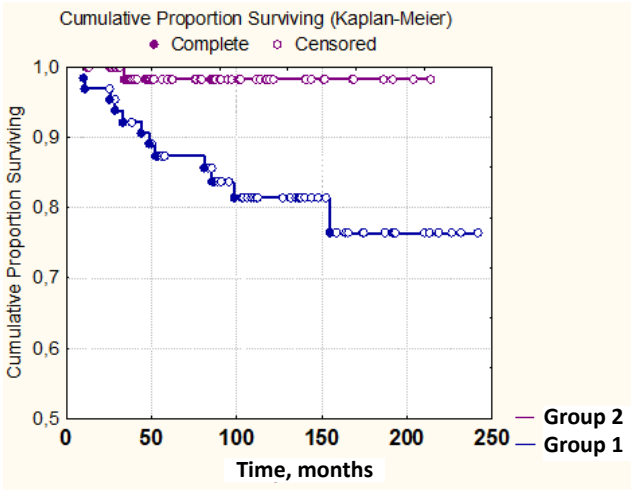
The impact of radical PM removal on the recurrence-free period duration within 20 years of the follow-up was more pronounced in case of type I-II SSS invasion (see Fig. 5, Table 5). In case of total tumor removal (Simpson I), only one of 72 patients had tumor recurrence within 5-10 years; the recurrence-free survival made 94.9% and 85.1%, respectively; on the other hand, 8-11 of 66 patients with incomplete tumor removal (Simpson II-V) had continued PM growth within 5 and 10 years of the follow-up, respectively. 86.6% and 78.3% of patients remained in the state of remission, which is, respectively, by 8.3% (p<0.01) and 6.8% (p<0.01) less than in the first group.

Significant differences between cumulative recurrence-free survival were noted when comparing Kaplan-Meier curves for different tumor sizes (GWT: p<0.001, LRT: p<0.001) (see Fig. 6). For instance, 4 of 125 patients with a tumor size ≤54 mm (group 1) had tumor recurrence in the 5-year follow-up period and 95.5% of the patients remained in the state of remission. In the group with a meningioma size >54 mm (group 2), 8 of 74 patients had tumor recurrence in the same follow-up period; the recurrence-free survival made 87.5%, which is by 8.0% less than in the first group (p<0.001). 4 patients in the first group and 13 patients in the second group had tumor recurrence within 10 years of the follow-up. The percentage of patients who did not demonstrate PM growth in this period in the second group was 18.9% less than in the first group — 72.5% vs. 91.4% (p<0.001).

Discussion.

In the studied category of patients, there was no significant association between parasagital meningioma recurrence or continued growth and CT/MRI signs of perifocal brain edema reported by other studies (Nakasu et al., 2020, Siempis et al., 2020, Huang et al. 2019) and no significant

Fig. 5. Cumulative Kaplan-Meier curves for the PM recurrence/continued growth depending on surgical radicality in types I-II SSS lesions according to M.P. Sindou and J. E. Alvernia.



Notes: 1. Group 1: Simpson I; group 2: Simpson II. 2. Statistical significance of inter-group differences according to the GWT criteria: p=0.009, LRT criteria: p=0.007.

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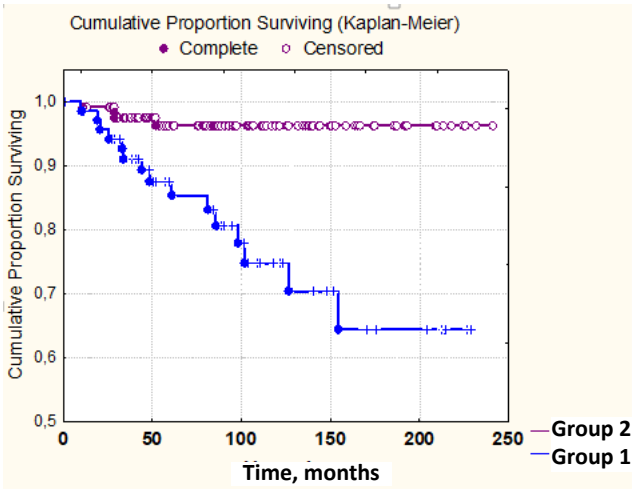
Fig. 6. Cumulative Kaplan-Meier curves for the PM recurrence/continued growth depending on tumor size.



Notes: 1. Group 1: tumor size ≤ 54 mm; group 2: tumor size > 54 mm. 2. Statistical significance of inter-group differences according to the GWT criteria: p=0.001, LRT criteria: p=0.001.

association with the computed tomography characteristics of the tumor (Yu et al., 2020).

However, the resulting prognostic factors of parasagital meningioma recurrence/continued growth in this study are consistent with the data from known literature sources (Behzadmehr et al., 2021, Balik et al., 2020, Cucu et al., 2020, Salah et al., 2019, Siempis et al., 2020). However, we found that recurrence-free 5- and 10-year survival in PM patients is as follows: 1) in case of total tumor removal (Simpson I), 96.0% and 85.5%, respectively; in case of non-radical removal (Simpson II-V), 88.9% (p<0.05) and 81.9% (p<0.05), respectively. At the same time, non-radical surgery in type I-II SSS invasion by the PM reduces 5- and 10-year recurrence-free survival to 86.6% (p<0.01) and 78.3% (p<0.01), respectively; in case of tumor size of up to 54 mm, the indicators are 95.5% and 91.4%; with tumor size >54 mm, they are as low as 87.5% (p<0.001) and 72.5% (p<0.001); in case of type I-III or V-VI SSS damage according to M. P. Sindou and J. E. Alvernia, 94.0% and 89.1%; and in case of type IV invasion, 66.5% (p<0.01) and 43.5% (p<0.001); in female patients, 95.2% and 88.5%; in male patients, 84.8% (p<0.05) and 73.0% (p<0.01). According to the Cox regression proportional hazards model, the relative risk of tumor recurrence/continued growth increases by: 1) 7.04 times (95% CI, 2.33-21.2) in case of initial PM size >54 mm (p<0.001); 5.57 times (95% CI, 1.27-24.34) in case of non-radical tumor removal during primary intervention (Simpson II-V) (P<0.05); 10.1 times (95% CI, 1.31-78.1) in case of type I-II SSS invasion by the PM or incomplete tumor removal (Simpson II-V) (p<0.05); 3.25 times (95% CI, 1.32-8.02) in male patients (p<0.01); 3.33 times (95% CI, 1.10-10.12) in case of type IV SSS invasion (according to M.P. Sindou and J.E. Alvernia) (p<0.05).

The identified prognostic factors for parasagital meningioma recurrence or continued growth shall be taken into account when planning the scope of surgical intervention and selecting the tactics of postoperative follow-up and patients' treatment.

Conclusions

1. The patient's gender must be taken into account when planning a particular surgical strategy for parasagital meningioma removal as men are more likely to experience tumor recurrence or continued growth.
2. Preoperative diagnosis of parasagital meningiomas must necessarily include brain CT/MRI with intravenous contrast and cerebral vascular system angiographic examination (CT angiography, selective subtraction digital cerebral angiography), followed by tumor size determination and the nature of its invasion into the superior sagittal sinus, as the tumor size of >54 mm and type IV SSS lesion according to M.P. Sindou and J.E. Alvernia is a significant risk factor for tumor recurrence/continued growth.
3. Surgical radicality shall be as close as possible to total (Simpson I) removal of parasagital meningioma, which will minimize the risks of postoperative tumor recurrence or continued growth, especially in case of meningiomas that extend to both walls of the superior sagittal sinus (type IV according to M.P. Sindou and J.E. Alvernia).
4. Adequate analysis of the results obtained will help the neurosurgeons plan the optimal surgery volume and ensure further postoperative recurrence-free period and improved long-term treatment outcomes.

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The authors state that there is no conflict of interest.

Consent to publication

All procedures performed for patients during the study comply with ethical standards of institutional and national ethics committees and the Declaration of Helsinki (1964), as amended, or similar ethical standards. All patients have provided their informed and voluntary written consent to participate in the study.

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Прогностичні фактори рецидиву/продовженого росту парасагітальних менінгіом

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Анотація: актуальність дослідження полягає в широкій розповсюдженості даної патології. Менінгіоми складають 18-34% від усіх первинних пухлин головного мозку. Серед них, парасагітальні менінгіоми зустрічаються в 24,3-38,6 % спостережень. Незважаючи на переважно доброякісний характер парасагітальні менінгіоми схильні до рецидиву/продовженого росту частіше ніж менінгіоми інших локалізацій (від 18% до 40%). Основною метою дослідження є вивчення прогностичних факторів рецидиву/продовженого росту парасагітальних менінгіом, що в подальшому впливатиме на покращення результатів хірургічного лікування. Нами проведено ретроспективний та проспективний аналіз 199 хворих із парасагітальними менінгіомами, які знаходились на лікуванні в комунальному підприємстві «Дніпропетровська обласна

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клінічна лікарня імені І.І. Мечникова» Дніпропетровської обласної ради» в період з 2000 по 2021 рік включно. В основу даної роботи покладено порівняльний аналіз результатів обстеження, хірургічного лікування та подальший аналіз патогістологічного заключення в двох групах спостереження. До першої групи включено 180 (90,5%) пацієнтів, що не мали рецидиву/ продовженого росту, а в другій групі спостереження 19 (9,5%) хворих із виявленим рецидивом/ продовженим ростом парасагітальної менінгіоми (ПМ) після хірургічного втручання. Серед відібраних пацієнтів проведено аналіз демографічних даних (стать, вік); результатів комп'ютерної томографії та магнітно-резонансної томографії головного мозку до та після внутрішньовенного контрастування за основними характеристиками; даних ангіографічних досліджень (комп'ютерно-томографічної ангіографії / селективної субтракційної дігітальної церебральної ангіографії); радикальності хірургічного втручання; результатів патогістологічних заключень; а також тривалість безрецидивного періоду (від одного до 20 років після проведеного хірургічного лікування). Протягом періоду спостереження рецидив/ продовжений ріст ПМ відзначено у 19 пацієнтів (9,5%). З них впродовж першого року після втручання зафіксовано лише 2 випадки продовженого росту ПМ, за 5 років (60 міс.) – 12, за 10 років – 17, а відсоток пацієнтів без рецидиву з урахуванням цензурованих даних (безрецидивна виживаність) склав 99,0 (95% ДІ 97,6-100) %, 93,1 (95% ДІ 89,3-96,9) % і 87,5 (95% ДІ 81,6-93,4) % відповідно до вищевказаних термінів спостереження. Фактична медіана часу до виникнення рецидиву в нашому дослідженні склала 44,1 (25,7; 85,4) місяці. Тобто більшість випадків продовженого росту ПМ зафіксовано протягом перших 5 років після втручання – 12 з 19 (63,2%). Останній випадок рецидиву ПМ відзначений через 13 років (154,5 міс.) спостереження. Таким чином, показники безрецидивної 5-ти і 10-ти річної виживаності у пацієнтів з ПМ: при тотальному видаленні пухлини (за Simpson I) становлять 96,0% і 85,5%, при нерадикальному підході (за Simpson II-V) – 88,9% ($p<0,05$) і 81,9% ($p<0,05$). При цьому нерадикальність хірургічного втручання при I-II типі інвазії ПМ у ВВС зменшує показники 5-ти і 10-ти річної безрецидивної виживаності до 86,6% ($p<0,01$) і 78,3% ($p<0,01$) відповідно; при розмірі пухлини до 54 мм становлять 95,5% і 91,4%, а при розмірах >54 мм зменшуються до 87,5% ($p<0,001$) і 72,5% ($p<0,001$); при ураженні ВСС I-III та V-VI типів за класифікацією M. P. Sindou and J. E. Alvernia дорівнюють 94,0% і 89,1%, а у випадках IV типу інвазії – 66,5% ($p<0,01$) і 43,5% ($p<0,001$); у пацієнтів жіночої статі становлять 95,2% і 88,5%, у чоловіків – 84,8% ($p<0,05$) і 73,0% ($p<0,01$). За результатами регресійного аналізу пропорційних ризиків Кокса відносний ризик рецидивування/ продовженого росту пухлини збільшується: в 7,04 разу (95% ДІ 2,33-21,2) при початковому розмірі ПМ понад 54 мм ($p<0,001$); в 5,57 разу (95% ДІ 1,27-24,34) при нерадикальному характері видалення пухлини при первинному втручанні (Simpson II-V) ($p<0,05$); в 10,1 разу (95% ДІ 1,31-78,1) при I-II типі інвазії ПМ у ВВС та неповному видаленні пухлини (Simpson II-V) ($p<0,05$); в 3,25 разу (95% ДІ 1,32-8,02) у пацієнтів чоловічої статі ($p<0,01$); в 3,33 разу (95% ДІ 1,10-10,12) при IV типі інвазії у ВВС (за M.P. Sindou and J.E. Alvernia) ($p<0,05$). Адекватний аналіз отриманих результатів допоможе нейрохірургу спланувати оптимальний об'єм хірургічного втручання із подальшим післяопераційним збільшенням тривалості безрецидивного періоду та покращенням віддалених результатів лікування.

Ключові слова: верхній сагітальний синус, менінгіома, прогноз, результати лікування, рецидив, фактори ризику.

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Stroke-associated pneumonia risk estimation in patients admitted to a comprehensive stroke unit at different phases after stroke

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Abstract: *stroke is one of the leading causes of death and acquired disability among adults worldwide. Various complications frequently occur in patients with stroke and can significantly increase the risk for poor outcomes. Stroke-associated pneumonia, with the rate of up to 15%, is considered the most common serious medical complication in stroke patients. The aim of the study was to determine the independent predictors of the stroke-associated pneumonia in patients admitted to a comprehensive stroke unit at different time from stroke onset, as well as to develop a prognostic model for stroke-associated pneumonia risk estimation. Medical complications, including stroke-associated pneumonia, were documented in patients with clinical diagnosis of intraparenchymal cerebral stroke at admission and during their stay on the comprehensive stroke unit in 2010 to 2018. The workup at admission included assessment using the National Institutes of Health Stroke Scale and the modified Rankin scale. The diagnosis of stroke-associated pneumonia was made by specialists, in accordance with Centers for Disease Control recommendations. Qualitative variables are displayed as numbers and percentages, quantitative variables are displayed using the median (interquartile range). The method of logistic regression models was used to quantitatively assess the impact of characteristics on the PSP risk. The analysis was carried out using the package MedCalc v. 19.1. The study enrolled 539 patients, 309 (57.3%) men and 230 (42.7%) women. Median age of the patients was 66.0 years (57.9-75.1). Among the participants 101 (18.7%) were diagnosed with intracerebral hemorrhage, and 438 (81.3%) were diagnosed with ischemic stroke. Median initial National Institutes of Health Stroke Scale total score was 11 (6–18), median baseline modified Rankin scale score was 4 (3–5). Majority (64.1%) individuals were admitted within the first 30 days from onset, while 194 (35.9%) patients presented later. History of medical complications before the admission was present in 192 (35.6%) of the study participants, while during our in-hospital stay they occurred in 103 (19.1%) of the patients. The rate of new medical complications at the unit was significantly lower ($p<0.001$) than prior to the admission. The diagnosis of stroke-associated pneumonia before the admission was established in 20 (3.7%), and during our in-patient treatment was made in 7 (1.3%) subjects ($p<0.001$). Independent predictors of the stroke-associated pneumonia development were older age (odds ratio 1.11; 95% confidence interval 1.02-1.21, on average, for each additional year, $p=0.02$) and history of stroke-associated pneumonia at admission (odds ratio 12.2; 95 % confidence interval 2.0-72.4, $p=0.006$). Excellent sensitivity (85.7%), good specificity (75.0%) and area under the operating characteristic curve of 0.86 (95% confidence interval 0.83 – 0.89) for the developed prognostic model*

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based on these of two variables, indicate their strong association with the risk of stroke-associated pneumonia during a comprehensive stroke unit stay. Therefore, stroke patients frequently develop medical complications at various stroke phases. The risk of stroke-associated pneumonia is higher in older patients and, especially, in those with stroke-associated pneumonia history. The lower rate of medical complications, in particular stroke-associated pneumonia, observed during in-hospital stay compared to the period prior to the admission may indicate the benefits of comprehensive stroke unit.

Keywords. humans, aged, stroke, pneumonia, prognosis, retrospective studies, multivariate analysis, severity of illness index.

Introduction

Cerebral stroke (CS) remains one of the leading causes of death and acquired disability among adults worldwide (Feigin et al., 2022; Tsao et al., 2022). According to 2019 global estimates, there were about 12.2 million CS, almost 6.6 million people died from CS (11.6% of the total number of deaths), and more than 143 million years of healthy life were lost due to premature death or acquired disability after CS (GBD 2019 Stroke Collaborators, 2021). Moreover, the burden of CS is projected to grow, and in 2050s the number of CS and deaths due to CS is expected to reach 30 million and 12 million respectively, while the number of CS survivors is going to exceed 200 million (Brainin et al., 2020). As of 2019, Ukraine was included in the group of countries with a very high CS incidence and mortality (Kim et al., 2020). Therefore, there is an urgent need to identify key elements of the chain of care for patients with CS that can be improved with maximum benefits both for individual patients and their families as well as communities and whole countries (Pandian & Sebastian, 2021).

