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DEAR READERS!

We introduce you the first issue of the scientific and practical journal "Interdisciplinary Approaches to Medicine" of Al-Farabi Kazakh National University.

Currently, medicine and the healthcare system are rapidly developing due to the infusion of new achievements in molecular biology, genetics, pharmacology, computer and management technologies. Based on the results of these achievements, new preventive, diagnostic and therapeutic approaches are being developed that require highly qualified specialists in each area.

The journal's concept is based on covering the results of advanced scientific research, presenting them to a wide circle, providing readers with an information link between basic research in the field of new medical technologies and scientific and practical medicine, promoting and disseminating advanced domestic and international scientific medical knowledge.

Our journal will publish results of original studies aimed at improving the health of the population and patients' quality of life; analytical articles, lectures, reviews in the field of fundamental and practical developments in physics, chemistry, biology, having a biomedical focus; the results of preclinical and clinical trials of new medical technologies for prevention, diagnosis, treatment and rehabilitation.

The quality control of articles is carried out by professional reviewers and an editorial board, represented by well-known scientists and experts. Requirements for authors are developed on the basis of domestic traditions, as well as the experience of international publications, recommendations from ethical committees and professional associations of editors of scientific journals.

We strive to create an open access Journal targeted at a wide international audience. We hope that the work applied by the authors will be rewarded by the growth of citations and other indicators of both individual articles and the Journal as a whole, thanks to the open model of distribution and its registration in various international and local citation indices and catalogs.

I thank the members of the editorial board, the editorial committee for the work done, and the authors for their interest in the Journal from the first days of its existence.

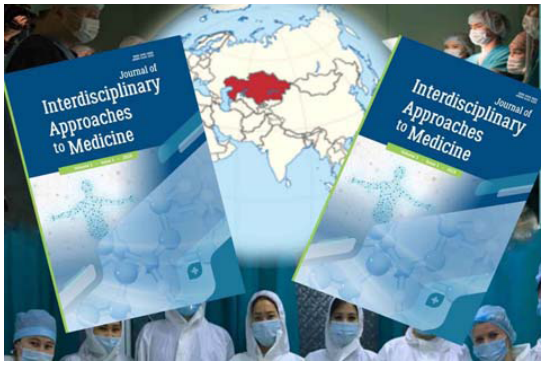
We invite practical health care professionals, the universities' faculty, medical colleges, doctoral students, undergraduates to cooperate. We are open for interesting and relevant articles.

Science editor
Scientific and practical journal
"Interdisciplinary Approaches to Medicine
Editor-in-chief
Kalmataeva Zhanna

A WELCOMED RECENT DEVELOPMENT

There is always an excitement when one encounters a new vehicle to disseminate knowledge and communication. We are fortunate to live in an area where knowledge and means to find them are available anywhere and everywhere. On the other hand, this impressive accomplishment can be a daunting task in finding our way through the vast quantity of data and maze of information. This is noticeable when we look for a piece of knowledge or information pertinent to our local works and practice. The essence of our medical practice today is to be familiar with recent information, data to for our domestic demand, the broader world knowledge, and other related subjects. Medicine is not one speciality, but interconnected different specialities and disciplines, interlocked with culture, art, and folklores. Thus, an interdisciplinary approach becomes essential to manage patients and the health of their community by having a continuous source of information in guiding practising clinicians and scientists through the maze of information, results of contemporary researches, theoretical, and empirical sciences, their applicability and their interconnection with a different discipline. This is how I see the new online **"Journal of Interdisciplinary Approaches to Medicine".**

The Journal will be issued twice a year in English and Russian to be the vehicle of communication of the Kazakhstani and the central Asia medical professionals with a global flavour. I have ascertained that the Journal will be an open-access journal. A recommended and preferred format to communicate science today, helping access to research and expansion of global knowledge. This will be especially welcomed to our young investigators, providing them with a platform for the exchange of information, discussing and working on analytical data with global researcher's community.



The Journal, like any respected source of communication, needs to be credible and accurate. Today propagation of mass free communication tools and social media have increased the unchecked information, knowledge and news and becoming a source of confusion and malpractice. Hence, the importance and urgent implementation of checking the integrity, accuracy and validity of data and knowledge. The applied tools of today's publication are the peer-review strategy, constant quality control of the editorial office and compliance with international principles of publishing ethics. These precepts are now the core strategies of this Journal.

Many congratulations to my Kazakhstani medical colleagues and their supporting staff, in particular, those working Al-Farabi Kazakh National University for creating the idea and managing this Journal and working hard for its realisation. I am hoping it will remain sincere to this mission and that the readers will appreciate, encourage, and enjoy.

Ghazwan Butrous
Professor of Cardiopulmonary Sciences; University of Kent, Canterbury, UK
President Emeritus, Pulmonary Vascular Research Institute
Senior Associate Editor: Pulmonary Circulation

IT IS WITH GREAT PLEASURE THAT I AM WRITING THESE GREETINGS TO THE INAUGURAL ISSUE OF THIS JOURNAL!

The Journal will provide a great opportunity for the colleagues in Kazakhstan and beyond, to express their clinical and scientific opinions. Countries with low and middle income do face their unique challenges in the healthcare and biomedical research. These challenges are often overlooked by the editors of established medical journals. With the access to own journal as the publishing venue, the colleagues in Kazakhstan and the neighbouring region will gain a convenient forum for discussions and exchange of ideas.

This being said, I also wish to this Journal to strive for excellence and aim for the highest possible quality of published articles. Many journals rise every year, but not so many become noticed worldwide. It is always hard to strike a perfect balance between focusing solely on the problems "close to home", and the issues that are of interest to the global readership. As each case is unique, there is no "cookbook" recipe for the global success. But being bold, courageous, and smart is, certainly, the necessary pre-requisite. It also helps immensely when one is passionate about one's goals.

I believe that the team behind this Journal has all these fine qualities and will skillfully steer the Journal towards success and global recognition!

I look forward to contributing to the success of this Journal.

With my warmest regards,

Nurlan Dauletbayev

Director, Translational Research Lab
Department of Internal, Respiratory and Critical Care Medicine
Philipps-University of Marburg
Biomedical Research Centre (BMFZ), Office +1/61300
Hans-Meerwein-Str. 2
35043 Marburg
Germany

Adjunct Professor
Division of Respiratory Medicine
Montreal Children's Hospital
Department of Pediatrics, Faculty of Medicine
McGill University
1001 Decarie Boulevard
Montreal, Quebec
H4A 3J1
Canada

Associate Investigator
Child Health and Human Development Program
Research Institute of
McGill University Health Centre
1001 Decarie Boulevard
Montreal, Quebec
H4A 3J1
Canada

Section 1
Reviews

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Nurlan Dauletbayev

MD, PhD, Adjunct Professor
Division of Respiratory Medicine, Montreal Children's Hospital
Department of Pediatrics, Faculty of Medicine
McGill University Canada, e-mail: nurlan.dauletbayev@mcgill.ca

ADVICES ON SEARCH AND CRITICAL APPRAISAL OF BIOMEDICAL LITERATURE PART I, GENERAL WORKFLOW

Both physician-scientists and practicing physicians regularly experience the need to browse, select, and critically appraise the current biomedical literature. There have been many useful reviews on each of the aforementioned topics. Still, having a unified and coherent workflow, feasible to fit into a busy clinical routine, would surely be appreciated by physicians. In addition, many of the aforementioned reviews have been written to target the audience in developed countries. In contrast, particularities of the access to the literature in developing countries (or economies in transition) have been addressed less frequently. Finally, new computational approaches, including machine translation and automated text mining, are rapidly emerging. These are indeed worthy addressing as the initiatives that could provide a great help to practicing physicians for rapid, yet comprehensive literature appraisals.

The present review aims to provide physicians with the workflow and methodological recommendation on browsing, selecting, and critical appraisal of the biomedical literature, with the specific focus on patient- and disease-oriented publications. The review further aims to overcome the aforementioned limitations of the previously published literature on this subject.

Key words: physician-scientist; physician; biomedical literature; critical appraisal; workflow; electronic databases; machine translation; data mining; algorithm.

Funding and Acknowledgements

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Introduction

The current time has been described as the Information Age (or Digital Age or Computer Age) [1]. This term implies that information, or rather the ability to extract and process information, is the key to success in modern society. In line with this, medicine has been undergoing a dramatic shift in both training and practicing aspects. While textbooks and monographies are still used by medical students, trainees and practicing physicians, there is an increasing need to consult the original information sources. The main driver behind this change is the desire to build one's own perspective on a particular aspect of a human disease. This is typically done by accessing online materials, such as biomedical publications or government documents.

The Information Age is coinciding with the introduction of genomic, transcriptomic and other "omics" technologies into clinical medicine, and with increased digitization of medicine. The latter advancements and changes fuel the expectations from patients, medical community, and the regulator that diagnostic and therapeutic procedures will soon be very individualized. The ability to "zoom in" on an individual patient is underlying the most recent clinical paradigm called Precision Medicine. As a consequence of this paradigm, we have been witnessing a major transformation of the medical practice. In fact, the scale of this transformation is comparable to what had followed the introduction of the concept of evidence-based medicine.

The evidence-based medicine concept has been introduced about three decades ago [2]. Fundamental to this concept is the need for standardized assessment of the strength of clinical evidence, which is reviewed according to the so-called Evidence Pyramid (Figure 1).

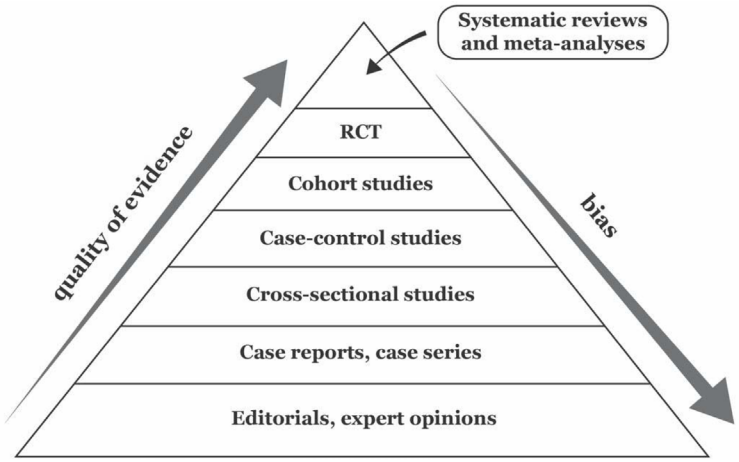

Figure 1 – Evidence Pyramid

Stemming from this are the expert panel guidelines. Said guidelines are used as the basis for the most current clinical decisions.

Since the introduction of the Evidence Pyramid, the way we deal with the patient- and disease-related information has been developed further. For instance, new tools for extracting information about patients have recently become available. In particular, we are now better able to regard the patient perspectives, such as quality of life, approach to the underlying disease, motivation and other critical factors by conducting qualitative studies (interviews, focus group discussions, observations [3, 4]; Figure 2).

Major methods of qualitive research	Explanation
Ethnography / Participant observation	Descriptive collection of data in their natural context
Interview / Unstructured interview	A "free-flowing" discussion
Interview / Semi-structured interview	A mixture of some predetermined questions and some spontaneous, "free-flowing" questions
Interview / In-depth interview	Interview aiming at detailed collection of personal memories, experiences, histories, perspectives, and opinions
Focus group	Unstructured group interview aiming at gathering behaviours, social norms, and interactions of participants in a group

Figure 2 – Qualitative studies

Electronic health-related data	Explanation
Electronic medical record	Digital equivalent of a medical chart that usually stays with one healthcare provider
Electronic health record	Also a digital equivalent of a medical chart; is meant to travel with the patient or to be shared between healthcare providers
Personal health record	An electronic collection of one's health record; is meant to be owned and managed by the patient

Figure 3 – Electronic health-related data

This valuable tool has yet to find its ranking within the aforementioned Evidence Pyramid.

Our ability to extract information has further been improved by the introduction of electronic health-related data. This digital tool has already evolved into splitting into several branches: Electronic Medical Records, Electronic Health Records, and Personal Health Records (Figure 3). The mining of these data also provides valuable patient-related information. Similar to qualitative studies, there is no consensus yet where electronic health data mining will fit into the aforementioned Evidence-Based Pyramid.

Given the multitude of information sources and the large volume of the current biomedical information, expert panels may not be able to update their recommendation in sync with the needs of clinical medicine. Thereby, practicing physicians will have to be able to find and assess the clinical literature on their own (that is, independently of the expert panels). This concerns both the physicians who are actively engaged in research (the so-called "physician-scientists") and physicians with predominantly clinical activities.