Various complications that frequently occur in patients with CS can significantly increase the duration of stay, the cost of treatment, and the risk for poor outcomes (Janus-Laszuk et al., 2017; Kumar et al., 2010; Verma, 2019). More than 20 years ago, it was shown that 25% to 50% of deaths after CS are related complications (Weimar et al., 2002). The most frequent type of complications in patients with CS are medical complications, such as respiratory and urinary tract infections, fluid / electrolyte and metabolic disturbances, cardiac disorders, venous thromboembolism, urinary and fecal incontinence, pressure sores and major bleeding, as well as trauma from falls and pain syndromes (Elkind et al., 2020; Ingeman et al., 2011; Kitisomprayoonkul et al., 2010; Kumar et al., 2010). Due attention to the prevention and treatment of complications is an important component of high-quality care for patients with CS (Kumar et al., 2010; Teasell et al., 2020). Stroke-associated pneumonia (SAP), with the rate of up to 15%, is considered the most common serious medical complication in patients with CS (Badve et al., 2019; Kishore et al., 2015; Westendorp et al., 2011). Previous studies have shown that SAP is associated with worse neurological and functional recovery and more than triples the risk of death (Armstrong & Mosher, 2011; Ingeman et al., 2011; Yuan et al., 2021). Despite the fact that reducing the risk of SAP could have a significant impact on CS outcome, effective medical (in particular, with antimicrobial agents) prevention of SAP has not yet been developed, and the risk factors of SAP in different periods of the disease have not been sufficiently studied (Grossmann et al., 2021; Liu et al., 2016; Zheng et al., 2017).

Aim

The aim of the study was to determine the predictors of the development of SAP in patients with CS during inpatient treatment in a comprehensive stroke unit (CSU) in different CS phases, as well as to build an appropriate prognostic model that allows for SAP risk estimation.

Material and methods

1. Study setting and selection criteria.

This retrospective observational study was conducted in the Stroke Center (SC) – a general university hospital department. The structure and processes in the SC correspond to CSU principles: evidence-based care is provided by a multidisciplinary team in compliance with established medical care standards; full primary and, if necessary, extended work-up (neuroimaging using

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multidetector spiral computer or 1.5T magnetic resonance imaging of the brain, visualization of extracranial and intracranial arteries using computer tomographic or magnetic resonance angiography, transthoracic echocardiography, 12-lead ECG, Holter heart rate monitoring for 24–72 hours, and a set of conventional laboratory tests) with the determination of the CS type and most likely etiological subtype is performed in every case; early comprehensive secondary prevention; a high volume of rehabilitation care during the entire stay. A complete neurological examination using a set of stroke assessment scales was performed upon admission. All patients were seen by a cardiologist and, if necessary, by other medical specialists. Laboratory tests were performed in a certified hospital laboratory.

The study inclusion criteria were a clinical diagnosis of intraparenchymal CS verified by neuroimaging, at least 3 days of inpatient treatment in the SC between February 2010 and September 2018, results of auxiliary investigations, internal medicine specialist or pulmonologist consultation, and the main stroke assessment scales scores available. Patients with subarachnoid hemorrhage or extremely severe comorbidity that significantly affected the course and outcome (e.g., advanced malignant neoplasm, end-stage renal failure, hematological diseases, unfused bone fractures, severe malnutrition, sepsis), as well as patients after revascularization procedures (systemic thrombolytic therapy and/or mechanical thrombectomy for ischemic CS), surgical interventions (e.g., removal of intracerebral hematoma) and patients requiring mechanical ventilation were excluded from the study.

2. Set of collected and analyzed variables.

The predetermined set of variables for each of the patients was entered into a special database. These included age, sex, CS type and subtype, baseline National Institutes of Health Stroke Scale (NIHSS) total score, and modified Rankin Scale (mRS) severity of disability after SCU admission. According to the pathophysiological type, all patients were divided into two groups: ischemic SC and intracerebral hemorrhage. Patients with ischemic CS, according to the developed algorithm, were divided into four main etiological subtypes: atherosclerotic (AT), cardioembolic (CE), lacunar (LA) and other (OT) (Flomin et al., 2022). In all patients, at SC admission, based on history and medical records, medical complications, such as SAP, which occurred between estimated CS onset and SC admission, were registered. If patients developed medical complications, including SAP, during their stay in the SC, these were documented as new complications. Considering the fact that there is no "gold standard" or universally recognized diagnostic criteria for SAP yet, the diagnosis of SAP was established by a pulmonologist or a internal medicine specialist based on clinical manifestations and the results of investigations (e.g., chest X-ray or multidetector spiral computer tomography), in accordance with the recommendations of the Centers for Disease Control and Prevention (Horan et al., 2008). According to the NIHSS total score, all cases were divided into mild (0-5), moderate (6-13), severe (14-20) and very severe (more than 20) CS (Zhuo et al., 2021). CS phases, depending on the time elapsed from the estimated CS onset to SC admission, were classified as hyperacute (0-24 hours), acute (1-7 days), early subacute (8 to 90 days), late subacute (91 to 180 days) and chronic (after 180 days) (Bernhardt et al., 2017).

3. Statistical analysis.

Qualitative variables are expressed through frequency and percentages. Quantitative variables are displayed using median and interquartile range (IQR). The chi-square test was used to compare qualitative features. The threshold for statistical significance was set at $p=0.05$. The method of constructing and analyzing logistic regression models was used to quantitatively assess the influence of variables on the risk of SAP development. The prognostic quality of the models was evaluated by its sensitivity (proportion of correctly predicted cases of SAP) and specificity (proportion of correctly predicted "non-cases", i.e., absence of SAP diagnosis) (Petrie, 2009). The corresponding 95% confidence interval (95% CI) was calculated for these values. Adequacy of the models was assessed by the method of construction and analysis of operating characteristic curves (ROC – Receiver Operating Characteris-

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tic curve analysis), while the area under the ROC curve (AUC – Area under the ROC curve) and its 95% CI were calculated. The model is considered adequate when the AUC value differs statistically from 0.5 (Gurianov et al., 2018). The influence of variables was assessed by the value of the odds ratio (OR), for which 95% CI was calculated (Petrie, 2009). To select the minimum set of variables independently associated with SAP in multivariable analysis, the method of stepwise rejection/addition was used. The optimal decision threshold for the model was determined by achieving maximum sensitivity and specificity according to the Youden index (Gurianov et al., 2018). Statistical analysis of the research results was performed using the MedCalc® Statistical Software package version 19.6.4 (MedCalc Software Ltd, Ostend, Belgium, 2021).

Results

The study enrolled 539 patients, including 309 (57.3%) men and 230 (42.7%) women. The age of patients varied from 20.4 to 95.6 years (median 66.0 years, IQR 57.9 - 75.1). In the study sample, 101 (18.7%) patients were diagnosed with intracerebral hemorrhage, and 438 (81.3%) subjects were diagnosed with ischemic CS. Among the latter, 177 (40.4%) participants were assigned to AT, 200 (45.7%) to CE, 30 (6.9%) to LA, and remaining 32 (7.0%) to OT ischemic CS subtype. Among the enrolled patients, 109 (20.2%) were admitted in the hyperacute phase, 113 (21.0%) in the acute phase, 199 (36.9%) in the early subacute phase, 36 (6.7%) in the late subacute phase, and 82 (15.2%) – in the chronic CS phase. In total, 345 (64.1%) individuals from the study sample were admitted to the SC within the first 30 days from the CS onset, while 194 (35.9%) patients were admitted later. The total baseline NIHSS score varied from 1 to 39 points (median 11 points, IQR 6 to 18). Among the studied patients, 119 (22.1%) had mild CS, 218 (40.5%) had moderate CS, 114 (21.2%) had severe CS, and 88 (16.3%) had very severe CS. According to the initial mRS assessment, 45 (8.3%) patients had a score of 0-1, 58 (10.8%) had a score of 2, 65 (12.1%) had a score of 3, 136 (25.2%) had a score of 4, and the majority of 235 (43.6%) patients had a score of 5. The median mRS score in the study sample was 4 (IQR 3-5).

The frequency of medical complications at admission and during the SC stay

Among the study participants, 192 (35.6%) had documented medical complications that occurred between the estimated stroke onset and the SC admission. Over the period of the SC stay, 103 (19.1%) patients developed new medical complications. While the most frequent type of medical complications registered in the SC was urinary tract infection, the serious medical complications were SAP and venous thromboembolism. The rate of medical complications that occurred prior to the SC admission was statistically significantly ($p<0.001$) higher than during the stay in the SC. Similarly, SAP rate before the admission was significantly ($p<0.001$) higher than SAP rate during the SC stay: prior to the SC admission diagnosis of SAP was made in 20 (3.7%) patients while it was diagnosed only in 7 (1.3%) SC in-patients.

Determination of new SAP predictors the prognostic model

In order to determine the predictors of SAP that occurred during the patient's inpatient treatment in the SC, an analysis of the selected patients' variables (CS type and subtype age, sex, time delay from the CS onset to the SC admission, initial NIHSS and mRS scores as well as the medical complications known at admission) was performed. The results of the univariate analysis are shown in Table 1.

The univariate analysis have identified three factors that are statistically significantly associated with the increased risk of SAP development: older age of the patient (OR 1.11; 95% CI 1.02–1.20 on average for each additional year, $p=0.014$), diagnosis of SAP before the SC admission (OR 11.4; 95% CI 1.1–63.0, $p<0.001$), and more severe CS at the SC admission (OR 1.13; 95% CI 1.03–1.23, on average, for each additional point of the NIHSS total score, $p=0.007$). No statistically significant relationships with the risk of SAP were found for other variables.

To identify independent predictors of SAP during the SC stay, a multivariate analysis was conducted. The results of multivariate analysis are shown in Table 2.

As shown in Table 2, only two variables were found to be independent predictors of a new SAP in CS patients during their stay at the SC: old-

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Table 1. Influence of selected variables on the new SAP risk: univariate analysis results

Variable		The model coefficient value, b±m	Level of significance, p‡	OR (95% CI)
Age		0.10±0.04	0.014	1.11 (1.02–1.20)
Sex	**Female**	**Reference**		
	Male	–0.01±0.77	0.992	–
SAP diagnosis prior to the SC admission	**No**	Reference		
	Yes	2.43±0.87	<0.001	11.4 (2.1–63.0)
Baseline mRS score		1.53±0.94	0.103	–
Baseline total NIHSS score		0.12±0.04	0.007	1.13 (1.03–1.23)
CS type and subtype	**AT**	**Reference**		
	LA	–18.4±10000	0.999	–
	OT	–18.4±9800	0.999	–
	ICH	–0.12±1.23	0.920	–
	CE	0.58±0.87	0.506	–
Time from the CS onset to the SC admission	**0-24 hours**	**Reference**		
	1-7 days	–1.68±1.10	0.127	–
	8-30 days	–1.77±1.10	0.109	–
	31+ days	–20.8±6600	0.999	–

‡Differences of the model coefficient from 0. ICH – intracerebral hemorrhage.

er age (OR 1.11; 95% CI 1.02-1.21, on average, for each additional year, p=0.02) and, predominantly, the history of SAP at admission (OR 12.2; 95% CI 2.0-72.4, p=0.006). Therefore, in contrast to the univariate analysis, the multivariate analysis did not confirm the influence of more severe baseline neurological deficit on the SAP risk. The ROC of the prognostic model is shown in Figure 1.

The model has AUC=0.86 (95% CI 0.83 – 0.89), which indicates a strong connection of the identified independent predictors with the SAP risk during the SC stay. The developed model with sensitivity of 85.7% and specificity of 75.0% has high accuracy. If its external validity is confirmed, it can be used in clinical practice to estimate the SAP risk.

Discussion

Therefore, in this retrospective observational study with a rather large cohort of in-patients with CS (N=539), who were thoroughly assessed upon admission to CSU at different CS phases and throughout their stay, the frequency of medical complications, in particular SAP, was determined, and independent predictors of a SAP development were identified. In general, the study sample was characterized by a high frequency of medical complications: more than a third (35.6%) of patients were diagnosed with medical complications prior to the SC admission, and almost

Table 2. Features of the model for predicting the risk of SAP during treatment in the SC

Variable		The model coefficient value, b±m	Level of significance, p‡	OR (95% CI)
Age		0.10±0.04	0.02	1.11 (1.02–1.21)
SAP diagnosis prior to the SC admission	No	Reference		
	Yes	2.50±0.91	0.006	12.2 (2.0–72.4)

‡Differences of the model coefficient from 0.

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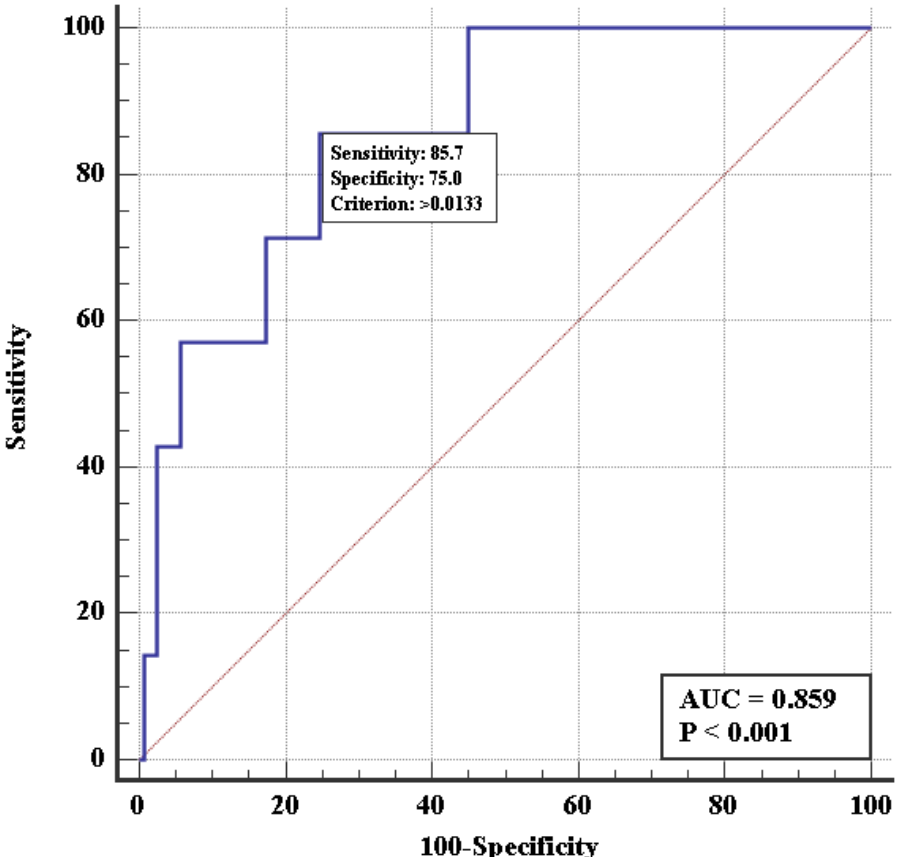

Figure 1. ROC of the prognostic model for assessing the risk of SAP during the SC stay.

one in five (19.1%) patients developed new medical complications during their stay at the SC. Our findings are in line with the results of other studies carried out over the last decades, which demonstrated that high overall frequency of complications in CS patients varied from 24% to 95%, and that some patients had two or more complications (Bustamante et al., 2017; Janus-Laszuk et al., 2017; Kitisomprayoonkul et al., 2010). The high rate of complications points out the importance of a multidisciplinary approach to CS care, including stroke physicians and other specialists as well as trained nurses, physical therapists and speech and language therapists. It also emphasizes the need for attention to the prevention, early diagnosis, and treatment of complications from the very admission and throughout the in-hospital stay of patients with CS.

We showed that, according to the results of univariate analysis, the risk of new SAP during inpatient treatment is higher in older people, patients with more severe CS, and especially in the case of a SAP history. However, in the multivariate analysis, only the older age and an SAP history retained their prognostic value as independent predictors of a new SAP development. The unfavorable prognostic role of SAP that developed in the earlier CS phases is probably related to the persistence of risk factors, such as dysphagia and/or immunosuppression, which increase the risk of pneumonia (Armstrong & Mosher, 2011; Grossmann et al., 2021). The prognostic model for assessing the risk of SAP proved adequate and was characterized by excellent (85.7%) sensitivity and good (75.0%) specificity. Therefore, in patients who have both independent predictors of a new SAP (i.e., older age and an SAP history) careful monitoring of body temperature and blood oxygen saturation, as well as chest radiography immediately upon admission and in case of deterioration may make sense regardless of the CS phase. In addition, in such patients, special preventive measures may be used in order to reduce the risk of SAP, including endoscopic examination of the function of swallowing to rule out “silent” aspiration, education on safer food consistency and intake, correct positioning in bed and during meals, early and sufficient mobilization by Nurses and Physical Therapists, breathing exercises and good nutritional support (Armstrong & Mosher, 2011; Grossmann et al., 2021; Tinker et al., 2021). Future studies should aim at identifying more SAP modifiable risk factors.

The fact that the frequency of any medical complications and, in particular, SAP, that occurred during the stay in the SC operating according to the principles of CSU, was significantly lower than those documented from CS onset to the SC admission, in our opinion, indicates the advantages of

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CSU as a model inpatient care regardless of the CS phase. In CS, the outcome, in addition to the CS type and subtype, the size and localization of the lesion and comorbidity, depends on medical and neurological complications, the time delay from the onset to hospitalization, medical interventions, the processes of the medical care, hospital resources, and the availability of rehabilitation (Harvey, 2015). The results of a meta-analysis have shown that a stay in a CSU, where treatment in the acute period of stroke is combined with early comprehensive secondary prevention, skilled nursing care and persistent interdisciplinary rehabilitation, is associated with a reduction in mortality and disability (Chan et al, 2013; Langhorne & Ramachandra, 2020). The benefits of Stroke Units, among other factors, result from successful prevention, early detection and correct treatment of complications (Govan et al., 2007; Janus-Laszuk et al., 2017). Our findings corroborate other studies that emphasize the importance of risk assessment, prevention, early diagnosis, and treatment of medical complications, such as SAP, in all hospitalized patients at any phase of CS.

Conclusions

1. Documented in one in three patients at the CSU admission and in one in five patients during the CSU stay, medical complications are common in patients in all CS phases.
2. As older age and an SAP history are independent predictors of a new SAP development during CSU stay, presence of both these factors at admission flags up the increased SAP risk.
3. The lower frequency of medical complications, in particular SAP, diagnosed during the CSU stay compared with documented at admission, indicates the advantages of CSU care.

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Conflict of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent to publication

All involved patients agreed on their data analysis and publication of this manuscript.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Оцінювання ризику інсульт-асоційованої пневмонії у пацієнтів, які перебували на лікуванні в інтегрованому інсультному блоці у різних періодах захворювання

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Анотація: інсульт є однією з головних причин смерті та набутої інвалідності серед дорослих у всьому світі. У пацієнтів з інсультом часто виникають різні ускладнення, які можуть значно підвищити ризик поганих результатів лікування. Пневмонія, що пов'язана з інсультом, має частоту до 15% і вважається найпоширенішим серйозним медичним ускладненням у пацієнтів з інсультом. Метою дослідження було визначення провісників інсульт-асоційованої пневмонії у пацієнтів з інсультом, які перебували на стаціонарному лікуванні в інтегрованому інсультному блоці у різних періодах захворювання, а також побудова прогностичної моделі для оцінювання ризику розвитку інсульт-асоційованої пневмонії. У пацієнтів, які у 2010–2018 рр. перебували на стаціонарному лікуванні в інтегрованому інсультному блоці з приводу інтрапаренхіматозного мозкового інсульту у різні періоди захворювання (від найгострішого до віддаленого), реєстрували соматичні ускладнення, зокрема інсульт-асоційовану пневмонію, як до госпіталізації, так і впродовж перебування. Після госпіталізації було проведене обстеження, що включало оцінку за допомогою Шкали інсульту Національних інститутів здоров'я та модифікованої шкали Ренкіна. Діагноз інсульт-асоційованої пневмонії встановлювали лікарі-спеціалісти, відповідно до рекомендацій Центрів з контролю захворювань. Якісні змінні відображені як число та проценти, кількісні змінні як медіана (міжквартильний інтервал). Для кількісної оцінки впливу ознак на ризик інсульт-асоційованої пневмонії був використаний метод моделей логістичної регресії. Аналіз проводився за допомогою пакету MedCalc v. 19.1. У дослідження були включені 539 пацієнтів, 309 (57,3%) чоловіків та 230 (42,7%) жінок. Медіана віку пацієнтів 66,0 років (57,9–75,1 років). У 438 (81,3%) учасників дослідження діагностовано ішеміч-

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ний інсульт, у 101 (18,7%) внутрішньомозковий крововилив. Більшість (64,1%) пацієнтів були госпіталізовані впродовж перших 30 днів від початку захворювання, проте 194 (35,6%) особи поступили пізніше. Медіана початкової загальної оцінки за Шкалою інсульту Національних інститутів здоров'я становила 11 балів (6–18 балів), за модифікованою шкалою Ренкіна – 4 бали (3–5 балів). Соматичні ускладнення в анамнезі захворювання мали місце у 192 (35,6%) пацієнтів, а протягом перебування вони виникли у 103 (19,1%) учасників дослідження. Частота нових соматичних ускладнень у нашому стаціонарі була значуще (p<0,001) нижчою, ніж у період до госпіталізації. Діагноз інсульт-асоційованої пневмонії до госпіталізації був встановлений у 20 (3,7%), а під час стаціонарного лікування – у 7 (1,3%) учасників дослідження (p<0,001). Незалежними провісниками розвитку інсульт-асоційованої пневмонії були старший вік пацієнта (відношення шансів 1,11; 95% довірчий інтервал 1,02-1,21, в середньому, на кожен додатковий рік, p=0,02) та інсульт-асоційована пневмонія в анамнезі (відношення шансів 12,2; 95% довірчий інтервал 2,0-72,4, p=0,006). Відмінна чутливість (85,7%), добра специфічність (75,0%) та площа під кривою операційних характеристик 0,86 (95% довірчий інтервал 0,83–0,89) для прогностичної моделі, що була побудована на основі цих двох чинників, свідчить про їх сильний зв'язок з ризиком розвитку інсульт-асоційованої пневмонії у період перебування в інтегрованому інсультному блоці. Отже у пацієнтів з інсультом у різних періодах захворювання часто виникають соматичні ускладнення. Ризик інсульт-асоційованої пневмонії є вищим у пацієнтів старшого віку й, особливо, у разі інсульт-асоційованої пневмонії в анамнезі захворювання. Нижча частота соматичних ускладнень, зокрема інсульт-асоційованої пневмонії, під час стаціонарного лікування у порівнянні з періодом до госпіталізації є свідченням переваг інтегрованого інсультного блоку.

Ключові слова. Люди, вік, інсульт, пневмонія, прогноз, ретроспективні дослідження, багатофакторний аналіз, індекс тяжкості хвороби.

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Prognostic factors of nervous system damage in children with COVID-19

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Abstract: *this work is devoted to the study of the features of the structure of symptoms related to the nervous system in children with coronavirus disease (COVID-19). During the COVID-19 pandemic, there is a rapid increase frequency of neurological lesions. The share of neurological manifestations in COVID-19 among adult patients is up to 82%, in children it ranges from 3% to 47%. The aim of the work was to study the frequency and structure of neurological symptoms in children who were hospitalized in an infectious disease hospital with a laboratory-confirmed diagnosis of COVID-19 during 2020-2022 and to determine prognostic factors of nervous system damage. Materials and methods: We retrospectively investigated 945 medical histories of children aged from birth to 18 years who were hospitalized at the Kyiv City Children's Infectious Disease Hospital ("KCCIDH") in Kyiv, Ukraine during the pandemic. Among them, we analyzed cases accompanied by neurological symptoms. Features of the clinical picture, laboratory and demographic-epidemiological data were determined. The statistical calculation of the obtained results was carried out by using the statistical package Statistical software EZR v. 1.54. Results: Neurological symptoms were detected in 142 (15%) children, the majority of them were adolescents (55.6%). The leading symptoms of nervous system involvement were headache, ageusia/anosmia, convulsive syndrome, acute polyneuropathy, and myalgia/arthralgia. According to the analysis of odds ratio developing of neurological symptoms among patients in our cohort, children of the older age group (10-18 years) had statistically greater chances developing of neurological manifestations. Odds ratio developing of the aforementioned symptoms depending on clinical syndromes were also analyzed. Among respiratory syndromes, the presence of cough (5.53; 95%CI 3.53-8.65) and signs of lower respiratory tract inflammation (1.8; 95%CI 1.21-2.67) were associated with a higher risk of nervous system symptoms damage. According to the study of laboratory indicators, an increased level of leukocytes (2.01; 95%CI 1.2-3.38) was associated with an increase frequency of neurological manifestations, and in groups of patients with an increased level of C-reactive protein (0.39; 95%CI 0.23-0.68) or procalcitonin (0.21; 95% CI 0.11-0.43), on the contrary, a lower frequency of neurological symptoms was observed. Conclusions: Neurological symptoms occur in 15% of children with COVID-19. According to the results of our work, the older age of the child, cough and symptoms of inflammation of the lower respiratory tract are the prognostic factors of the occurrence of neurological symptoms in children with COVID-19. In addition, our study demonstrated the prognostic value of the appearance of neurological symptoms with an increase in the leukocyte index, as well as the absence of a correlation of neurological symptoms with an increase in CRP and procalcitonin.*

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Key words: children, neurological manifestations, central nervous system, COVID-19, cerebrospinal axis.

Introduction

COVID-19 continues to pose a challenge to the pediatric population. Since the fall of 2020 and over the course of three years, the share of children in the structure of patients with COVID-19 in Ukraine has been increasing significantly. According to the data from Ministry of Health of Ukraine, since the beginning of 2022 the number of children hospitalized with or suspected of having COVID-19 has increased almost fourfold. The frequency of hospitalization of children with serious and complicated cases also continues to rise (Cloete H., et al., 2022; Khandia R., et al., 2022). Although, in general, published data from various countries indicate that the share of children among patients with COVID-19 is relatively small and amounts to 5%, there are also risks of developing severe and complicated forms of the disease (Moreira A., et al., 2021).

A rapid increase quantity of reports about neurological complications in patients with COVID-19 has been observed increasingly during the pandemic. The spectrum of COVID-19 neurological manifestations among adult patients is, according to various data, up to 82% and is represented in the acute period by delusions and convulsions (34 %), fatigue (32%), myalgia (20%), impaired smell or taste and headache (13%). Patients are also diagnosed with stroke in 2% of cases, meningoencephalitis and Guillain-Barré syndrome in 10% of cases (Misra S., et al., 2021). Anosmia was observed in patients with a mild course with a frequency from 34% to 89% (Giacomelli A., et al., 2020; Lechien J.R., et al., 2020). According to the description of neurological manifestations published by the Ministry of Health of Ukraine, in the post-covid period was registered such clinical symptoms in patients, as fatigue (63%), myalgia (63%), sleep disturbances (26%), anxiety disorders and depression (23%), difficulty concentrating (24%), headaches (13%), dizziness (12%), confusion (11%), nervous excitement (45%) and cognitive impairment (15%). Numerous neurological and psychiatric disorders can be observed even during six months after COVID-19. According to published studies, where more than 230,000 patients were analyzed, the frequency of neurological and psychiatric diagnoses in patients after COVID-19 in the next six months amounted to more than 33%, and in almost 13% of cases the diagnosis was established for the first time. In patients who were treated in the intensive care unit, this frequency was 46.42%, and was represented by ischemic stroke, dementia, intracranial hemorrhages, parkinsonism, psychotic and anxiety disorders (Taquet M., et al., 2021).

This aspect remains understudied among children. From 3% to 47% of children with COVID-19 may have symptoms of nervous system damage according to available meta-analyses and literature data (Garazzino S., et al., 2020; Frank C.H., et al., 2020; Sandoval F., et al., 2021). The most common symptoms are headache (61%), encephalopathy (15.3%) and pyramidal signs (7.6%). Symptoms of peripheral nervous system damage include muscle weakness (61.5%), hypo/areflexia (23%), ageusia (15.3%) and anosmia (7.6%). The frequency of the peripheral nervous system damage in children is 7-15%, according to a study in Great Britain (Abdel-Mannan O., et al., 2020). Guillain-Barre syndrome in children is described with a frequency of 15 cases per 100,000 of population, and convulsions in 20-30%. Common symptoms of Guillain-Barre in children included weakness of the lower and upper extremities, paresthesia, and ataxia. (Panda P.K., et al., 2021; Kurd M., et al., 2021).

There is information about the association between severe neurological complications in children and multisystem inflammatory syndrome (MIS-C). In particular, according to American scientists, 31–47% of children diagnosed with MIS-C had neurological symptoms, including headache, encephalopathy, and altered mental status (Cheung E.W., et al., 2020; Dufort E.M., et al., 2020). According to the results of a multicenter study in the United States, 5% of children diagnosed with MIS-C had serious neurological complications such as seizures, coma, encephalitis, demyelinating disorders, and serous meningitis (Feldstein L.R., et al., 2020). Another study in the United Kingdom demonstrated the presence

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of neurological symptoms in 4 of 27 patients with MIS-C, including dysarthria, dysphagia, encephalopathy, cerebellar ataxia, and peripheral neuropathy. Neuropathy was characterized by general weakness of proximal muscles and decreased reflexes (Abdel-Mannan O., et al., 2020).

Aim

To investigate the frequency and structure of neurological symptoms in children who were hospitalized in an infectious disease hospital with a laboratory-confirmed diagnosis of COVID-19 during 2020-2022 and to determine prognostic factors of the nervous system damage.

Materials and methods

There was a retrospective, single-center and cohort research. The exploration of 945 medical histories of children who were hospitalized to the Kyiv City Children's Clinical Infectious Diseases Hospital (KCCCIDH) (Kyiv, Ukraine) with COVID-19 in the period from June 2020 to February 2022 was conducted.

The study is part of the research work "Modern features of acute neuroinfectious in children" which is perform by Pediatric infectious diseases department of the Bogomolets National Medical University, state registration number №0119U103914.

Among 945 medical histories, 142 cases with neurological symptoms were analyzed. The main inclusion criteria for the study were children with PCR-confirmed COVID-19 who had symptoms of headache, ageusia/anosmia, myalgia/arthralgia, convulsions, polyneuropathy without any organic causes in the anamnesis. Among the exclusion criteria, it should be noted that the study did not include cases of refuted COVID-19, congenital malformations of the central nervous system, oncological diseases of the nervous system, perinatal brain lesions, and any neurological diagnoses in the anamnesis. The conduct of this study was agreed with the hospital's bioethics committee. A retrospective evaluation of routine medical information did not involve obtaining patients informed agreement.

Due to the International Classification of Diseases (ICD) we determined the diagnostic code U07.1. In accordance with the current protocol, laboratory confirmation was carried out using a one-time PCR study of a nasopharyngeal swab. The PCR study was conducted in the hospital's local laboratory. In the presence of a positive PCR test for SARS-Cov-2, the case was confirmed.

We analyzed the medical records regarding the anamnesis of the disease, clinical-epidemiological and laboratory data of the patients.

If the children had symptoms of cough, nasal congestion, rhinorrhea or runny nose than an upper respiratory tract infection (URTI) was diagnosed. Indicators of lower respiratory tract infection (LRTI) included cough, dyspnea, auscultatory changes or parenchymal changes on chest X-ray examination.

With the aim to study the age-related clinical and epidemiological characteristics of all patients, we divided them into four age categories: less than 12 months, 1-5 years, 6-9 years and 9-18 years.

The statistical analysis results of the research provided by the statistical package Statistical software EZR v.1.54 and performed point, interval distribution estimates and used the D'Agostino-Pearson test.

Figure 1. Age structure of patients with COVID-19 and neurological manifestations

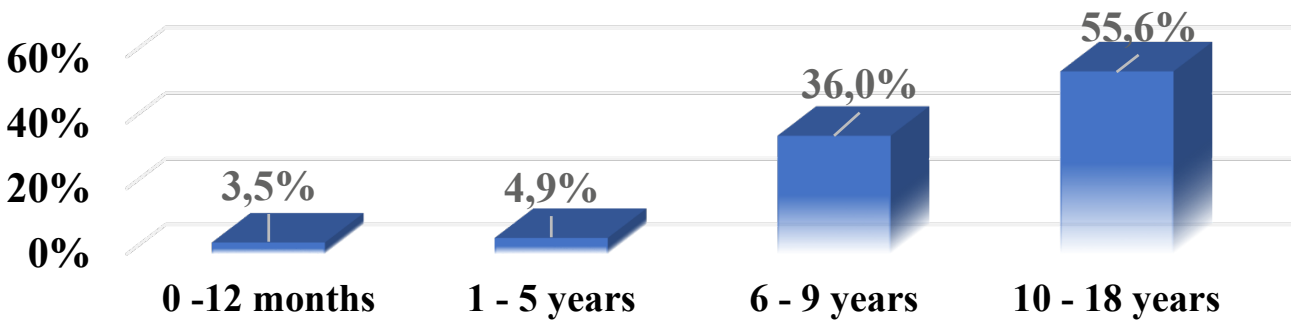

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Table 1. Interval assessment of the frequency of neurological symptoms in children

Symptoms	The number of patients with this manifestation, n	Frequency of neurological manifestations, % (95% CI)
Headache	45	31,7 (24,3-39,6)
Ageusia/anosmia	34	23,9 (17,3-31,3)
Seizure syndrome	3	2,1 (0,4-5,1)
Polyneuropathy	12	8,5 (4,4-13,6)
Myalgia/arthralgia	18	12,7 (7,7-18,7)

Results

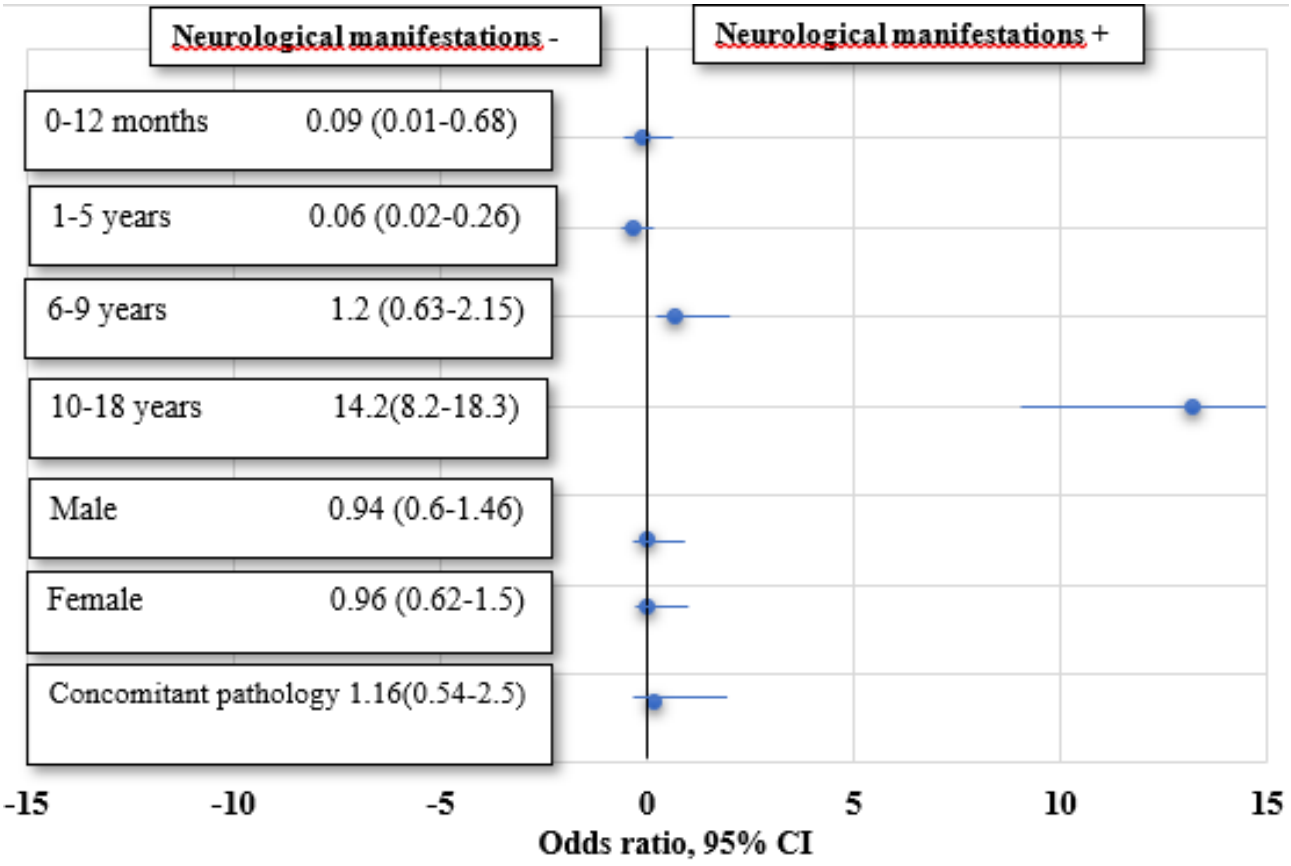
Among this cohort of children, neurological symptoms were noted in 142 (15%) patients. The age structure of the patients is shown in Figure 1.