Furthermore, the very implementation of Precision Medicine may depend on the physicians' ability to make informed decisions about individual patients, especially when regarding rare diseases or rare forms of common diseases. Thereby the skill to retrieve, assess, and appraise biomedical information is expected to become increasingly relevant for physicians.

There are many useful and comprehensive reviews on how physicians can access biomedical information. However, not so many of these reviews address the particular needs of physicians in developing countries and economies in transition.

These particular needs, from the author's point of view, are the following.

First, reviews describing comprehensive literature searches (that is, how to conduct "systematic reviews") often assume that the reader has a full and comprehensive access to biomedical literature. However, even in developed countries this may not always be the case. For example, physicians employed outside of major academic centres habitually have only a limited access to biomedical literature. Furthermore, access to biomedical literature is even scarcer in low- and middle-income countries [5, 6].

Second, current biomedical literature is increasingly published in English, even by the journals published outside of the USA, Canada, UK, the European Union, Australia and New Zeeland. Depending on the underlying language proficiency, physicians, whose native language is not English, may experience substantial problems with comprehending the literature. Especially the English medical terminology, abbreviations, and scientific units may be confusing for a non-native speaker. We believe that this justifies an adaptation of the systematic review recommendations to permit the readership from non-English speaking countries to fully enjoy the benefits of international electronic literature databases. The latter are typically run in English language.

Given the aforementioned particularities, the present review will be the first one of the review series, which will collectively aim to address the following objectives.

First, these reviews will provide the reader from a low- or middle-income with an easily understandable workflow of how to work with biomedical literature. The focus will be made specifically on the patient- and disease-related literature. Second, these reviews will aim to adapt the recommendations on systematic literature review and literature appraisal, such that these recommendations can be utilized by

physicians in low- and middle-income countries. Finally, the newest computational advances, such as utilization of machine translation, will also be discussed.

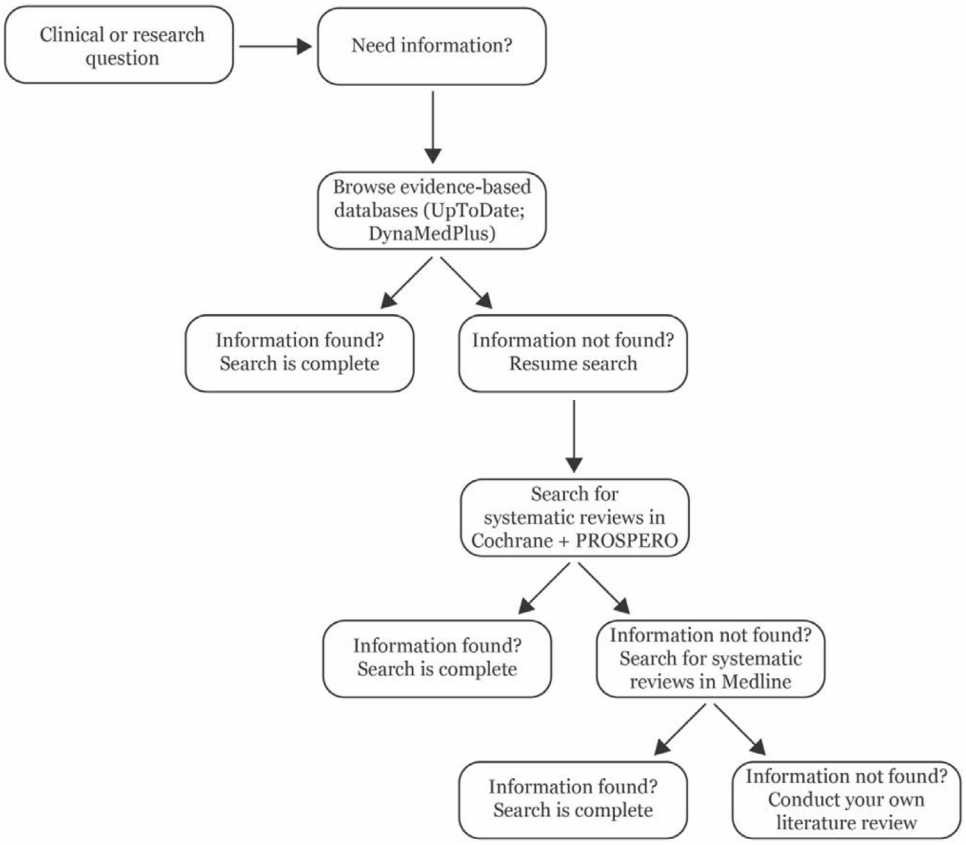

Figure 4 – Suggested workflow

General workflow: electronic databases on evidence-based medicine

To gain insights into a particular clinical topic, the author of this review usually starts with consulting the available clinical literature (**Figure 4**). In particular, the electronic databases on evidence-based medicine or the latest review papers provide the desired insights (**Figure 4**).

With regard to electronic databases on evidence-based medicine, the author of this report has a preference for beginning with consulting the UpToDate database (**Figure 4**). This is a US-based electronic database of evidence-based medicine (www.uptodate.com), covering a multitude of clinical topics. These topics are written and updated on a regular basis by expert groups. Importantly, UpToDate habitually indicates when (a) the literature search has been renewed and (b) when the UpToDate topic of interest has been revised. This permits the reader to make an individual informed decision as to whether further literature searches would be necessary. Specifically, if the topic of interest has been recently updated, and all clinical questions have been covered, then there may not be a need for further literature searches (**Figure 4**).

The use of the UpToDate database requires subscription, which includes the use of a phone app. An individual user needs to pay a subscription fee for access to this database. Alternatively, his or her university or hospital can purchase a collective licence. For users from certain regions (often referred to as "resource-limited settings"), the UpToDate database offers topics pertinent to Global Health (https://www.uptodate.com/home/uptodate-resource-limited-settings). In addition, various discounts are given to countries in acute need (such as, following a natural disaster) [7]. Furthermore, subscription options may be different between different countries, so it is worth checking the coun-

try-specific pricing for subscription (https://www.uptodate.com/home/uptodate-around-world).