According to the age distribution, adolescents from 10 to 18 years of age prevailed, 55.6%, (79/142), p=0.058. The next largest number was the group of children aged from 6 to 9 years, 36%, (51/142), p<0.001. Patients from birth to 12 months were 3.5%, (5/142) and children aged 1 to 5 years - 4.9%, (7/142), p<0.001. No significant difference was observed in the gender structure.

The leading neurological symptoms in children were headache, ageusia/anosmia, convulsive syndrome, acute polyneuropathy and myalgia/arthralgia. Interval assessment of the frequency of the above-mentioned symptoms is presented in Table 1.

Headache was observed in 31.7%, (45/142) of cases and its duration was from 1 to 14 days (median - 2 days). Symptoms of ageusia and anosmia were observed in 23.9%, (34/142), of which 97% (33) of patients were children over 10 years old. The average age of patients with anosmia/ageusia

Figure 2. Adjusted odds ratio for neurological symptoms among hospitalized patients with COVID-19.



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was 14.9 years. The duration of these symptoms was from 2 to 14 days (median - 7 days). Convulsive syndrome was observed in 2.1%, (3/142) of children, the duration varied from 1 to 4 days (median – 1 day). Acute polyneuropathy was observed in 8.5% (12/142) of patients, with an average duration from 5 to 10 days (median–7 days), myalgia/arthralgia in 12.7%, (18/142) of children with an average duration from 1 to 15 days (median – 4 days). It should be noted that the symptoms of headache, anosmia and ageusia were not determined in children under the age of 1 year. In all these cases, there was a rapid recovery of neurological dysfunction with complete clinical recovery at the time of discharge.

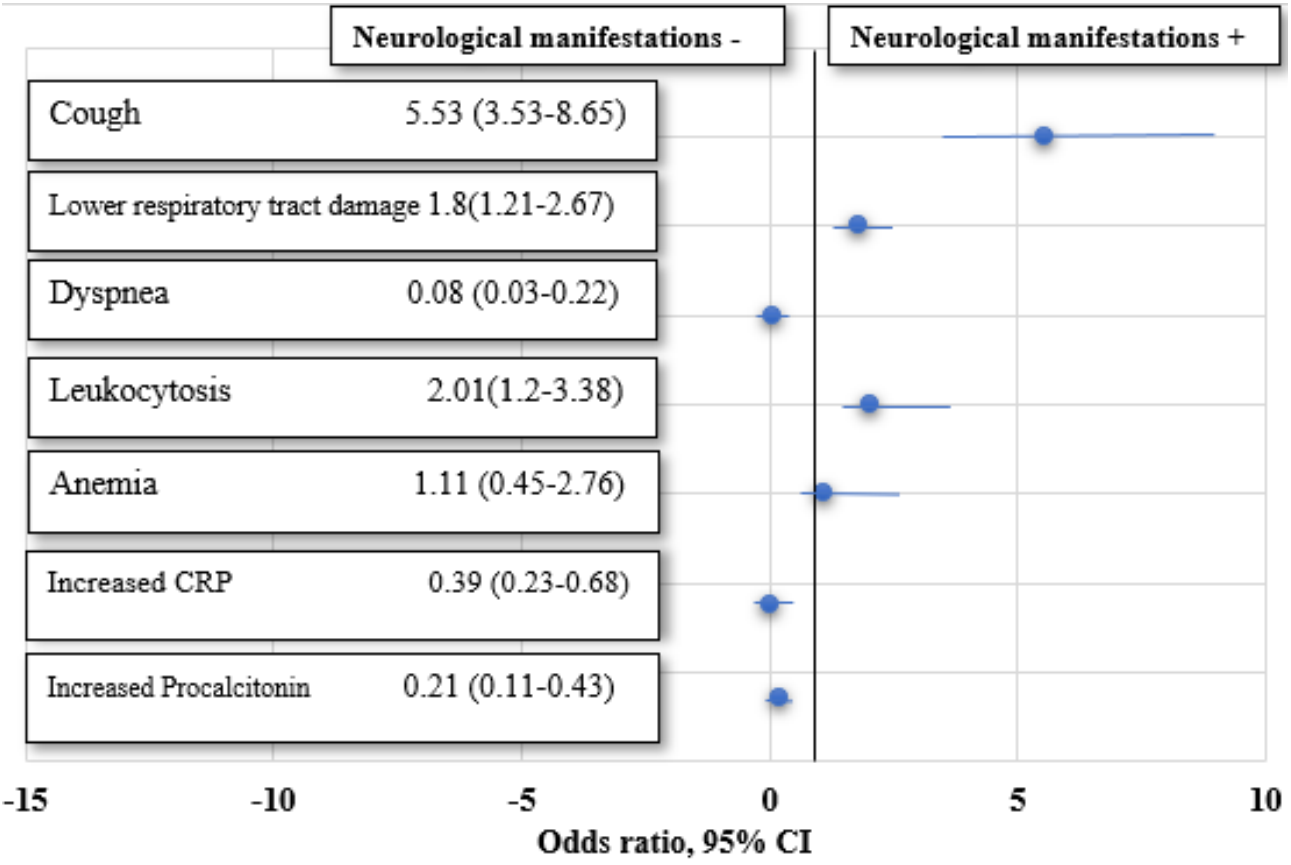
We analyzed the relationship between neurological symptoms (presence of at least one neurological symptom) and other factors, in particular, demographic data (age, gender, comorbidities), respiratory symptoms (cough, LRTI), shortness of breath), the presence of anemia (hemoglobin level <110 mg/l), severity of inflammatory reaction (increased level of leukocytes (>9 G/l), increased C-reactive protein (CRP>6 mg/l) and increased level of procalcitonin (PCT>0.05 ng/ml)).

Figure 2 shows the adjusted odds ratio for the development of neurological symptoms in children with COVID-19.

According to the results of the data analysis among the patients of our cohort (Fig. 2), children of the older age group (10-18 years) had a statistically higher chance of developing neurological symptoms (14.2; 95%CI 8.2-18.3). At the same time, other age categories and gender did not have a significant relationship with the frequency of neurological symptoms.

We found concomitant pathology in 6% (9/142) of patients, which was presented in the form of allergic dermatitis, obesity, bronchial asthma, and Minkowski-Shofar anemia. There was no reliable connection with the frequency of neurological symptoms in children with existing concomitant pathology.

Figure 3. Adjusted odds ratio for neurological symptoms in COVID-19 depending on clinical syndromes and laboratory parameters



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Odds ratio of the development of neurological symptoms depending on clinical syndromes and laboratory parameters were also analyzed, shown in Figure 3.

Cough (5.53; 95% CI 3.53-8.65) and signs of lower respiratory tract inflammation (1.8; 95% CI 1.21-2.67) were associated with a higher risk of neurological manifestations (Fig. 3). At the same time, shortness of breath (0.08; 95% CI 0.03-0.22) was accompanied by a lower frequency of neurological symptoms.

Indicators levels of leukocytes (2.01; 95% CI 1.2-3.38), C-reactive protein (0.39; 95% CI 0.23-0.68) and procalcitonin (0.21; 95% CI 0.11-0.43) had prognostic value for the appearance of neurological symptoms. But, if an increased level of leukocytes in the peripheral blood was associated with an increase frequency of neurological symptoms, then in groups of patients with an increased level of C-reactive protein or procalcitonin, on the contrary, a lower frequency of neurological symptoms was observed.

Discussion

This study was carried out in a specialized children's infectious hospital in Kyiv, which from the first days of the pandemic became a specialized hospital for patients with COVID-19. It's determining the representativeness of this research from the point of studying view of the disease characteristics among the children's population of the largest city in Ukraine.

Having analyzed the relationship of neurological manifestations with such factors, as age, sex, concomitant pathology, respiratory symptoms and laboratory indicators, we found statistically greater chances of developing neurological symptoms in adolescents, compared to other age groups of patients. In addition, the older age group of children (10-18 years) prevailed in the age distribution of the studied cohort, p=0.058. Numerous studies also indicate the predominance of adolescents in the structure of neurological complications of COVID-19 (Siracusa L., et al., 2021; Siddique R., et al., 2022). Most of older pediatric patients have neurological manifestations, mainly represented by symptoms of headache, anosmia, ageusia. Manifestations are mild and usually do not complicate the course of the disease. However, in some cases, severe complications associated with changes in neuroimaging and electroencephalography may develop. Encephalopathy, encephalitis, central or peripheral acute flaccid paralysis, acute disseminated encephalomyelitis, convulsions, and stroke are found in children with laboratory-confirmed SARS-CoV-2 infection (Singer T.G., et al., 2021; Principi N., et al., 2021).

However, symptoms such as headache, ageusia, and anosmia are difficult to assess in young children, so the dependence of such manifestations on age has certain limitations here is a need to pay attention to other important signs. Overall, there is little published data on neurological symptoms in infants with COVID-19. Available case reports have limited generalizability, and many lack sufficient detail to establish a causal relationship between SARS-CoV-2 and neurological symptoms (Stafstrom C.E. et al., 2020). In published studies, the authors describe neurological symptoms in infants in the form of hypotension, drowsiness, upward deviation of the eyes, stiffness, lethargy, encephalopathy, stiff legs, convulsions, irritability, and hypertonia (Nathan N.et al.,2020; Chacon-Aguilar R. et al., 2020; Lorenz9999N. et al.,2020; Dugue R. et al., 2020; Vivanti A.J. et al.,2020).

According to the literature, severe neurological manifestations in children with COVID-19 are associated with a complicated course of the disease, accompanied by MIS-C and concomitant chronic pathology. The frequency of nervous system damage in case of MIS-C can reach 55% (Lin J.E., et al., 2021; Esposito S., Principi N., 2021). In a study by Chen TH., et al., 2020, 34% of children with MIS-C had meningitis, encephalitis, manifested by headache, positive meningeal signs and changes in mental status.

When we evaluated the odds ratio development of symptoms as a signs of nervous system damage depending on the existing respiratory manifestations, cough and signs of lower respiratory tract inflammation were correlated with a higher risk of the study complications.

There are no similar comparisons in the data of published sources, but numerous authors also emphasize the development of neurological symptoms against the background of acute respiratory symptoms (Whittaker A., et al., 2020; Berlit P., et al., 2020; Harapan B.N., et al., 2021).

We singled out such a symptom as cough in the evaluation of the relationship with neurological

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symptoms, because this respiratory sign can be associated with lesions of nervous system. Cough is a reflex that is modulated by the cerebral cortex and mediated by control centers in the respiratory regions of the brainstem. Researcher Al-Biltagi M et al.,2022, described a wide range of neurological disorders in which the sensitivity of the cough reflex may be increased. These include, in particular, brainstem lesions, secondary bone marrow lesions, tics, somatic cough, cerebellar neurodegenerative diseases, and neuropathies. Cough sensitivity may also decrease in multiple sclerosis, cerebral hypoxia, cerebral-hemispheric stroke with brainstem shock, peripheral neuropathy, and hereditary sensory and autonomic neuropathy type IV. In the case of our study, the cough is directly related to the underlying respiratory disease, but it is worth remembering the importance of assessing the cough reflex during the cranial nerves examination in order to timely identify lesions of the nervous system.

Among the laboratory data, we found a prognostic value for the appearance of neurological symptoms in the leukocyte index, CRP and procalcitonin. An increase level of leukocytes was correlated with an increase frequency of neurological symptoms. However, a lower frequency of detection of neurological manifestations was observed in patients with elevated levels of procalcitonin and CRP. The obtained data correlate with the results of published studies of a relatively easy and uncomplicated course of COVID-19 (Li Y., et al., 2020). Severe and complicated cases are accompanied by a high level of inflammatory markers (CRP, ESR, fibrinogen, D-dimer, procalcitonin) (Cheung E.W., et al., 2020; Dufort E.M., et al., 2020; Carter M.J., et al., 2020). The main reason for these changes, which is explained in the literature, is the hyperreactivity of the immune system, which leads to a violation of the hematoencephalic barrier due to the action of pro-inflammatory cytokines IL-1β, IL-6, TNFα and IL-17. Cytokines activate glial cells and stimulate neuroinflammation, leading to increased neuronal excitability, seizures and main manifestations (Dantzer R., 2018; Helms J., et al., 2020).

Our research has certain limitations. In particular, the retrospective nature and limitation of the sample to one clinical center. In addition, there is a problem of terminology, since the concept of neurological symptoms currently does not have a clear, generally recognized spectrum. The quality of statistical processing and the determination of statistical relationships could also be affected by the analysis of data from patients of different age groups, which covered the period of infancy, younger and older childhood. In particular, this concerned subjective symptoms, the assessment of which is difficult in younger children. Further research in this direction is needed to clarify the frequency and spectrum of neurological disorders in children with coronavirus disease. It is advisable to expand the collection of medical data also due to the post-infection period.

Conclusions

Neurological symptoms occur in 15% of children with COVID-19. According to the results of our work, the older age of the child, cough and symptoms of inflammation of the lower respiratory tract are the prognostic factors of the occurrence of neurological symptoms in children with COVID-19. In addition, our study demonstrated the prognostic value of the appearance of neurological symptoms with an increase in the leukocyte index, as well as the absence of a correlation of neurological symptoms with an increase in CRP and procalcitonin. Further observations and conducted studies will include a larger patient cohort, the acute onset of neurologic symptoms, rates of progression, and long-term outcomes of neurological disorders in children with COVID-19.

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This study did not receive funding.

Conflict of interests

The authors declare no conflict of interests.

Consent to publication

Consent was obtained from participants included in the study.

ORCID ID and Author contributions

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Прогностичні фактори ураження нервової системи у дітей з COVID-19

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Анотація: ця робота присвячена вивченню особливостей структури симптомів пов'язаних з нервовою системою у дітей з коронавірусною хворобою (COVID-19). За час пандемії COVID-19 спостерігалося стрімке збільшення частоти уражень неврологічного характеру. Частота неврологічних проявів при COVID-19 серед дорослих пацієнтів становить до 82%, у дітей коливається від 3% до 47%. Метою роботи було дослідження частоти та структури неврологічних симптомів у дітей, які перебували на стаціонарному лікуванні в дитячій інфекційній лікарні з лабораторно підтвердженим діагнозом COVID-19 впродовж 2020-2022 років та визначення прогностичних факторів ураження нервової системи. Матеріали і методи: Було проведено ретроспективний аналіз 945 історій хвороб дітей віком від народження до 18 років, які

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були госпіталізовані до Київської міської дитячої інфекційної лікарні (КНП «КМДКІЛ») міста Києва, Україна в період пандемії. Серед них було проаналізовано випадки, що супроводжувались неврологічними симптомами. Визначались особливості клінічної картини, лабораторні та демографічно-епідеміологічні дані. Статистичний аналіз отриманих результатів проводився із використанням статистичного пакету Statistical software EZR v. 1,54. Результати: Неврологічні симптоми були виявлені у 142 (15%) дітей, з них переважну кількість становили підлітки (55,6%). Провідними симптомами ураження нервової системи були головний біль, агевзія/аносмія, судомний синдром, гостра полінейропатія та міалгія/артралгія. За результатами аналізу даних відношення шансів розвитку неврологічних симптомів серед пацієнтів нашої когорти, статистично більші шанси розвитку неврологічних проявів мали діти старшої вікової групи (10-18 років). Також були проаналізовані коефіцієнти відношення шансів розвитку вищезгаданих симптомів залежно від клінічних синдромів. Серед респіраторних синдромів наявність кашлю (5.53; 95%ВІ 3.53-8.65) та ознаки ураження нижніх дихальних шляхів (1.8; 95%ВІ 1.21-2,67) асоціювались із вищим ризиком появи симптомів ураження нервової системи. За даними дослідження лабораторних показників, збільшений рівень лейкоцитів (2.01; 95%ВІ 1.2-3.38) асоціювався із зростанням частоти неврологічних проявів, а в групах пацієнтів із підвищеним показником С-реактивного білку (0.39; 95%ВІ 0.23-0.68) або прокальцитоніну (0,21; 95%ВІ 0,11-0,43), навпаки, спостерігалась менша частота виявлення неврологічної симптоматики. Висновки: Неврологічні симптоми виникають у 15% дітей з COVID-19. За результатами нашої роботи прогностичними факторами виникнення неврологічної симптоматики у дітей із COVID-19 є старший вік дитини, кашель та симптоми ураження нижніх дихальних шляхів. Крім того, наше дослідження продемонструвало прогностичну цінність появи неврологічної симптоматики з підвищенням лейкоцитів, а також відсутність кореляції неврологічних проявів з підвищенням СРБ і прокальцитоніну.

Ключові слова: діти, неврологічні прояви, центральна нервова система, COVID-19.