A regular use of the UpToDate database by practicing physicians improves the level of provided clinical care [8]. This highlights the high level of clinical recommendations provided in this evidence-medicine clinical database. Furthermore, the use of UpToDate (that is, if the medical topic of interest is available) is faster than getting the same information using a biomedical search engine PubMed [9].

Apart from UpToDate, other evidence-based clinical databases are available, including DynaMedPlus (http://www.dynamed.com/home/), Medscape (https://www.medscape.com/), or ClinicalKey (https://www.clinicalkey.com). Among these alternative databases, the author's individual preference is DynaMedPlus (**Figure 4**). This database is maintained by EBSCO Health. While it features fewer clinical topics than UpToDate (respectively, ~3,300 vs. >10,000), the use of DynaMedPlus offers, in the author's view, three distinct advantages.

First, the information presented in DynaMedPlus is concise and provided in "bulleted" chapters and subchapters. Thereby, it is easier for a busy clinician to quickly find the topic of interest.

Second, DynaMedPlus provides ICD codes, which is another useful feature in a clinical practice.

Third, this database permits subscribing to regular electronic updates. Importantly, DynaMedPlus, similar to UpToDate, is available as a mobile version.

If the topic of interest is not available in the UpToDate, or DynaMedPlus or other databases, or the topic of interest has not been updated recently, the next steps can be undertaken.

General workflow: identification of available or prospective systematic reviews

The author habitually looks for a systematic review (**Figure 4**). Systematic reviews, which aim at both clinicians and expert panels, are the overviews written with the goal of critical and comprehensive synthesis of the literature. They are written according to specific guidelines [10, 11] to increase accuracy and consistency.

To identify systematic reviews on the topic of interest, the author conducts searches in databases of systematic reviews (**Figure 4**).

Cochrane Library (https://www.cochranelibrary.com/) is one such database. It comprises systematic reviews conducted by the standards agreed upon by the contributors of the Cochrane Library, which is considered by many as the highest standard among systematic reviews. Cochrane Library is run by a UK-based charity organization called Cochrane Collaboration, whose main goal is to promote evidence-based medicine. The access to the Cochrane Library is per subscription, although users from certain countries are eligible for a free access. Furthermore, a yearly subscription is not needed to access individual systematic reviews. In particular, a user can purchase only specific reviews.

As mentioned above, the advantage of Cochrane Library is that it requests the contributors to follow a specific pre-determined template for systematic reviews. Therefore, there is a great consistency in the review format, which makes it easier for the reader to absorb the information. The Cochrane Library is fully searchable, and one can use combinations of keywords and specific terminology called Medical Subject Heading (MeSH), combined for higher precision using Boolean logic operators "AND", "OR", or "NOT". The searches can also be refined by adding the information on authors or titles of the publications. Alternatively, Cochrane Library can be browsed for clinical topics (e.g., "gastroenterology" or "rheumatoid arthritis").

Importantly, Cochrane Library provides information when a systematic review has last been updated. Thereby a reader can see for himself/herself whether the information in Cochrane Library is up-to-date, accurately reflecting the newest developments on the topic of interest.

It is possible that a systematic review on the topic of interest would not be available in both UpToDate / DynaMedPlus and Cochrane Library. If this is the case, it makes sense to conduct own review of biomedical literature.

Systematic reviews are time-consuming and are usually conducted by team of investigators. It is possible that one such systematic review is being worked upon. To verify this, the author checks for prospective systematic reviews, which are underway on the topic of interest. A typical way how to find such prospective reviews is through searching of a register of prospective systematic reviews (**Figure 4**).

One such register, called PROSPERO, is managed by the University of York, United Kingdom (https://www.crd.york.ac.uk/prospero/#aboutpage). This particular register is fully searchable, and the access to the registered protocols is free. These protocols are done for both ongoing and prospective systematic reviews. The protocols habitually indicate the proposed date when a systematic review is to be finalized. It is important to keep in

mind, however, that there is always some lag time between completion of a systematic review and the publication date. Therefore, an immediate availability of a particular systematic review following its completion should not be expected. If the desired information is not available in the aforementioned electronic databases on evidence-based medicine or in databases of systematic reviews, the author then conducts a scoping review of biomedical literature. The essential steps of conducting a scoping review will be described in the next review of this review series.

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Ghazwan Butrous

Professor of Cardiopulmonary Sciences; University of Kent, Canterbury, UK
President Emeritus, Pulmonary Vascular Research Institute,
e-mail: G.Butrous@kent.ac.uk

THE CURRENT TREATMENTS OF PULMONARY ARTERIAL HYPERTENSION

Pulmonary hypertension is a debilitating chronic disease. In the last 20 years, there has been impressive progress in the treatment strategy of pulmonary arterial hypertension. This led to a significant increase in the awareness and improvement in the clinical outcome, though there was no substantial improvement in the rate of mortality. This review summarizes the current state of the art of the treatment of pulmonary arterial hypertension, including the three main categories of pulmonary hypertension specific medication which were introduced in the last 20 years. Mainly drugs that restore prostaglandins function of the endothelial cells, drugs that restore Cyclic GMP in the endothelial cells and various forms of medication that inhibit Endothelin receptors. The current strategy to treat patients with pulmonary arterial hypertension is to initiate drug therapy as early as possible and to adopt combinational therapy using two or more classes of drugs simultaneously. There are current efforts to introduce future medication that can be more specific to a phenotype of pulmonary hypertension.

Key words: hypertension, arterial, physical activity.

Introduction

The normal mean pulmonary arterial pressure (mPAP) at rest is 14 ± 3 mm Hg. When this pressure increases significantly, it will cause a debilitating chronic disease known as pulmonary hypertension. It is customarily defined as an increase in mean pulmonary arterial pressure of ≥25 mmHg (and pulmonary vascular resistance (PVR) ≥3 Wood Unit) but with normal pulmonary capillary wedge pressure of ≤ 5 mm Hg when measured during the right heart catheterization [1]. However, in 2018, the 6th World Symposium on Pulmonary Hypertension in Nice, France suggested that the condition should be redefined and proposed revising the haemodynamic definition by lowering the threshold from ≥25 mmHg to >20 mmHg [2]. This is still debatable as no clinical data available and that the new definition may lead to overdiagnosis and overtreatment pulmonary hypertension. The general trends to recommend adopting this new definition [3]. The definition also considered mPAP during exercise (>30 mmHg) (4,5), but once again during the 6th World Symposium on Pulmonary Hypertension this notion has been challenged and the subject needs further evaluation [2].

Pulmonary hypertension should be considered as a syndrome because of many local and systemic diseases. It was classified from the early days of the World Symposium on Pulmonary Hypertension into five groups depending on the clinical presentation, pathological findings and haemodynamic characteristics. These groups are continuously changing by the World Symposium on Pulmonary Hypertension as per the emerging data [1]. Table 1 summarises the up-to-date classification as per the latest 6th World Symposium on Pulmonary Hypertension in Nice, France [2]. In this review we are focusing on group I, that is pulmonary arterial hypertension.

Furthermore, pulmonary hypertension is scored based on the severity of specific symptoms into four different World Health Organisation (WHO) functional classes [6] [7]:

WHO functional class I: Patients with pulmonary hypertension, but without resulting limitation of physical activity.

WHO functional class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity, being comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue.

WHO functional class IlI: Patients with pulmonary hypertension resulting in marked limitation of physical activity.

WHO functional class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms.

This system helps clinicians to guide their decisions regarding appropriate treatment and

accurate assessment of prognosis. The functional status, the levels of PVR and mPAP ultimately determine the outcome and treatment of patients with pulmonary arterial hypertension.

In the last 20 years there has been progress in the management of pulmonary hypertension with the introduction of many modalities of treatments including drugs, and interventions. However, despite this progress we still have no cure for pulmonary hypertension, other than lung transplantation, and more works are needed.

Pathology

The main pathology of pulmonary hypertension **is** the proliferation and remodelling of small pulmonary arteries of 500 μm down to 20 μm. It is often associated (*in situ*) with thrombotic lesions and with different perivascular types of inflammatory cells. These will cause stiffening of large elastic arteries, mainly lobar and segmental pulmonary arteries. Although these pathological changes are common in most types of pulmonary hypertension, the causes and molecular changes and types of changes in the pathology can vary according the aetiology.

The remodelling causes construction and lose of vascular reactively which results in the rise in pulmonary arterial pressure and an increase in PVR, remodelling, and altered pulmonary vascular hemodynamic [8– 10].

Natural history of pulmonary hypertension

Pulmonary Hypertension is a progressive condition that eventually increases the burdens on the right ventricle leadings to hypertrophy and failure. It does not determine symptoms in the early and intermediate stages if not diagnosed early. If left untreated, patient condition can deteriorate rapidly, leading to signs of right ventricular failure [11– 13]; see Figure 1.

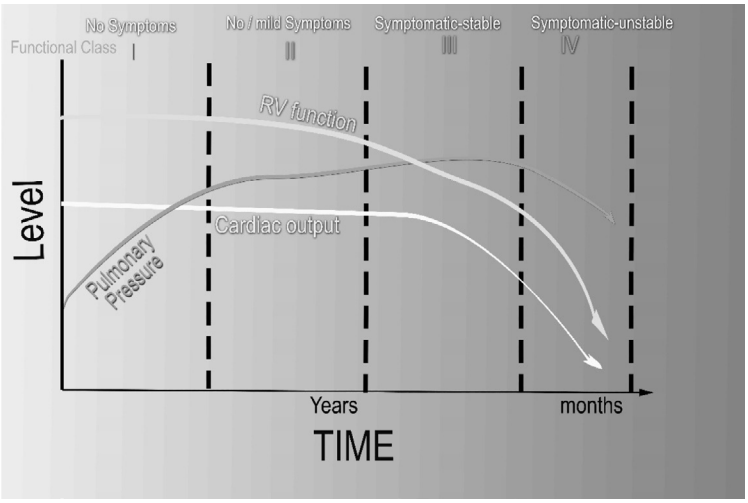

Figure 1 – schematic representation of the natural history of pulmonary hypertension

Management approach

Pulmonary arterial hypertension remains a challenging disease. In most patients a meticulous approach is necessary to arrive at the correct diagnosis, i.e. excluding PH due to left heart disease, PH due to lung disease, PH due to chronic thromboembolic disease. Clinical diagnoses started with a routine investigation like history and highly suspicious of pulmonary hypertension, as the symptoms are often nonspecific. Clinical examination involves signs of right heart failure, the accentuated pulmonary component of the second heart sound and a pansystolic murmur of tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation. Chest Radiography, Electrocardiography, Echocardiography and Pulmonary Function Tests are the minimum early diagnostic work up. Routine clinical examination like a blood test pulse oximetry, assessment of arterial gases and measurement of brain natriuretic peptide (BNP) levels. BNP levels are often elevated in patients with pulmonary hypertension, loosely correlate with the severity of right ventricular hypertrophy and failure, allows an assessment of prognosis and thus predictive of clinical outcomes. Finally, If pulmonary hypertension is suspected then

right heart catheterisation is essential to confirm and grade the severity of the hemodynamic derangement, with appropriate and accurate measurement of all elements of pulmonary pressure and wedge pressure; and assessment of vasoreactivity testing. genetic assessment to rule out any family history is also essential.

It's vital to assess the functional capacity of the patient who is diagnosed with pulmonary arterial hypertension to help with further follow up and part of the routine assessment of the medications, the most common, easy to perform and inexpensive is the 6-minute walking test (6MWT). This is a submaximal exercise testing. The 6MWT must always be interpreted with the clinical context. The absolute values, but not changes in 6MWD, provide some prognostic information, further detail of the 6MWT is beyond the scope of the article, but can be found more in these references [14–17].

Although cardiopulmonary exercise testing as a maximal exercise test and provides important information on exercise capacity, this test is not commonly used because of expenses and a need of standardisation and expertise [18]. Recently, some cents started to use cardiovascular diagnostic technique like CMR and PET scanning, especially for the assessment of and measurements of right ventricular function and structure.

Current guidelines provide a detailed diagnostic algorithm and risk stratification for the diagnosis and a long-term management of patients with pulmonary hypertension, which can be consulted in these resources [5,19,20].

Finally, the management of patients with pulmonary hypertension, including confirmation of the diagnosis, start of management and long term follow up should always be done in a well-trained, specialised and designated centres. Many countries have already established such centres.

Treatment of pulmonary arterial hypertension

The therapy for pulmonary arterial hypertension has evolved in the past two decades and is characterised by a complex strategy that includes the initial evaluation of severity and the subsequent outcomes, rather than just drug prescriptions.