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Skin care interventions and early complementary food introduction for the prevention of atopic dermatitis in infants

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Abstract: *atopic dermatitis and food allergy are common diseases that usually begin in early childhood and can occur together in the same individuals. The aim of this study was to assess the significance of interventions such as skin care products for the skin barrier improvement, breastfeeding and early complementary foods introduction for the primary prevention of atopic dermatitis and food allergy in infants by building logistic regression models. We performed a survey of 97 parents of children. The survey was conducted with the help of Google forms and distributed on the Internet. Method of building and analysing logistic regression models was used to analyse the association of the risk of atopic dermatitis in children with the factor characteristics. Characteristics were as follows: "Skin care 1: application moisturizers to the infant's skin", "Skin care 2: bathing infants with water containing moisturizing substances or moisturizing oils", "Skin care 3: usage of less soap, bathing the child less often", "paternal history of atopy", "duration of breastfeeding less than 1 year", "early introduction of supplementary food (up to the 6th month of life)". We obtained the following results: 42.2% of respondents reported about the application of moisturizing cream, parents of 16.5% of children were using moisturizing oil for bathing the child, 12.4% of parents used less soap and bathed the child less often, 28.9% reported that they were not using any interventions. It was established that when applying care method 1, namely applying moisturizing agents to the infant's skin, the risk of developing atopic dermatitis increases, OR=12.8 (95% CI 3.89 - 42.3) (p<0.0001). When constructing a three-factor logistic regression model for predicting the risk of food allergy, no dependence was found between the development of food allergy and the presence of allergic diseases in parents, the period of introduction of complementary foods, and the duration of breastfeeding. Thus, this study did not reveal the protective role of skin care products, breastfeeding, and early introduction of complementary foods for the development of atopic dermatitis and food allergies in children. Multivariate analysis showed that atopic dermatitis is associated with emollients application to the infant's skin. The use of moisturizing creams for the treatment of already existing atopic dermatitis or the path of percutaneous sensitization to allergens could have influenced the data.*

Key words: atopic dermatitis, breastfeeding, children, emollients, food allergy.

Introduction

Atopic dermatitis (AD) and food allergy are common diseases that usually begin in early childhood and can occur together in the same individuals (О.П. Волосовець та ін., 2021). These conditions may be associated with a violation of the skin barrier in early childhood. Whether trying to prevent or correct skin barrier disruption

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early in life is effective in preventing AD or food allergy remains to be elucidated. In general, emollients are considered safe agents with few side effects. However, applying enough emollients every day can sometimes have a negative impact on the child and family due to burning sensation, especially on skin with existing eczema (Oakley R & Lawton S, 2016). There is a concern that emollients can actively sensitize to individual components, leading to skin reactions (Danby et al., 2011, Kunkiel et al., 2022) and even systemic allergic reactions (Voskamp et al., 2014).

Skin barrier protection can also be achieved by limiting water loss through the skin or by limiting skin contact with potentially harmful substances or irritants. Activities and substances that can damage the skin barrier, especially in people with existing eczema, include excessive bathing, detergents, and hard water. Thus, addressing any of these factors in the first months of life could potentially improve skin hydration and barrier function, thereby reducing further AD deterioration.

The close relationship between AD and food allergy suggests that reducing clinical manifestations of AD may potentially reduce the risk of food allergy, even if it is simply delaying the onset of AD in early childhood period (Martin et al., 2015). A small pilot study of the effectiveness of a ceramide-based emollient reported a reduction in allergic sensitization to food products (Lowe et al., 2018).

A Cochrane review of studies examining the value of infant skin care interventions for the development of AD and food allergy included 33 studies involving 25,827 infants (Kelleher et al., 2021). Skin care was compared with no skin care or usual care (standard care). A study on the development of AD, which included data from 3075 participants in seven randomized controlled trials, found that skin care interventions were unlikely to affect the development of AD between one and two years of age in healthy full-term infants compared with standard care. This Cochrane review also found that the skin care interventions were unlikely to change the time of eczema onset compared with the standard care (based on 3,349 participants in nine studies). This is thought to be important for the interaction between eczema and food allergy, as increased duration of eczema is associated with an increased likelihood of food sensitization (Tsilochristou et al., 2019).

Aim

The aim of this study was to assess the significance of interventions such as skin care products for the skin barrier improvement, breastfeeding and early complementary foods introduction for the primary prevention of atopic dermatitis and food allergy in infants by building logistic regression models.

Materials and methods

We performed a survey of 97 parents of children in the period from May till June 2022. The survey was conducted with the help of Google forms and distributed on the Internet.

We included in the questionnaire all skin care interventions that could potentially enhance skin barrier function, reduce dryness, or reduce inflammation. They include:

- applying moisturizing agents to the child's skin;
- bathing infants with water containing moisturizing substances or moisturizing oils;
- use less soap, bathe the child less often.

During the survey, it was possible to indicate one, several or all options. The presence of undesirable effects from the use of the means was determined, in particular, the presence of irritation, burning, redness. The survey included questions about the presence of AD, defined as rash\dryness\flaking\crusting\itching of the skin lasting more than 4 weeks. The age of onset of the disease was also determined. The presence of a food allergy was defined as a reaction to food products that occurs within 2 hours after consuming the product; the questionnaire also included questions about the parent's allergic history, the duration of breastfeeding, and the age at which complementary foods were introduced. Children with parental allergy history were defined as a risk group.

Statistical processing of the obtained data was carried out using the statistical package IBM SPSS Statistics Base (version 22), EZR version 1.32 (graphical interface of the R environment (version 2.13.0). The research database was systematized in the Microsoft Excel editor.

ROC-analysis with construction of a characteristic curve (ROC-curve, receiver operator

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characteristic curve) was used. When constructing it, the sensitivity values for each value of the characteristic (the frequency of true positive results) are placed on the vertical axis, and 1 minus the specificity (the frequency of false positive results) is placed on the horizontal axis. The diagonal line shows the value of a completely uninformative random test result. Curves with greater significance are located closer to the upper left corner of the graph. The value of the area under the characteristic curve shows the ratio of sensitivity and specificity. The quality of the scale was assessed using the area under the curve (AUC): in the interval 0.9–1.0 – excellent, 0.8–0.9 – very good, 0.7–0.8 – good, 0.6 –0.7 is mediocre, 0.5–0.6 is unsatisfactory. The larger the area under the ROC curve was, the higher was the predictive value of the predictor.

The prognostic significance of factors regarding the formation of AD was assessed by the odds ratio (OR) with a confidence interval (CI) of 95%. To determine independent predictors of the occurrence of adverse allergic events, stepwise multivariate regression analysis of Cox proportional hazards was used. The determination of standardized regression coefficients (β) and determination of their exponents reflected the increase in the risk of occurrence of the expected event when the value of the factor changes by one unit. Factors that remained significant in multivariate analysis were interpreted as independent predictors. For all types of analysis, differences were considered probable at $p < 0.05$.

Results

Parents of 97 children were involved in our survey between May 2022 and June 2022. The average age of the children was 6.5±3.92 years. 33.0% of the respondents reported that their children had an atopic parental history. According to the survey data, 42.2% of children received a moisturizing cream, parents of 16.5% of children reported using moisturizing oil for bathing the child, 12.4% of parents used less soap and bathed the child less often, 28.9% reported that they did not use none of these methods and means of care. 7.2% of respondents reported that skin irritation, redness, burning was noted when using the products, 92.8% did not encounter any unwanted effects or adverse reactions.

AD occurred in 23.7% children of interviewed. 18.6% of respondents reported that the child has reactions to food that occur within 2 hours after eating it.

Method of building and analyzing logistic regression models was used to analyse the association of the risk of AD in children (Y) with the factor characteristics. The characteristics were as follows: “Skin care 1: application moisturizers to the infant’s skin” (X1), “Skin care 2: bathing infants with water containing moisturizing substances or moisturizing oils” (X2), “Skin care 3: usage of less soap, bathing the child less often “ (X3), “paternal history of atopy “ (X5), “duration of breastfeeding less than 1 year “ (X6), “early introduction of supplementary food (up to the 6th month of life)” (X7). The analysis was conducted on the results of the examination of 97 children.

Based on the calculations in the EZR package, the ROC curve of the six-factor logistic regression model of AD risk prediction was obtained (see Fig. 1).

When building a six-factor model, the dependence of AD risk on factor characteristics was revealed, the area under the ROC curve AUC = 0.83 (95% CI 0.73 – 0.92), statistically significance ($p<0.05$) exceeded 0.5, which was the evi-

Fig. 1. ROC curve of the six-factor logistic regression model of AD risk prediction.

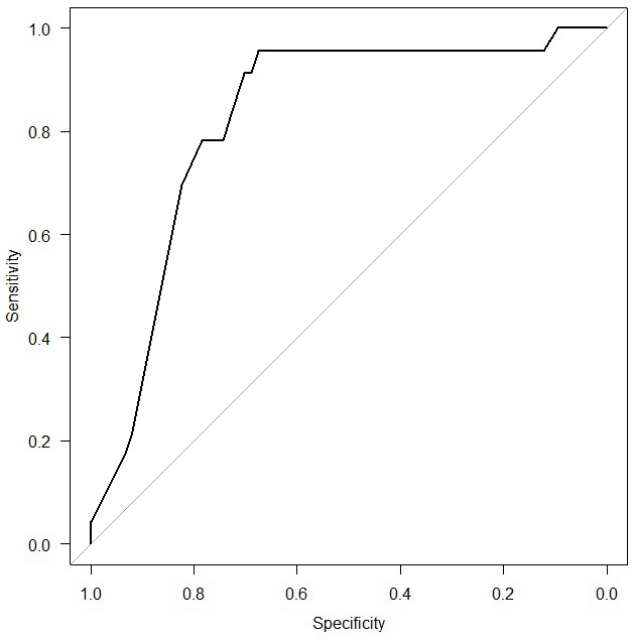

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Table 1. Coefficients of the 6-factor logistic regression model for predicting the risk of AD

Potential risk factors	The value of the coefficient of the model, b±m	The level of significance of the difference of the coefficient of the model from 0, p	OR (95% CI)
X1 Care (1) application moisturizers to the infant's skin	3,19±1,09	0,003*	24,2 (2,8–204)
X2 Care (2) bathing infants with water containing moisturizing substances or moisturizing oils;	1,39±1,3	0,29	4,0 (0,3–51,7)
X3 Usage of less soap, bathing the child less often	0,64±1,47	0,67	1,9 (0,1–33,8)
X5 Paternal history of atopy	0,52±0,6	0,39	1,7 (0,5–5,5)
X6 Duration of breastfeeding less than 1 year	–1,2±0,76	0,11	0,3 (0,1–1,3)
X7 Early introduction of supplementary food (up to the 6th month of life)	0,27±0,74	0,71	1,3 (0,3–5,6)
Constant	–3,21±1,06	0,002 *	

*Note: * – p<0.05.*

dence of the adequacy of the built model according to the quality scale "good".

Table 1 shows the results of estimating model coefficients.

To select the minimum set of factor characteristics associated with the original variable, the method of stepwise rejection/inclusion of variables ("Stepwise") was used. A single factor sign associated with the risk of AD was highlighted: "Skin care 1: applying moisturizers to the child's skin". When comparing the prognostic characteristics of the one-factor logistic forecasting model (the area under the ROC curve AUC=0.78 (95% CI 0.68–0.87), statistically significance (p<0.05) exceeds 0.5. Quality of the model built on all six variables did not reveal their deterioration. Table 2 shows the results of estimating model coefficients.

The obtained mathematical model of AD risk prediction can be expressed by the formula:

$$\ln(Y/1\text{-}Y) = -2.6 + 2.55X1$$

Thus, it was established that AD is associated with "Care (1) application of moisturizing agents to the infant's skin" (p<0.05). It was established that when applying care method 1, namely applying moisturizing agents to the infant's skin, the risk of developing AD increases, OR=12.8 (95% CI 3.89 - 42.3) (p<0.0001) (Table 2).

When constructing a three-factor logistic regression model for predicting the risk of food allergy, no dependence was found between the development of food allergy and the presence of allergic diseases in parents, the period of introduction of complementary foods, and the duration of breastfeeding.

Table 1. Coefficients of the one-factor logistic regression model of AD risk prediction

Potential risk factors (factor sign)	The value of the coefficient of the model, b±m	The level of significance of the difference of the coefficient of the model from 0, p	OR (95% CI)
X1 Care (1) application moisturizers to the infant's skin	2,55±0,61	<0,0001 *	12.8 (3.89 - 42.3)
Constant	–2,60±0,52	<0,0001*	

*Note: * – p<0.05.*

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Discussion

In this study the dependence of AD risk on factor characteristics was revealed by building a six-factor model. The role of such factors as skin care interventions (application moisturizers to the infant's skin, bathing babies with water containing moisturizing substances or moisturizing oils and usage of less soap), paternal history of atopy, duration of breastfeeding and early introduction of supplementary food was studied. The area under the ROC curve AUC = 0.83 (95% CI 0.73 – 0.92) was statistically significant ($p<0.05$), so the adequacy of the built model according to the quality scale was "good". Multivariate analysis showed that AD is associated with emollients application to the infant's skin (OR=12.8 (95% CI 3.89 - 42.3) ($p<0.0001$). Although the questionnaire determined the use of emollients from birth, i.e. for the prevention of AD, there is a possibility that the use of moisturizing creams for the treatment of already existing AD could have influenced the data. In the opposite case, the path of percutaneous sensitization cannot be excluded, when microparticles of food or other allergens can get into the cream during the application of the emollient to the skin (Ryczaj et al., 2022).

Although studies on the effects of skin care and feeding interventions on the development of allergies are described in the literature, these practices vary greatly between countries and depend on traditional, cultural, socio-economic and other factors.

The BEEP trial of 1,394 infants, the first large randomized controlled trial to examine whether emollients could prevent eczema, found no evidence to support the hypothesis that the use of emollients daily could prevent AD (primary outcome), food allergy, sensitization, allergic rhinitis or asthma (secondary effects) (Chalmers et al., 2020). In addition, there was a slight increase in food allergy in the emollient group compared to the control group. The lack of benefit of emollients for the prevention of AD found in that study, same as in ours, was unexpected, especially given the reports in previously published pilot studies, and has serious implications for the primary prevention of AD and other diseases (Horimukai et al., 2014, Simpson et al., 2014). The increased risk of food allergy is likely due to the increased transfer and absorption of food antigens through the skin when emollients are applied, leading to the epicutaneous sensitization (Brough et al., 2020).

Understanding of the properties of skin barrier function at an early age has improved, and it is possible that other approaches to strengthening the skin barrier, based on new knowledge, may have a preventive effect. These approaches may include the use of newly developed emollients with improved skin barrier properties or a comprehensive intervention that includes additional measures such as low-pH detergents, infrequent washing, or softened water.

Conclusions

In this study we didn't find out the protective role of skin care products, breastfeeding, and early introduction of complementary foods for the development of atopic dermatitis and food allergies in children. Multivariate analysis showed that atopic dermatitis is associated with emollients application to the infant's skin. The use of moisturizing creams for the treatment of already existing atopic dermatitis or the path of percutaneous sensitization to allergens could have influenced the data.

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Conflict of interest

The authors declare no conflicts of interest.

Consent for publication

Authors have obtained consent for publication of this work from all patients relevant to this manuscript.

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Догляд за шкірою та раннє введення прикорму для профілактики атопічного дерматиту у немовлят

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Анотація: атопічний дерматит і харчова алергія є поширеними захворюваннями, які зазвичай починаються в ранньому дитинстві і можуть виникати разом в одних і тих самих людей. Метою цього дослідження було оцінити значення втручань, таких як засоби по догляду за шкірою для покращення шкірного бар'єру, грудне вигодовування та раннє введення прикорму для первинної профілактики атопічного дерматиту та харчової алергії у немовлят шляхом побудови логістичних регресійних моделей. Ми провели опитування 97 батьків дітей. Опитування було проведено за допомогою гугл-форм і розповсюджено в Інтернеті. Метод побудови та аналізу моделей логістичної регресії використано для аналізу зв'язку ризику розвитку атопічного дерматиту у дітей із факторними характеристиками. Характеристики були такими: «Догляд за шкірою 1: нанесення зволожуючих засобів на шкіру немовляти», «Догляд за шкірою 2: купання немовлят водою, що містить зволожуючі речовини або зволожуючі масла», «Догляд за шкірою 3: використання меншої кількості мила, купання дитини рідше», «атопія в анамнезі батьків», «тривалість грудного вигодовування менше 1 року», «раннє введення прикорму (до 6-го місяця життя)». Згідно з даними опитування, 42,2% дітей отримували зволожуючий крем, батьки 16,5% дітей повідомили, що використовували для купання дитини зволожуючу олію, 12,4% батьків використовували менше мила і рідше купали дитину, 28,9% повідомили, що не використовувати жодного з цих методів і засобів по догляду. Встановлено, що при застосуванні методу догляду 1, а саме нанесення зволожуючих засобів на шкіру немовляти, підвищується ризик розвитку атопічного дерматиту, ВШ=12,8 (95% ДІ 3,89 - 42,3) ($p<0,0001$). При побудові трифакторної логістичної регресійної моделі прогнозування ризику харчової алергії не виявило залежності між розвитком харчової алергії та наявністю алергічних захворювань у батьків, періодом введення прикорму та тривалістю грудного вигодовування. Таким чином, дане дослідження не виявило захисної ролі засобів по догляду за шкірою, грудного вигодовування та раннього введення прикорму для розвитку атопічного дерматиту та харчової алергії у дітей. Багатофакторний аналіз показав, що атопічний дерматит пов'язаний із застосуванням пом'якшувальних засобів для шкіри немовляти. Використання зволожуючих кремів для лікування вже наявного атопічного дерматиту або шлях черезшкірної сенсибілізації до алергенів могло вплинути на дані.

Ключові слова: атопічний дерматит, грудне вигодовування, діти, прикорм, емолієнти, харчова алергія.