There are general management issues like lifestyle, pregnancy, birth control and post-menopausal hormonal therapy, elective surgery, infection prevention, psychosocial support, adherence to treatments, genetic counselling and travels. Supportive therapy should also be considered like the use of anticoagulants, diuretics, oxygen, digoxin [5]. Anticoagulants might be warranted because of a high prevalence of vascular thrombotic lesions in patients with pulmonary arterial hypertension and as an adjunct treatment to prevent risk of catheter-associated thrombosis during treatment of specific intravenous treatment with Epoprostenol [21].

Decompensated right heart failure leads to fluid retention, therefore some centres may prescribe diuretics and even digoxin and other cardiovascular drugs. This is an empirical approach as there is yet no evidence-based data of their clinical benefit [22].

There are no sufficient data to support the clinical benefit of long-term oxygen administration in patients with pulmonary arterial hypertension, except in a certain condition where occasional use of oxygen may be clinically warranted [23].

Currently approved drugs Calcium channel blockers

Calcium channel blockers were the first drugs introduced to treat pulmonary

hypertension [24,25], with a high dose of nifedipine, diltiazem or amlodipine. The current recommendation is that only patients who show a significant vasoreactivity testing can be prescribed calcium channel blockers. These are the only specific patients with pulmonary hypertension who may benefit. Therefore, this class of drugs should not be considered as the first-line therapy [5,25,26].

Restoring prostaglandins of the endothelial cells

Prostacyclin is a potent pulmonary and systemic vasodilator and an inhibitor of platelet aggregation. It is well known that endothelial cells of blood vessels in pulmonary hypertension produced less endogenous prostacyclin [27,28]. This led to the suggestion that prostacyclin administration will be beneficial as it may compensate for that decrease. During the 1990s a synthetic prostaglandin I2 (PGI2) were suggested for the treatment of pulmonary arterial hypertension and was supported by three unblinded clinical trials that showed an improvement of symptoms, exercise capacity, haemodynamic and a reduction of mortality [29–31].

The first commercially available compound was an intravenous formulation of Epoprostenol (known commercially as Flolan® (GlaxoSmithKline) or Veletri® (Actelion). Generic formulation is also available now. These formulations came in different size and packaging. Epoprostenol has a very short half-life of 2–3 min. This compound needs special diluent. Therefore the administration will be by continuous IV infusion through a central venous

catheter using an ambulatory infusion pump. The drug needs to be continuously infused for 24 hours. A special care for preparation and to prevent the risks of infection and thrombosis, blocking of the catheter and the adequate functionality of the pump. Abrupt interruption of the Epoprostenol infusion should be avoided, because in some patients this may lead to a pulmonary hypertension rebound with symptomatic deterioration and even death. Thus, the administration of this medication needs a special trained enters and adequate patient training. The started dose of 2–4 ng/kg/min, which can be increased gradually. The average dose used is 20 and 40 ng/kg/min. The main adverse effects are related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis

Treprostinil is another prostaglandin analogue, with enough chemical stability to be administered at ambient temperature. Either intravenously or subcutaneously, making it relatively easier to administer [32–35]. The optimal dose varies between 20 to 80 ng/kg/min. The common adverse effects when admitted subcutaneously are infusion site pain and bleeding. Inhaled and oral form of this medication are also available in some countries [36,37].

Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral or aerosol administration. The inhaled formulation (brand name Ventavis®) is the most common formulation used today [38,39]. It needs a daily repetitive dosing (six to nine times of 2.5–5 μg per inhalation, median 30 μg daily) [40,41].

Oral prostaglandin analogues are also available. Beraprost was launched in Japan and Korea, but due to long term inefficiency it is now unavailable [42–44].

Selexipag is a new oral formulation with a selective prostacyclin IP receptor agonist, but structurally unique from prostacyclin [45,46]. It has recently been approved with the brand name of (Uptravi®). GRIPHON study [47,48], which is one of the largest clinical trials in pulmonary arterial hypertension (enrolled 1,156 patients) showed a 40% risk reduction in the composite endpoint of death or a complication related to pulmonary hypertension in both naïve patients (patients who were not yet on any treatment for pulmonary hypertension) and those on the background medical therapy. The initial dose of 200 μg twice daily, and can be escalated to the highest tolerated dose of 1600 μg twice daily. Thai main side effects are like other prostacyclin therapy, mainly headache, diarrhoea as well as muscle and joint pain.

Restoring Cyclic GMP in the endothelial cells

It was noticed the reduction in the expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension [49], consequently reducing the level of cyclic guanosine monophosphate (cGMP). cGMP regulates many cellular functions, ranging from contractility to growth [50,51]. Therefore, enhancing the level of cGMP can be beneficial to ease the increase in pulmonary pressure.

There are many ways to increase the cGMP level. The first is inhibition of the enzyme that inactivates and degrades cGMP; mainly Phosphodiesterase 5 (PDE5). Many drugs (now called PDE5 inhibitors) were introduced; the most common are sildenafil, vardenafil, and tadalafil. PDE5 inhibitors have become the leading oral therapy for pulmonary hypertension worldwide, especially in the developing world, mainly due to the availability at a reasonable price compared to other classes of pulmonary hypertension-specific drugs. However, PDE5 inhibitors are not universal and its effects depend on the aetiology. They are most effective in idiopathic and primary pulmonary hypertension. PDE5 inhibitors are less effective in other forms, such as for patients with pulmonary arterial hypertension due to sickle cell anaemia.

Sildenafil is an orally active, potent and selective PDE5 inhibitor [52]. It is approved for the treatment, patients with pulmonary arterial hypertension in WHO functional class II–III in Europe and WHO functional class II–IV in the USA as per the SUPER-1 and SUPER-2 clinical trials [53,54]. The recommended dose is 20 mg three times a day. The main side effects related to vasodilation (headache, flushing, epistaxis and hypotension).

Tadalafil is another oral PDE5 inhibitor like sildenafil, but with a longer half-life, thus a once-daily dosing (of 2.5, 10, 20 or 40 mg). It is approved in the USA, Europe and several other countries for the treatment of patients with pulmonary arterial hypertension with WHO functional class II–III based on the results of PHIRST-1 and PHIRST-2 clinical trials [55–57]. The side-effect profile is like that of sildenafil.

Vardenafil another oral PDE5 inhibitor given twice-daily (5 mg). It showed favourable results on exercise capacity, haemodynamic and time to clinical worsening [58,59]. The side-effect profile like that of other PDE5 inhibitors.

Another modality to increase cGMP level is by stimulating the enzyme that helps in producing it, mainly soluble guanylyl cycles (sGC). The main example of this class of drugs (called sGC

stimulator) is Riociguat. This drug was found efficacious in improving exercise capacity, haemodynamic, WHO-functional class and time to clinical worsening [60–62]. The recommended dose is up to 2.5 Mg three times a day. The most common serious adverse events are syncope bleeding, hypotension, and headache. Riociguat is the only pharmacotherapy to be approved for the treatment of two pulmonary hypertension indications, pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (CTEPH) (61). Combination of sildenafil with Riociguat can cause severe hypotension; thus, it is recommended not to combine these two drugs.

The third method to enhance cGMP is by introducing Nitric Oxide gas (NO). It is an endogenous gas produced by vascular endothelial cells enzyme NO synthase. This raises the concentration level of intracellular cGMP enhancing the vasodilatory and antiproliferative activities. Nitric oxide has been used as a therapeutic option of pulmonary hypertension since 1990s [63,64], especially in paediatric age group, intensive care or post-operative period. The administration can be via face mask or nasal prong connected to a cylinder (can be a mobile cylinder) or via a centralised system in some hospitals.

Inhibiting Endothelin receptors

Endothelins (ET) are endogenous peptides. It is produced primarily in the endothelium and are very potent vasoconstrictors when binds with either ET-A and ET- B receptors [65,66]. Various studies support a prominent role for the endothelin system in the pathogenesis of pulmonary arterial hypertension [67]. Thus, inhibition of these receptors can alleviate pulmonary hypertension symptoms. Many drugs (commonly referred as an Endothelin Receptor antagonist (ERA) were approved for the management of pulmonary arterial hypertension.

The first drug introduced in this class was Bosentan [68]. It is an oral active dual endothelin receptor (ET-A and ET-B) antagonist. Various clinical trials (BREATHE- 1BREATHE-2, BREATHE-5, EARLY, and COMPASS 2) showed improvement in exercise capacity, WHO functional classes and haemodynamic [69]. It is approved in 2001 in the USA but now available in many parts of the world. It is an oral medication with the initial dose of 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily. The main side effects are anaemic; diarrhoea; gastrointestinal disturbances, flushing; and headache. It is important to note that this drug may cause hepatic disorders. Thus, liver function testing should be performed monthly in patients receiving Bosentan.

The second drug introduced in this class was Ambrisentan, which preferentially binds with endothelin receptor type A [70]. Ambrisentan has been evaluated in two clinical trials that have demonstrated efficacy on symptoms, exercise capacity, haemodynamic and time to clinical worsening in patients with pulmonary arterial hypertension [71,72]. It is given once daily (5 mg), but can be increased to 10 mg once daily. The side effects are mainly peripheral oedema, abdominal pain; anaemia; gastrointestinal disturbances, bleeding, headaches and hypersensitivity. The incidence of abnormal liver function tests ranges from 0.8 to 3%, but monthly liver function assessment is not recommended in some countries.

The most recently introduced drugs of in this category are the dual ERA, Macitentan [73,74]. The Clinical trials showed a significant reduction in the composite endpoint of morbidity and mortality and increased of the exercise capacity among patients with pulmonary arterial hypertension [75,76]. These benefits were shown in patients who had not received treatment previously and for those receiving additional therapy for pulmonary arterial hypertension. The current recommended dose is 10 mg daily. Its main side effects are anaemia; headache; increased risk of infection; nasal congestion, but liver toxicity was not a significant finding.

Current strategy for the treatment of pulmonary arterial hypertension

The current strategy to treat patients with pulmonary arterial hypertension is to initiate the drug therapy as early as possible and to adopt combinational therapy using two or more classes of drugs simultaneously [77–82]. Combination therapy reduces the risk of clinical worsening, increases the 6MWD,reduces further the mean PAP and PVR, but the reduction in all-cause mortality was not statistically significant [82] if applied early in naïve patients [20]. The combination therapy may be applied initially (i.e. upfront) or sequentially. There is no clinical study to compare the best combination, as this depend on the aetiology and the stage of the disease, as well as the tolerance to any medication. It is an empirical decision of the treating physicians.

The early initiation of the medication or upfront combination therapy has been recommended by many trails (54,77,81,83), however this strategy still need further evaluation [20].

Future potential drugs for the treatment of pulmonary arterial hypertension

Despite recent advances in pulmonary arterial hypertension treatment, this condition is still characterised by an extremely poor prognosis. The currently used drugs described above did not show a significant improvement of mortality, though there were improvement of quality of life and symptoms.

Therefore, a move to more drugs effect on the core pathogenesis of pulmonary hypertension. There now current efforts to test drugs that affect genetically determined mechanisms or epigenetic modification of pulmonary arterial hypertension. Also, drugs that antagonise various growth factors, repair the DNA damage, modulation of metabolism, oxidative and hypoxic stress or influencing the Inflammation and immune reaction. The subject is beyond the scope of this article, but more can be found in these reviews [84–86] .

Other non-pharmacological treatment tools

Clinicians always face with patients who are not adequately managed with the current medical therapy. Therefore, many modalities and intervention were adopted or used with various degrees of potential success [84].

Balloon atrial septostomy [85] is a procedure where a small hole is made in the wall between the left and right atria of the heart using a cardiac catheter to reduces the pressure in the right side of the heart, thus decompress the right heart chambers and increase left ventricular preload and cardiac output [86].

In severe cases of non-responded patients lung or a heart-lung transplantation is recommended. The overall 5-year survival following transplantation for pulmonary arterial hypertension in experienced centres was considered to be 45–50%, with evidence of continued good quality of life [87,88].

There is however now potential intervention which is still in early trials like pulmonary artery denervation [89] or stem cell therapy [90,91].