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Аналіз асортиментної структури антидепресантів на вітчизняному фармацевтичному ринку

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Анотація: *особливістю перебігу захворювань, корекція яких потребує використання антидепресантів, є мала кількість звернень за спеціалізованою допомогою на ранніх стадіях розвитку психічних розладів. Це створює певні обмеження для швидкої та ефективної терапії. Проте, з огляду на те, що депресія є найпоширенішим психічним розладом у світі, з'являється певний науковий інтерес для дослідження цієї патології. Метою роботи є комплексний асортиментний аналіз групи N06A «Антидепресанти» на фармацевтичному ринку України. Вивчення асортименту зареєстрованих на фармацевтичному ринку антидепресантів проводили відповідно до Анатомо-терапевтично-хімічної класифікації та даних Державного реєстру лікарських засобів України. Об'єктами досліджень була інформація щодо зареєстрованих в Україні лікарських засобів, які належать до категорії N06A «Антидепресанти». Відповідно до даних Державного реєстру лікарських України, станом на січень 2022 року з урахуванням препаратів, що виробляються у різних дозуваннях, зареєстровано 149 торгових найменувань лікарських засобів, які належать до категорії N06A «Антидепресанти» та представлені 20 міжнародними непатентованими назвами. Із усіх зареєстрованих на фармацевтичному ринку України антидепресантів слід відмітити 52 препарати із обмеженим терміном дії реєстраційного посвідчення. На ринку ЛЗ для лікування депресії чітко домінують іноземні фармацевтичні компанії, а частка вітчизняних виробників представлена лише 18,1%, що свідчить про потребу розширення даної групи лікарських засобів, адже 9 із 20 міжнародних непатентованих назв не мають жодного вітчизняного препарату. На фармацевтичний ринок України антидепресанти імпортують із 19 країн світу. Основними країнами імпортерами є: Індія – 18,9%, Словенія – 12,3 %, Німеччина – 9,0 %, Польща та Туреччина – по 7,4 %, Угорщина – 5,7 %. Інші країни сумарно займають 39,3 % фармацевтичного ринку імпортних лікарських засобів із категорії N06A «Антидепресанти». Але важливо, що відповідно анатомо-терапевтичної-хімічної класифікації, в Україні дана група лікарських засобів класифікується лише на 3 підгрупи. Слід зазначити, що в Україні гармонізовані протоколи, де, згідно рекомендацій для*

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лікування депресії, пропонуються препарати, які, на жаль, не зареєстровані на вітчизняному ринку, (підгрупи N06AF та N06AG), що створює певні проблеми доступу пацієнтів до якісної та ефективної терапії, рекомендованої «Протоколами діагностики та лікування пацієнтів з психічними розладами (фінська версія)» 2020 року.

Ключові слова: антидепресанти, депресія, маркетинг, психічне здоров'я, COVID-19.

Вступ

За визначенням Всесвітньої організації охорони здоров'я (ВООЗ), психічне здоров'я не є просто відсутністю психічного розладу, це стан благополуччя, при якому кожна людина може реалізувати свій власний потенціал, впоратися із життєвими стресами, продуктивно та плідно працювати, а також робити внесок у життя своєї спільноти (Розпорядження Кабінету Міністрів України № 1018-р, 2017). У сучасному світі багато чинників впливають на порушення цього стану. Тому, згідно *досліджень* останніх років, на захворювання, що пов'язані з психічним здоров'ям, страждає понад 13 % населення планети (Mental health statistics, 2022). До 2020 року саме психічні розлади мали високий глобальний тягар хвороб (Santomauro, Mantilla Herrera, Shadid, Zheng, Ashbaugh, et. al., 2021). Проте, в період пандемії COVID-19 такі порушення значно збільшились в популяціях та мали значну кількість хворих (WHO, 2022). До прикладу, у США пандемія вплинула на психічне здоров'я 59 % респондентів (Mental health statistics, 2022).

Особливо важливим є те, що люди рідко звертаються за спеціалізованою допомогою на ранніх стадіях розвитку психічних розладів, коли ще є можливість більш ефективно вплинути на їх подальший перебіг. Тому, у зв'язку з підвищеним інтересом суспільства до такої нагальної проблеми, у 2013 році Всесвітня асамблея охорони здоров'я прийняла Комплексний план дій з психічного здоров'я на 2013–2020 рр., який зобов'язав всіх держав-членів вживати конкретних заходів для покращення психічного здоров'я (WHO, 2013). Однак, підсумувавши зроблене за цей період, ВООЗ констатує, що кінцеві очікувані точки в плані вдосконалення психічного здоров'я, які наведені в цьому плані, на жаль, не досягнуті. Тому терміни досягнення Комплексного плану було продовжено до 2030 року (WHO, 2021). І у новому виданні Атласу психічного здоров'я, який опубліковано ВООЗ, зазначається, що в час пандемії COVID-19, коли людство потребує особливої уваги до психічного здоров'я, на жаль, недоодержує якісної послуги, що автоматично створює додаткову увагу до цього питання (WHO Report highlights global shortfall in investment in mental health, 2021).

Підвищена потреба у зв'язку з пандемією COVID-19 не оминула і Україну. Окремої уваги додають назрілі питання реформування підходів до лікування психічних розладів з оптимальним розподілом та використанням бюджетних коштів, так і питання ефективності існуючої системи лікування пацієнтів з психічними розладами (Чому Україні потрібен новий закон про психічне здоров'я?, 2022).

З цього контексту депресія як найпоширеніший психічний розлад, від якого у світі потерпають майже 300 мільйонів людей, видається цікавим з наукової точки зору, а дослідження ринку препаратів, які використовуються для корекції цього стану – надважливим.

Саме антидепресанти зазвичай застосовують при клінічній депресії, але їх ефективність досі залишається предметом обговорень і суперечок. А огляд сучасних літературних джерел, наукометричних баз за ключовими словами «депресія» і «антидепресанти» лише додав сумнівів у цій проблемі (Гузій, 2019). Оскільки клінічна депресія є доволі дискутабельною темою, то логічним видається початок роботи з огляду ринку антидепресантів. Як відомо, відповідно до міжнародної класифікації, група ЛЗ для лікування депресії кодуються як N06A – антидепресанти, які, в свою чергу, поділяються на підкатегорії: N06AA Non-selective monoamine reuptake inhibitors, N06AB Selective serotonin reuptake inhibitors, N06AF Monoamine oxidase inhibitors,

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non-selective, N06AG Monoamine oxidase A inhibitors, N06AX Other antidepressants (WHO ATC/DDD Index 2022, 2021). Згідно протоколів діагностики та лікування пацієнтів з психічними розладами (Нові клінічні протоколи: психіатрія: (фінська версія), 2020), які імплементовані в Україні, для ефективного лікування депресії потрібен індивідуальний підхід з можливістю застосування різноманітних препаратів з різних підгуп групи N06A. А станом на 2022 рік класифікація антидепресантів, що представлені на ринку України, включає лише підгрупи N06AA, N06AB та N06AX, що створює невідповідність між міжнародними рекомендаціями та реальною ситуацією на ринку.

Мета

Метою даної статті є комплексний асортиментний аналіз групи N06A «Антидепресанти» на фармацевтичному ринку України.

Матеріали і методи

Вивчення асортименту зареєстрованих на фармацевтичному ринку антидепресантів проводили відповідно до Анатомо-терапевтично-хімічною класифікацією (АТС-класифікація) та даних Державного реєстру лікарських засобів (ЛЗ) України (Державний реєстр лікарських засобів України). Об'єктами досліджень була інформація про зареєстровані в Україні ЛЗ, які належать до категорії N06A «Антидепресанти», а саме групи N06AA «Неселективні інгібітори зворотного нейронального захвату моноамінів», N06AB «Селективні інгібітори зворотного нейронального захвату серотоніну» та N06AX «Інші антидепресанти». Як додаткові інформаційні матеріали було використано: Нормативно-директивні документи Міністерства охорони здоров'я (МОЗ) України (НДД МОЗ України) та довідник ЛЗ «Компендіум онлайн».

Під час дослідження використовували системний, структурний, графічний та узагальнюючий методи.

Результати

Відповідно до даних Державного реєстру ЛЗ України станом на січень 2022 року з урахуванням препаратів, що виробляються у різних дозуваннях зареєстровано 149 торгових найменувань ЛЗ, які належать до категорії N06A «Антидепресанти» та представлені

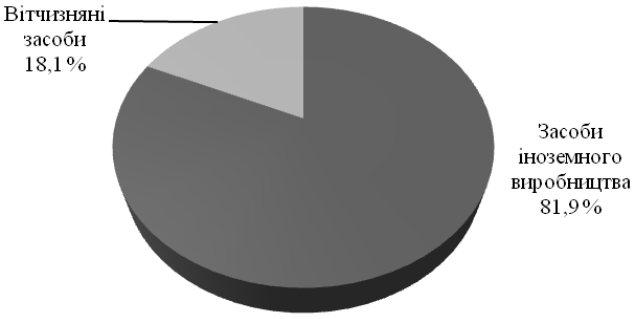

Рис. 1. Сегментація антидепресантів за виробником

20 міжнародними непатентованими назвам (МНН). Із усіх зареєстрованих на фармацевтичному ринку України антидепресантів слід відмітити 52 препарати із обмеженим терміном дії реєстраційного посвідчення.

Також слід відмітити, що фармацевтичний ринок антидепресантів є імпортозалежним, частка даних препаратів іноземного виробництва складає 81,9 %, та лише 18,1 % складають ЛЗ вітчизняного виробництва (рис. 1).

На фармацевтичний ринок України антидепресанти імпортують із 19 країн світу. Основними країнами імпортерами є: Індія – 18,9 %, Словенія – 12,3 %, Німеччина – 9,0 %, Польща та Туреччина – по 7,4 %, Угорщина– 5,7 %. Інші країни сумарно займають 39,3 % фармацевтичного ринку імпортних ЛЗ із категорії N06A «Антидепресанти».

Щодо вітчизняних виробників, то їх частка на фармацевтичному ринку є незначною, лише 6 вітчизняних фармацевтичних компаній представляють дану групу препаратів. За обсягом виробництва даних ЛЗ домінуючі позиції займають ТОВ «Харківське фармацевтичне підприємство «Здоров'я народу» – 25,9 %, ТОВ «Фарма Старт» – 18,5 %, ТОВ Фармацевтична *компанія* «Здоров»я» – 14,9 %, АТ «Київський вітамінний завод» – 11,1 %, ПАТ «Фармак» – 11,1 %, *ПрАТ* «Технолог» та *ТОВ* «Дослідний завод "ГНЦЛС» по – 7,4 % та АТ «Київмедпрепарат» – 3,7 %.

Більшість ЛЗ для лікування депресії виробляються у вигляді твердих лікарських форм, а саме таблеток – 71,8 % та капсул – 26,8 %. ЛЗ для парентерального застосування займають 1,4 % досліджуваного асортименту ЛЗ (рис. 2).

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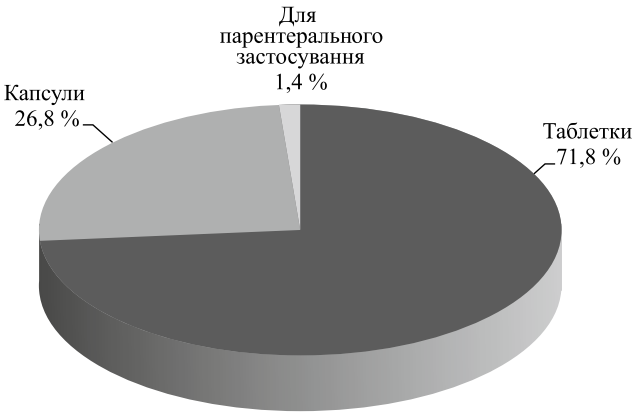

Рис. 2. Сегментація антидепресантів за формою випуску

Найчисельнішою групою за кількістю позицій на фармацевтичному ринку є група N06AX «Інші антидепресанти», яка займає 47,60 % та не належить до жодної категорії, адже за хімічним складом, а також механізмом дії вони відрізняються. Серед групи N06AX найчисельнішими є підгрупи: дулоксетину – 25 ЛЗ, венлафаксину 16 ЛЗ та міртазапіну – 11 ЛЗ, які представлені на рисунку 3.

Обговорення

Відповідно до АТС класифікації, група N06A «Антидепресанти», класифікується на підгрупу N06AA «Неселективні інгібітори зворотного нейронального захвату моноамі-

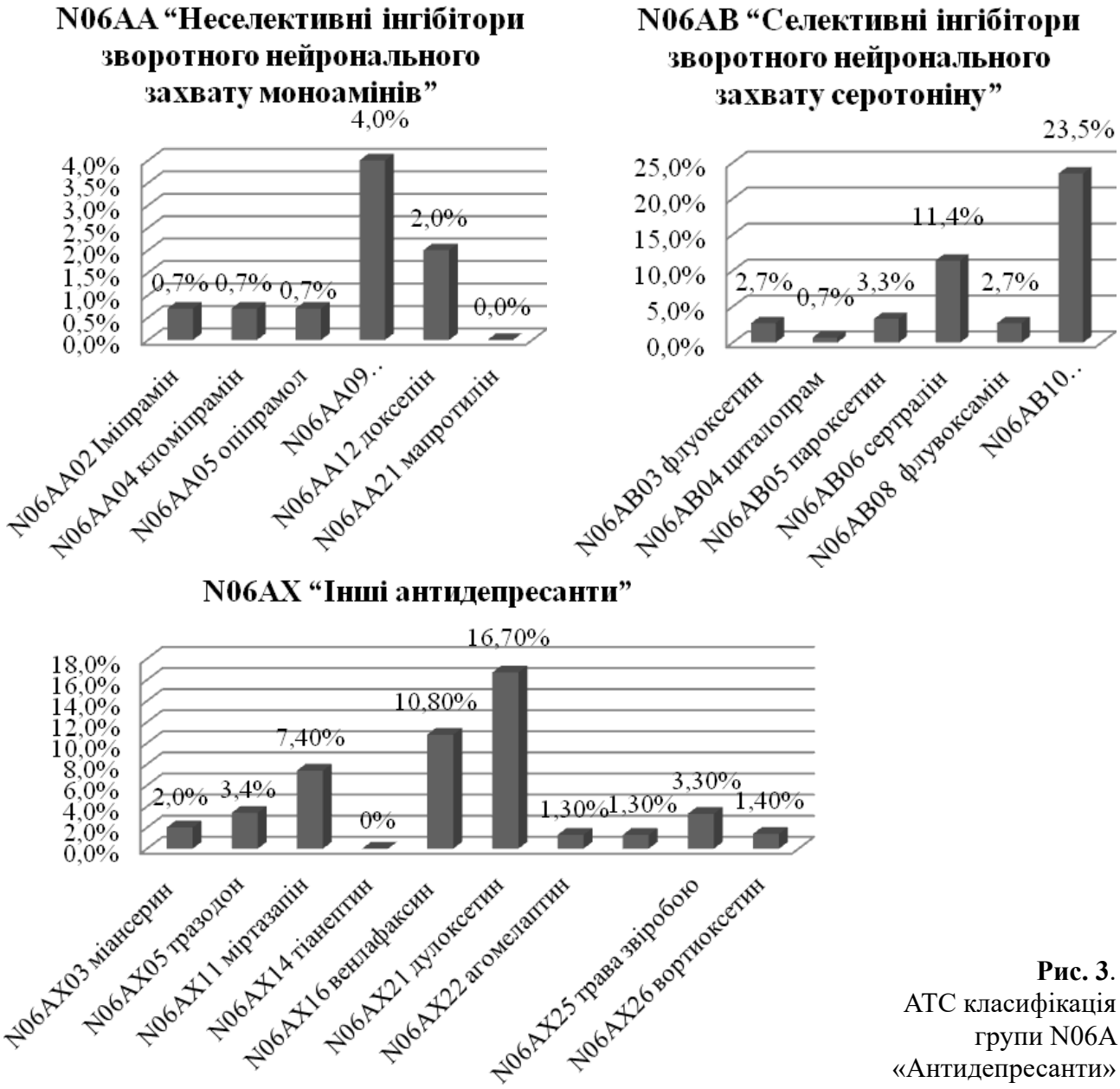

Рис. 3. АТС класифікація групи N06A «Антидепресанти»

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нів», які почали використовувати із 1950-х років та на сьогодні вони складають лише 8,1 % ринку, що можна пояснити механізмом їх дії, адже представники даної групи (класичним із яких є амітриптилін) блокують і інші медіатори, чим зумовлюють небажані побічні ефекти. Серед яких втома, сонливість, закреп, надмірне потовиділення, тахікардія, запаморочення, проблеми із сечовивідною системою та ін (Opoc, 2020). Підгрупу N06AB «Селективні інгібітори зворотного нейронального захвату серотоніну» займають 44,3% та мають значно меншу кількість побічних ефектів, ніж група N06AA, так як механізм їх фармакологічної дії заснований на збільшенні концентрації серотоніну у мозок, що регулює настрій.

Важливою особливістю групи N06A «Антидепресанти» є той факт, що усі ЛЗ є монопрепаратами, що пояснюється механізмом їх дії. Також, більша частка досліджуваної групи є синтетичного походження – 96,6 %, та лише 3,4 % - ЛЗ на основі лікарської рослинної сировини, а саме – трави звіробою (підгрупа N06AX25), ефективність якого доведена у декількох метааналізах (Bongiorno, 2010). Трава звіробою гальмує синаптосомальне поглинання нейропереносників серотоніну, норадреналіну, допаміну. Наптодіантрони (гіперицин, псевдогіперицин), похідні флороглюцину (гіперфорин) і флавоноїди забезпечують дану фармакологічну дію. Також слід відмітити, що саме ЛЗ на основі трави звіробою є безрецептурними, тоді як понад 96 % ЛЗ даної категорії дозволені до відпуску лише за рецептом лікаря.

Але слід зазначити, що відповідно АТС-класифікації України, дана група ЛЗ класифікується лише на 3 підгрупи. На фармацевтичному ринку відсутні ЛЗ ще з двох підгруп, що створює додаткове ринкове вікно. Проте, в Україні гармонізовані протоколи, де, згідно рекомендацій для лікування депресії, пропонуються препарати (наприклад, Моклобемід, Нортриптилін, Триміпрамін, Мілнаципран та ін) які, на жаль, не зареєстровані в Україні.

Висновки

Огляд асортименту препаратів групи N06A «Антидепресанти» на вітчизняному фармацевтичному ринку у 2022 р. показав, що:

1. Номенклатура антидепресантів сформована 149 ЛЗ та представлена 20 МНН;
2. На ринку ЛЗ для лікування депресії чітко домінують іноземні фармацевтичні компанії, а частка вітчизняних фірм представлена лише 18,1%, що свідчить про потребу розширення даної групи ЛЗ, адже 9 із 20 МНН не мають жодного вітчизняного препарату.
3. Відсутність на ринку двох підгруп (N06AF та N06AG) створює певні проблеми доступу пацієнтів до якісної та ефективної терапії, рекомендованої «Протоколами діагностики та лікування пацієнтів з психічними розладами (фінська версія)», 2020 року.

Фінансування

Дана стаття не отримувала зовнішнього фінансування.

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Всі автори ознайомлені з текстом рукопису та надали згоду на його публікацію.

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Analysis of the assortment structure of antidepressants on the domestic pharmaceutical market

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Abstract: a feature of the course of diseases, the correction of which requires the use of antidepressants, is the small number of requests for specialized help in the early stages of the development of mental disorders. This creates certain limitations for fast and effective therapy. However, given that depression is the most common mental disorder in the world, there is a certain scientific interest in researching this pathology. The purpose of the work is a comprehensive assortment analysis of the group N06A «Antidepressants» on the pharmaceutical market of Ukraine. The study of the assortment of antidepressants registered on the pharmaceutical market was carried out in accordance with the Anatomical-Therapeutic-Chemical classification and the data of the State Register of Drugs of Ukraine. The objects of research were information on drugs registered in Ukraine, which belong to category N06A «Antidepressants». According to the data of the State Register of Drugs of Ukraine, as of January 2022, taking into account drugs produced in different dosages, 149 trade names of drugs belonging to category N06A «Antidepressants» and represented by 20 international non-proprietary names were registered. Of all the antidepressants registered on the pharmaceutical market of Ukraine, 52 drugs with a limited validity period of the registration certificate should be noted. The pharmaceutical market of Ukraine for the treatment of depression is clearly dominated by foreign pharmaceutical companies, and the share of domestic companies is represented only by 18.1%, which indicates the need to expand this group of drugs, because 9 out of 20 international non-proprietary names do not have a single domestic drug. Antidepressants are imported to the Ukrainian pharmaceutical market from 19 countries. The main importing countries are: India – 18.9%, Slovenia – 12.3%, Germany – 9.0%, Poland and Turkey – 7.4% each, Hungary – 5.7%. Other countries collectively occupy 39.3% of the pharmaceutical market of imported drugs from category N06A «Antidepressants». But it is important that according to the Anatomical-Therapeutic-Chemical classification, in Ukraine this group of drugs is classified only into 3 subgroups. It should be noted that in Ukraine there are harmonized protocols, where, according to the recommendations for the treatment of depression, drugs are offered that, unfortunately, are not registered on the domestic market, which is reflected in the absence of two subgroups: N06AF and N06AG, which creates certain problems of patient access to high-quality and effective therapy recommended by the 2020 «Protocols for the diagnosis and treatment of patients with mental disorders (Finnish version)».

Key words: antidepressive agents, depression, marketing, mental health, COVID-19.

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Development and technological research of medicated lozenges for catarrhal and aphthous stomatits` symptoms relief

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Abstract: *inflammatory diseases of the oral cavity, in particular catarrhal and aphthous stomatitis, create significant discomfort for patients in everyday life. The occurrence of stomatitis in adolescents can be associated with numerous factors: bacterial and viral infection, insufficient oral hygiene, trauma of the mucous membrane, unbalanced nutrition, allergic reactions, some types of systemic diseases etc. Medicated lozenges have advantages for use in adolescents, as they have an interesting appearance (resembling a candy), pleasant taste and aroma, do not require swallowing or washing down with water, release active pharmaceutical ingredients by gradual dissolution in the oral cavity, which ensures their local action. The present work is aimed to develop different formulations of medicated lozenges for catarrhal and aphthous stomatits` symptoms relief. The objects of the study were experimental samples of lozenges with licorice root and propolis extracts. They were chosen as active ingredients due to their antimicrobial properties, as well as their ability to improve the general condition of the periodontium and reduce the outbreak of aphthae in stomatitis. Lozenges were prepared by heating and congealing method using different concentrations of active pharmaceutical ingredients and excipients (candy base substances – sugar substitute (isomalt), glucose syrup, carboxymethyl cellulose). 3 best formulations that had a uniform color distribution and were transparent, not sticky, had no external surface defects were subjects of the development and analysis. Obtained medicated lozenges were evaluated for physical parameters like weight variation, diameter and thickness, and pharmacotechnological evaluations like friability and hardness by pharmaceutical standard methods from State Pharmacopoeia of Ukraine 2.0 (2.9.5, 2.9.7, 2.9.8). Selected samples had homogeneous physical parameters: average weight in the range of 6.98-7.00 g (none of the formulations had a deviation of more than ± 5%), diameter 3.51 cm, thickness 5.04-5.11 mm. The obtained values of hardness and friability (less than 1% for all formulations) indicate satisfactory mechanical strength of the dosage form. Stability study was carried out at (15-25) ºC and 60±5 % humidity rate and was determined by evaluating the appearance and pharmacotechnological parameters. The values of hardness and friability were constant throughout the storage period for all formulations. Stability studies indicated that the formulations № 1 and 2 were stable for 30 days. The present research allowed to develop formulations for obtaining a pleasant-tasting dosage form intended for relatively slow dissolution in the oral cavity – medicated lozenges for use in adolescents to alleviate the symptoms of catarrhal and aphthous stomatitis.*

Key words: dosage forms, glycyrrhiza, oromucositis, licorice, stomatitis.

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Introduction

Inflammatory diseases of the oral cavity, in particular catarrhal and aphthous stomatitis, create significant discomfort for patients in everyday life. With untimely medical care and the use of self-treatment methods, the disease progresses and leads to the formation of significant and painful ulcers (aphthae) in the oral cavity, fever, general weakness, etc. Since the prevalence of the disease is extremely high (up to 25% of the population suffers from stomatitis) and has a high risk of recurrence (up to 50%), timely diagnosis and therapy are key in the treatment of this health status (Koberová et al., 2020). The occurrence of stomatitis in adolescents can be associated with numerous factors: bacterial and viral infection, insufficient oral hygiene, trauma of the mucous membrane, including in the case of improper selection of hygiene products (hard toothbrush, too large interdental bristles, improper brushing technique), unbalanced nutrition, allergic reactions, some types of systemic diseases (Hara et al., 2019, Koberová et al., 2020). As noted by Koberová et al. (2020), extremely important factors in the treatment of stomatitis in adolescents, in addition to drug treatment, are compliance with a special diet (non-traumatic for the oral mucosa) and thorough and gentle brushing of teeth and interdental spaces, which sometimes is impossible for adolescents to do on their own without the help and control of parents.

In order to ensure the required level of compliance, we chosed a solid form of hard candy lozenges group as a dosage form – lollipop. Medicated lozenges have advantages for use in adolescents, as they have an interesting appearance (resembling a candy), pleasant taste and aroma, do not require swallowing or washing down with water, release active pharmaceutical ingredients by gradual dissolution in the oral cavity, which ensures their local action, so they can be alternative dosage forms (Hordiienko & Nroshovyi, 2017, Pawar et al., 2018, Shetty et al., 2019, Hejaz et al., 2020, Sahoo et al., 2021). In addition, from a technological point of view, lozenges are quite simple to produce, process do not require special equipment and expensive excipients (Jagadeesh et al., 2017).

Classically, the basis of lozenges is a candy base (caramel), consisting of sugar or its substitutes. From the point of harmlessness to the oral cavity, isomalt is an alternative to sugar, because oral bacteria cannot convert it into polyglucan, from which, in turn, plaque is formed (Kini et al., 2011, Hordiienko & Nroshovyi, 2017).

The choice of formulation`s components was based on the analysis of scientific publications. It has been proven that licorice extract prevents the formation of caries, as it has an antimicrobial effect on *Streptococcus mutans* and *Lactobacillus acidophilus* (Messier et al., 2012, Almaz et al., 2017, Moritani et al., 2018, Chen et al., 2019, Rai et al., 2020). It is worth noting that excessive consumption of licorice can lead to high blood pressure, hypokalemia, swelling of the legs, bloating, headaches, and fatigue. Licorice also has estrogenic activity and can have an abortifacient effect, so it is contraindicated during pregnancy (Nazari et al., 2017, Al-Snafi, 2018, Sharifi-Rad et al., 2021). Preparations containing licorice extract are not recommended for children under 12 years of age. If the normal level of consumption is observed in adequate doses, licorice extract does not show or shows small amounts of adverse reactions (Al-Snafi, 2018). The European Food Safety Authority panel specify that licorice extract is safe up to 100 mg daily as a food additive (Sharifi-Rad et al., 2021). It is suggested that the acceptable daily dose of glycyrrhizin (as one of the main chemical components) is 0.015–0.229 mg/kg body weight/day (Isbrucker et al., 2006 as cited in El-Saber Batiha, 2020).

Propolis is able to inhibit the growth of bacteria in the oral cavity, improve the general condition of the periodontium and reduce the outbreaks of aphthae in stomatitis (Samet et al., 2007, Saeed et al., 2021). In combination, these components can reduce the impact of risk factors for the development of inflammatory diseases of the oral cavity and alleviate the symptoms of their mild manifestations.

Aim

To develop a formulation of medicated lozenges with licorice root extract and propolis oil extract by comparing the physical and pharmacotechnological parameters of experimental samples.

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Materials and methods

Such active pharmaceutical ingredients and excipients were used: licorice root extract (Zagros Licorice Co., Iran), propolis oil extract (Ingredient China Group Ltd., China), isomalt (Laped, Italy), glucose syrup (Laped, Italy), carboxymethyl cellulose FH 6000 (supplier «Ingredia» LLC, Ukraine), purified water, citron flavoring. Lozenges were prepared by heating and congealing method: the required amount of water, isomalt and glucose syrup was heated to a temperature of 160-170 ºC until the isomalt crystals were completely dissolved. The flavor was added at a reduced temperature to 120-130 ºC. Introduction of licorice root extract and propolis oil extract, carboxymethyl cellulose to the mixture was carried out at 80 ºC. The homogeneous mixture was poured into calibrated molds and left to congealing for 1 hour at room temperature 20±5 ºC. The obtained lozenges were subjected to various physical and pharmacotechnological evaluations immediately after congealing, and after 7 and 30 days storage period at (15-25) ºC temperature and 60±5 % humidity rate (formulations were wrapped in foil and storaged in a hermetically sealed polymer container). The pharmacotechnological parameters of the dosage form were determined. 20 lozenges were weighed on an electronic balance TBE-0.5-0.01 and the average weight and weight variation were calculated (the permissible deviation from the average should be not more than ± 5%). The diameter and thickness were measured for 10 lozenges with a Dnipro-M HP-15 caliper. Determination of friability was carried out on the PTF 10E single-drum tablet friability test instrument, Pharma test for 5 lozenges (permissible value – not more than 1%). 10 lozenges were subjected to the hardness test on PTB-M manual tablet hardness testing instrument, Pharma test (SPhU 2.9.5, 2.9.7, 2.9.8, Jagadeesh et al., 2017, Shetty et al., 2019).

Results

3 formulations formed visually the best lozenges after numerous experimental attempts (Table 1). They were subjects of the development and analysis. The obtained samples had a uniform color distribution, were transparent, not sticky, had no external surface defects.

Obtained medicated lozenges were evaluated for physical parameters like weight variation, diameter and thickness, and pharmacotechnological evaluations like friability and hardness by pharmaceutical standard methods from State Pharmacopoeia of Ukraine 2.0 (2.9.5, 2.9.7, 2.9.8) immediately after congealing and after 7 and 30 days storage period (Table 2). Selected samples had homogeneous physical parameters: average weight in the range of 6.98-7.00 g (none of the formulations had a deviation of more than ± 5%), diameter 3.51 cm, thickness 5.04-5.11 mm. The obtained values of hardness and friability (less than 1% for all formulations) indicate satisfactory mechanical strength of the dosage form. Stability study was carried out at 20±5 ºC temperature and 60±5 % humidity rate and was determined by evaluating the appearance and pharmacotechnological parameters. The values of hardness and friability were constant throughout the storage period for all formulations. Stability studies indicated that the formulations № 1 and 2 were stable for 30 days.

Table 1. Formulation table of licorice root extract and propolis oil extract medicated lozenges

Ingredients (%)	Formulation №1	Formulation №2	Formulation №3
Licorice root extract	1,5	1,5	1,5
Propolis oil extract	1,5	1,5	1,5
Isomalt	80	80	80
Glucose syrup	-	2	1
Carboxymethyl cellulose	1	-	1
«Citron» flavour	1 drop	1 drop	1 drop
Purified water	16	15	15

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Table 2. Physical and pharmacotechnological evaluations of lozenges formulations after congealing and during stability studies

Evaluation	Formulation №1	Formulation №2	Formulation №3
Storage period - 0 days			
Appearance	Light yellow transparent lozenges, uniform in shape, without external surface defects, sometimes with air bubbles		
Weight Variation (gm)±SD	7,00±0,06	6,98±0,07	6,99±0,08
Diameter (cm)	3,510±0,010	3,510±0,008	3,510±0,008
Thickness (mm)	5,11±0,04	5,04±0,05	5,04±0,06
Friability (%)	0,52	0,38	0,43
Hardness (N/ cm2)	92,58±0,05	73,62±0,27	73,66±0,24
Storage period - 7 days (stability studies)			
Appearance	Unchanged		Sticky and shiny surface
Friability (%)	0,54	0,46	0,49
Hardness (N/cm2)	92,64±0,11	73,71±0,19	73,85±0,26
Storage period - 30 days (stability studies)			
Appearance	Unchanged		Sticky and shiny surface
Friability (%)	0,54	0,49	0,49
Hardness (N/cm2)	92,69±0,08	73,78±0,22	73,97±0,25

Discussion

There are few publications of design and development lozenges` various formulations with herbal ingredients. Hu et al. (2011) developed a sugar-free candy formulation with licorice root extract using a mixture of starch hydrolysate and acesulfame potassium (as a candy base), flavors and colors. The use of this sweetener raises some questions, because acesulfame potassium is a substance that is regulated in European consumption standards – it can`t be used in food processing industry in the European Union (Commission regulation (EU) 2018/97, 2018). Bane et al. (2022) formulated a candy base of lozenges with *Emblica officinalis* extract with a mixture of isomalt and mannitol.

Technologically, the manufacturing process consisted of 3 main stages: preparation of the candy base (caramel), the introduction of active ingredients and the formation of lozenges. All these stages caused certain difficulties in implementation. For example, the slightest deviation from the optimum temperature led to unsatisfactory performance, the caramel formed a viscous mass that did not congeal. Increasing or decreasing the percentage of both the sum of active ingredients and water affected the hardness and quality of the formed candy structure, some experimental samples melted in the hands (at body temperature). The ratio of the content of isomalt, glucose syrup and carboxymethyl cellulose had an influence on the hardness of the obtained dosage forms as well. It should be noted that the primary obtaining of the hard candy structure of the candy base with active ingredients immediately after congealing does not guarantee the preservation of the structure during storage period. The lozenges with a mixture of carboxymethyl cellulose and glucose syrup (formulation № 3) formed a solid solution and congealed in a certain period of time, but during storage the lozenges became sticky, liquid drops appeared on the surface. That indicates a high level of formulation hygroscopicity. Formulation № 1 formed a thick consistency, which formed a very hard candy structure. The presence of carboxymethyl cellulose prolongs the action of the lozenges in the oral cavity due to high hardness and increased dissolution time of the dosage form. Formulation № 2 containing 80% isomalt and 2% glucose syrup formed a classic caramel structure, which congealed within 1 hour, forming a lozenge of a certain shape that did not

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change its structure during the storage period. In the process of resorption, the lozenges did not lose their shape (did not disintegrate) and did not stick to the teeth. The proposed formulations № 1 and № 2 allow to form medicated lozenges of pleasant taste, moderate sweetness, sufficient or high hardness and stability. Further studies on the release of active ingredients are necessary.

Conclusions

The present research allowed to develop formulations for obtaining a pleasant-tasting dosage form intended for relatively slow dissolution in the oral cavity – medicated lozenges for use in adolescents to alleviate the symptoms of catarrhal and aphthous stomatitis.

Financing

This study did not obtain any external funding or financial support.

Conflict of interests

Authors have no conflict of interest to declare.

Consent to publication

All authors have read and approved the final version of this manuscript. All authors agreed to publish this manuscript.

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Розробка та технологічне дослідження льодяників для полегшення симптомів катарального та афтозного стоматитів

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Анотація: запальні захворювання ротової порожнини, зокрема катаральний та афтозний стоматити створюють значний дискомфорт для пацієнтів у повсякденному житті. Поява стоматитів у підлітків може бути пов'язаною із численними факторами: бактеріальною та вірусною інфекцією, недостатньою гігієною ротової порожнини, травмуванням слизової оболонки, в тому числі при неправильному підборі засобів гігієни, незбалансоване харчування, алергічна реакція, деякі види системних захворювань. Льодяники володіють перевагами для застосування у підлітковому віці, оскільки мають цікавий зовнішній вигляд (нагадують цукерку), приємний смак та аромат, не потребують ковтання чи запивання водою, вивільняють активні фармацевтичні інгредієнти при поступовому розчиненні у ротовій порожнині, що забезпечує їхню місцеву дію, тому можуть бути альтернативними лікарськими формами. Метою дослідження було розробити рецептуру льодяників для полегшення симптомів катарального та афтозного стоматитів. Об'єктами дослідження були експериментальні зразки льодяників із екстрактами солодки кореня та прополісу. Їх було обрано активними інгредієнтами зважаючи на антимікробні властивості, а також здатність покращувати загальний стан пародонту та зменшувати

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спалахи афт при стоматиті. Для одержання льодяників використовували метод нагрівання та застигання різних концентрацій активних інгредієнтів та допоміжних речовин (складових цукеркової основи – замінника цукру (ізомальту), глюкозного сиропу, карбоксиметилцелюлози). Візуально найкращі льодяники формували 3 рецептури, які в подальшому і підлягали напрацюванню та аналізу. Одержані зразки мали рівномірний розподіл кольору, були прозорими, не липкими, не мали зовнішніх дефектів поверхні. Проводили визначення фізичних показників (середня маса та однорідність маси, діаметр та товщина) та фармакотехнологічних параметрів (стиранність та стійкість до роздавлювання) одержаних льодяників відповідно методик Державної фармакопеї України 2.0 (2.9.5, 2.9.7, 2.9.8). Відібрані зразки мали однорідні фізичні параметри: середню масу у межах 6,98-7,00 г (жоден із зразків не мав відхилення більше допустимого ±5 %), діаметр 3,51 см, товщину 5,04-5,11 мм. Одержані значення стійкості до роздавлювання та стиранності (менше 1 % для усіх експериментальних зразків) свідчать про задовільну механічну міцність лікарської форми. Стабільність льодяників визначали оцінюючи зовнішній вигляд та технологічні показники після зберігання при температурі (15-25) ºС та вологості 60±5 %. Значення стираності і стійкості до роздавлювання були сталими протягом усього терміну спостереження для усіх експериментальних зразків. Дослідження стабільності показали, що експериментальні зразки № 1 та 2 були стабільними протягом 30 днів. Наявне дослідження дозволило сформувати рецептури для одержання приємної на смак лікарської форми, призначеної для відносно повільного розчинення у порожнині рота –льодяників для застосування дітям та підліткам з метою полегшення симптомів катарального та афтозного стоматитів.

Ключові слова: лікарська форма, солодка, льодяники, прополіс, стоматит.

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Retrospective analysis of the use of benzodiazepines in anxiety disorders

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Abstract: *in times of great social shocks, economic crises, epidemics and pandemics, military conflicts, usually can be observed the spread of such a group of psychological diseases as anxiety disorders (ADs). ADs are a widespread group of human behavior disorders characterized by a wide range of symptoms that cause significant changes in behavior and reduce the patient's quality of life and may lead to deterioration of his social activity. This group of diseases includes a number of behavioral disorders, the characteristic feature of which is the patient's feeling of fear and/or anxiety, which is usually an excessive and unmotivated reaction to a stimulus or an event that caused them. As a result of the analysis of available data, it was revealed that benzodiazepines are actively used as second-line drugs in ADs pharmacotherapy. The pharmacological effect of this group of medications is associated with an agonistic interaction with $GABA_A$ receptors of the central nervous system. It has also been established that this group of drugs is an effective element of complex therapy together with antidepressants or as monotherapy of such ADs as generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), selective mutism (SM) etc. During ADs therapy with benzodiazepines, a number of side effects, such as excessive sedation, cognitive impairment, and psychomotor disorder of coordination of movements, have been identified. This group of drugs requires special caution when used in elderly patients due to possible excessive sedation and impaired cognitive function. But if the recommended course of treatment is followed, benzodiazepines are a safe to use group of drugs that have a wide spectrum of pharmacological action. The purpose of this work was to study the available data on the pharmacological properties of benzodiazepine anxiolytics for the purpose of their use in the pharmacotherapy of diseases belonging to the ADs group. To achieve this goal, publications and articles devoted to ADs pharmacotherapy methods were reviewed and analyzed. Materials were searched using the databases Pud Med and Google Scholar.*

Keywords: antidepressive agents, anxiolytics, anxiety disorders, benzodiazepines, pharmacotherapy.

Introduction

In the modern world, the problem of the therapy of psychological disorders is attracting more and more attention from health care professionals due to the steady trend of their spread among the population of most countries of the world. In times of great social shocks, economic crises, epidemics and pandemics, military conflicts, usually can be observed the spread of such a group of psychological diseases as anxiety disorders (ADs).

According to the modern classification of ICD-11, this group of disorders represents a wide range of diseases, such as generalized anx-

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iety disorder (GAD, 6B00), panic disorder (PD, 6B01), agoraphobia (6B02), social phobia (SP, 6B04), separation anxiety disorder (SAD, 6B05), selective mutism (SM, 6B06), hypochondriasis (6B23.0-6B23.Z), substance-induced anxiety disorders (6C40.71- 6C4G.71), Secondary anxiety syndrome (SAS, 6E63) (WHO, 2022).

A key feature of ADs is the presence of the patient's feelings of fear and/or anxiety, which are usually an excessive and unmotivated response to the stimulus or event that caused them. The anxious state of the patient can last for several weeks, months and years after the end of the stimulus that caused such a state. At that time, anxiety in a healthy person passes much faster. In addition, most ADs have their own characteristics of the course and stimuli that cause them. For example, PD is characterized by the development of short-term panic attacks in the patient, accompanied by an accelerated heartbeat, lack of sensitivity in the limbs, nausea or vomiting and fear of death (WHO, 2022, Copchak O. O. 2018, Oros & M. M., Sabovchyk A. Ya., 2019). In turn, GAD manifestations are more chronic: sleep disturbances, irritability, nausea, stomach disorders, subjective feeling of anxiety, dry mouth (WHO, 2022, Copchak, O. O. 2018). Other ADs, such as social anxiety disorder (CTP, 6B04) and selective mutism (CM, 6B06) lead to deterioration of the patient's social life and his communication skills (WHO,2022, Avramchuk O. 2018, Schiele M. A. & Domschke K., 2021).

Another feature of ADs is the high degree of comorbidity with other psychological disorders of other classification groups (depression, obsessive-compulsive disorder, schizophrenia, etc.), which complicates the diagnosis of the disease in an individual patient (WHO, 2022).

Some ADs are common among patients of specific age groups. As an example, SM (6B06) and separation anxiety disorder (SAD, 6B05) are common among children and adolescents (up to 18 years) (Schiele M. A. & Domschke K., 2021).

Thus, ADs is a widespread group of human behavior disorders, which is characterized by a wide range of symptoms that reduce the patient's standard of living and can lead to deterioration of his social activity. Therefore, the question of ADs therapy is becoming an increasingly relevant problem in the field of health care.

Aim

The task of this work was to study the available data on the pharmacological properties of benzodiazepine tranquilizers with the aim of using them in the pharmacotherapy of diseases belonging to the AD group.

Materials and methods

Publications and articles devoted to ADs pharmacotherapy methods were reviewed and analyzed in order to determine the role of benzodiazepines in the treatment scheme of this group of diseases. Materials were searched using the databases Pud Med and Google Scholar.

Review and discussion

Pharmacotherapy is an integral part of ADs treatment along with psychological therapy. Medicines began to be actively used in ADs therapy almost immediately after the discovery of this group of disorders.

Antidepressants belonging to the groups of selective serotonin reuptake inhibitors (SSRIs) and Serotonin–norepinephrine reuptake inhibitors (SNRIs) are used as first-line agents in the pharmacotherapy of ADs (Copchak O. O., 2018, Garakani et al., 2020, Karvatska N. S., Burla Sh. S. & Tkach S. D., 2020). However, therapy with the mentioned pharmacological means is characterized by the use of medications for a long time, the slow development of the therapeutic effect, the presence of side effects (gastrointestinal disorders, sedation, insomnia, sexual dysfunction, dry mouth, diarrhea or constipation) (Strawn J.R., Mills J. A., Sauley B. A. & Welge J. A., 2018).

Therefore, benzodiazepines are actively used as second-line drugs in ADs pharmacotherapy. This group of medicines has been actively used in medical practice since the middle of the 20th century. On the pharmaceutical market of Ukraine, this group of medications is represented by medications, which are shown in the Table 1.

During more than half a century of use, a large volume of data on the effectiveness of pharmacotherapy, side effects, and metabolism of this group of drugs has been accumulated. The pharmacological effect of this group of agents is associated with an agonistic interaction with $GABA_A$ receptors of the central nervous system (Gomez A. F., Barthel A. L. & Hofmann S. G., 2018).

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Table 1

Trade name	Active substance	Manufacturer
Diazepam-3H	Diazepam	"People's Health" LLP, Kharkiv
Lorazepam-3H	Lorazepam	
Alprazolam-3H	Alprazolam	
Sibazon IC	Diazepam	SLC "InterChem", Odesa
Gidazepam IC	Gidazepam	
Levana IC	Levana	
Phenazepam IC	Phenazepam	
Clonazepam IC	Clonazepam	
Diazepex	Diazepam	AS "Kalceks", Latvia

Unlike most antidepressants, the therapeutic effect of benzodiazepines begins much faster, although it lasts for a shorter time (Garakani, A. et al. 2020). The pharmacological effect is observed within 1-2 days after the start of administration (Burchinskii, S. G., 2018).

A number of long-acting benzodiazepines (diazepam, clonazepam, and lorazepam) are actively used in the pharmacotherapy of GAD (Strawn, J. R., Geracioti, L., Rajdev, N., Clemenza, K. & Levine, A. 2018). Due to a long half-life, these drugs are able to maintain a high concentration in the blood plasma for a longer time, which is an important measure for the effectiveness of drugs during the treatment of GAD.

However, there is conflicting data regarding long-term (more than 4 weeks) benzodiazepine therapy. Some researchers believe that due to the risk of developing addiction and side effects, the use of this group of drugs in the treatment of GAD and other ADs with a chronic course is appropriate only in the absence of the effect of SSRIs and SNRIs (Karvatska N. S. et al., 2020). At the same time, there is a point of view according to which the long-term use of benzodiazepines is justified if there is a pronounced therapeutic effect during the first 4 weeks of treatment (Rickels K. & Moeller H. J., 2019). Therefore, drugs of this group are used for short-term therapy of AD.

Benzodiazepines with a pronounced anticonvulsant and muscle relaxant effect, such as clonazepam and midazolam can be used to reduce the somatic manifestations of AD, such as tremors or muscle spasms, which are very common symptoms in patients with PD (Fogari R. et al., 2019).

Benzodiazepines can be used together with antidepressants in the ADs pharmacotherapy scheme. Thus, it was established that the simultaneous appointment of sertraline (SSRI) and clonazepam leads to a decrease in the side effects of the antidepressant and an increase in the pharmacological effect of both drugs (Hovenkamp-Hermelink J. H. et al., 2021).

However, this class of drugs also has a number of disadvantages. A number of side effects, such as excessive sedation, cognitive impairment, and psychomotor disorder of coordination of movements, have been identified during ADs therapy with benzodiazepines. This group of drugs requires special caution when used in elderly patients due to possible excessive sedation and impaired cognitive functions (Gomez A. F., Barthel A. L. & Hofmann S. G., 2018). In addition, the long-term use of benzodiazepines by patients of this age group is associated with a high probability of developing dementia, tolerance to the drug, or even addiction (Garakani A. et al., 2020).

Also, the ability of diazepam to affect blood pressure and heart rate, which can be observed at night, has been revealed. At the same time, no changes in blood pressure were observed during

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the day. A similar phenomenon is usually observed in elderly patients (Fogari R. et al., 2019). There is a point of view that a similar phenomenon is explained by the increased volume of distribution of diazepam in the body of elderly patients, although a similar effect of the drug is observed in patients of other age groups (Fogari R. et al., 2019, Costa A. et al., 2018).

Another significant disadvantage of benzodiazepines is their ability to affect the ability to drive and cause cognitive impairment (Jongen S., Vuurman E. F. P. M., Ramaekers J. G. & Vermeeren A., 2018).

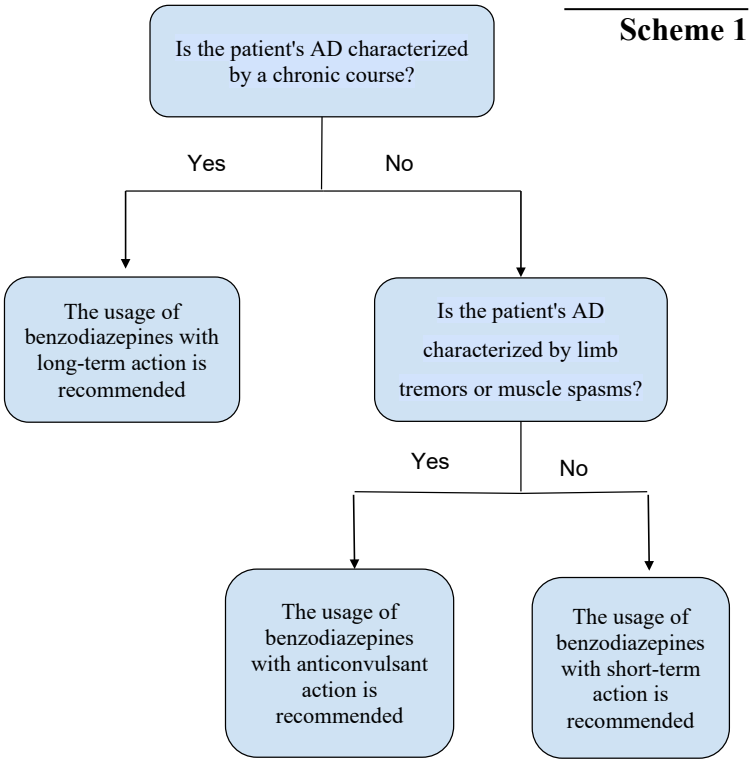
This pharmacological group of drugs has a number of contraindications for use, which must be taken into account when prescribing the drug. Most benzodiazepines are characterized by the following number of contraindications:

1. *History of abuse of psychoactive substances or drugs by the patient*. Patients with a history of addiction to opioids and other psychoactive substances or medications have been found to be more likely to develop tolerance to benzodiazepine anxiolytics (Gomez A. F., Barthel A. L. & Hofmann S. G., 2018). Therefore, the appointment of the future remedy requires a preliminary analysis of the patient's history of addiction to psychoactive substances.
2. *Liver and/or kidney function disorders*. In the case of liver/kidney failure, the use of agents whose active substance has a long half-life (diazepam, midazolam, clonazepam, etc.) requires special caution (Mathé A. A., Michaneck M., Berg E., Charney D. S., & Murrough J. W., 2020). In the case of drugs that have a pharmacologically active metabolite (midazolam, diazepam, etc.), it can lead to an increase and prolongation of the therapeutic effect (Marçon F. et al., 2018).
3. *Sensitivity to the active substance or components of the medication.*

Conclusions

Thus, benzodiazepines may become a possible alternative to antidepressants in the pharmacotherapy of ADs. However, this group of drugs has a number of disadvantages, including the presence of side effects and a limited recommended course of treatment due to the probable development of tolerance and/or addiction to the drug. But if the recommended course of treatment is followed, benzodiazepines are a safe to use group of drugs that have a wide spectrum of pharmacological action. A general tactic for the use of benzodiazepines during AD has been proposed in Scheme 1. Thanks to this, it becomes possible to prescribe a drug capable of eliminating the individual manifestations of ADs of an individual patient. Agents with anxiolytic and anticonvulsant effects (midazolam, clonazepam) may be the drug of choice for PD to eliminate limb tremors, muscle spasms, and other manifestations of panic attacks.

Scheme 1



Benzodiazepines with a long half-life are able to provide a pharmacological effect that will persist for a long time, which in turn can be useful in the treatment of GAD and other ADs with chronic symptoms.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Ретроспективний аналіз застосування бензодіазепінів при тривожних розладах

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Анотація*:* у період великих соціальних потрясінь, економічних криз, епідемій і пандемій, військових конфліктів зазвичай спостерігається поширення такої групи психологічних захворювань, як тривожні розлади (ТР). ТР — широко поширена група розладів поведінки людини, що характеризується широким спектром симптомів, які викликають суттєві зміни в поведінці та знижують якість життя пацієнта, можуть призвести до погіршення його соціальної активності. До цієї групи захворювань входить низка поведінкових розладів, характерною рисою яких є відчуття страху та/або тривоги у пацієнта, яке зазвичай є надмірною та невмотивованою реакцією на подразник або подію, що їх викликала. У результаті аналізу наявних даних виявлено, що бензодіазепіни активно використовуються як препарати другого ряду у фармакотерапії ТР. Фармакологічний ефект цієї групи препаратів пов'язаний з агоністичною взаємодією з $ГАМК_А$-рецепторами центральної нервової системи. Також встановлено, що дана група препаратів є ефективним елементом комплексної терапії разом з антидепресантами або як монотерапія таких ТР, як генералізований тривожний розлад (ГТР), панічний розлад (ПР), соціальний тривожний розлад (СТР), селективний мутизм (СМ) тощо. Під час терапії ТР бензодіазепінами може виникнути ряд побічних ефектів, таких як надмірна седація, когнітивні порушення та психомоторні розлади. виявлено координацію рухів. Ця група препаратів потребує особливої обережності при застосуванні пацієнтам літнього віку через можливу надмірну седативну дію та порушення когнітивних функцій. Але при дотриманні рекомендованого курсу лікування бензодіазепіни є безпечною для застосування групою препаратів, які мають широкий спектр фармакологічної дії. Метою даної роботи було вивчення наявних даних про фармакологічні властивості бензодіазепінових анксіолітиків з метою їх використання у фармакотерапії захворювань групи ТР. Для досягнення поставленої мети було розглянуто та проаналізовано публікації та статті, присвячені методам фармакотерапії ТР. Пошук матеріалів здійснювався за допомогою наукометричних баз даних Pud Med та Google Scholar.

Ключові слова*:* антидепресивні засоби, анксіолітики, тривожні розлади, бензодіазепіни, фармакотерапія.

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