Table 1 – Updated clinical classification of pulmonary hypertension (2)

Group 1 Pulmonary Arterial Hypertension
1.1 Idiopathic Pulmonary arterial hypertension
1.2 Heritable Pulmonary arterial hypertension
1.3 Drug- and toxin-induced Pulmonary arterial hypertension
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 Pulmonary arterial hypertension long-term responders to calcium channel blockers
1.6 Pulmonary arterial hypertension with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent Pulmonary hypertension of the new-born syndrome
Group 2 Pulmonary hypertension due to left heart disease
2.1 Pulmonary hypertension due to heart failure with preserved left ventricular Ejection fraction
2.2 Pulmonary hypertension due to heart failure with reduced left ventricular Ejection fraction
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary Pulmonary hypertension
Group 3 Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease

3.3 Other lung disease with mixed restrictive/obstructive pattern

3.4 Hypoxia without lung disease

3.5 Developmental lung disorders

Group 4 Pulmonary hypertension due to pulmonary artery obstructions

4.1 Chronic thromboembolic Pulmonary hypertension

4.2 Other pulmonary artery obstructions

Group 5 Pulmonary hypertension with unclear and/or multifactorial mechanisms

1.1 Haematological disorders

1.2 Systemic and metabolic disorders

1.3 Others

1.4 Complex congenital heart disease

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Yu. Khaidarova[1,2], M. Masoodi[2], G. Kurmanova[3], B. Seizhanova[1]

[1]Al-Farabi Kazakh National University, Almaty, Kazakhstan, e-mail gkurman@mail.ru
[2]Municipal rheumatology center, Almaty, Kazakhstan
[3]Jawahar Lal Memorial Hospital Srinagar Kashmir

POLYMORPHISM OF OSTEOARTICULAR MANIFESTATION OF BRUCELLOSIS INFECTION. A REVIEW

Brucellosis is a common zoonosis which still remains as a major health problem in certain parts of the world. Kazakhstan remains among the most disadvantaged territories of brucellosis from Commonwealth of Independent States countries. The involvement of the musculoskeletal system is one of the most common systemic manifestations in brucellosis infection. The frequency of osteoarticular involvement of brucellosis varies between 10% and 85%. Osteoarticular involvement includes spondylitis, sacroiliitis, osteomyelitis, peripheral arthritis, bursitis, and tenosynovitis. Sacroiliitis is the most common osteoarticular finding in adults. A high degree of suspicion in the diagnosis of brucellar spondylitis is essential to reduce the delay for the treatment. Thus, it should be essentially included in the differential diagnosis of longstanding back pain particularly in regions where brucellosis is endemic. Screening serologic tests for brucella should be used more widely even in presence of low index of suspicion, especially in endemic areas. According to studies, when diagnosed with chronic brucellosis, the results of serological studies were unreliable: the result of the standard agglutination test (SAT) - Wright's reaction was negative in 32.7% of cases in patients with chronic brucellosis. Imaging studies, including radiography, computed tomography (CT), magnetic resonance (MR) imaging, and bone scintigraphy, have been used for diagnosis. Radiography is limited to evaluating the focal form of spinal brucellosis and advanced disease at the joints. For instance, MR imaging has a low specificity to predict the exact cause of an osteoarticular lesion, and in case of arthralgia or symptoms of osteomyelitis or spondylodiscitis, the index of suspicion should be high in regions where the disease is endemic.

Key words: Brucellosis, osteoarticular manifestation, brucellar sacroiliitis, spinal brucellosis, Spondylodiscitis, discitis.

Introduction

Brucellosis is a relatively common zoonosis worldwide, caused by small coccobacilli of Brucella species, which are intracellular gram-negative facultative bacteria. B. melitensis and B. abortus are the main causes of human brucellosis. Human brucellosis is a systemic infection that involves many organs and tissues in the pathological process. The relevance of this problem is the late diagnosis, which indicates the lack of alertness and knowledge among medical personnel regarding brucellosis even in areas where the infection is widespread. According to Professor Amireev S.A. in Kazakhstan (20000 *cases of brucellosis,* 1986-1994 y.) despite the typical clinical manifestations of acute brucellosis, in 1/3 of the patients the initial diagnoses were incorrect: 12% of the patients were mistakenly diagnosed as pneumonia, 7% of the patients as an acute respiratory infection, and some patients even received treatment diagnosed with viral hepatitis, acute rheumatic fever and others [10]. This fact once again proves the polymorphism of the clinical manifestation of brucellosis and the low awareness doctors of all specialties. If such difficulties exist during the diagnosis of acute brucellosis, verification of chronic brucellosis in the presence of systemic manifestations and with low sensitivity of laboratory tests is a real medical problem.

The incidence of brucellosis in the world has increased in recent years. From the literature it is evident that the current rate is lower than the actual incidence because of under diagnoses and underreporting. Although the diagnosis of brucellosis is usually not difficult, its misleading and multifarious manifestations, especially in case of localized, sub-acute or chronic infections might lead to misdiagnosis and delayed treatment [1].

Brucellosis is the most frequent zoonotic infectious disease in the world, affecting more than 500 000 people each year. Its prevalence is

more than 10/100 000 population in some endemic countries In endemic countries, brucellosis is more prevalent in the 15–35 years age group [3,4]. In a recent study by T. Buzgan et al. (*1028 cases of brucellosis*, Turkey) 53.4% of patients were between 13 and 34 years of age [2]. In a recent study by Gu¨l et al. from Turkey (140 patients between January 1997 and December 2006), a mean age of 27 ±3.6 years was reported in a population comprising 80.7% male and 19.3% female. Gender differences between these results could be explained by the diversity of populations, because the latter study was performed in a military hospital [12,13].

According to research Gu¨ r et al. (*283 cases,* Turkey) 138 (49%) were female, 145 (51%) male and 53 (19%) were younger than 15 years old [11].

An alarming fact is that brucellosis mainly affects a young rural contingent from among indigenous ethnic groups (90%), including children under 14 years of age. The professional composition of patients has undergone significant changes: the proportion of people constantly associated with animal husbandry (shepherds, milkmaids, hunters and others) is steadily decreasing: from 36.5% in 1961-1965 to 13.8% in 1994 of the total Today, there is a tendency to increase the proportion of persons professionally not associated with animal husbandry. However, according to a study by prof. Amireeva S.A. the majority of patients with acute and subacute brucellosis (76%) had professional contact (permanently or temporarily) with animals, its raw materials, or animal products [6].

Infection of a person with brucellosis can occur not only as a result of his direct contact with animals affected by brucellosis, but through livestock products, in particular, in the process of removing and processing skins infected with brucellosis in areas that are often quite remote from the immediate location of the source of infection. The primary transmission route of brucellosis is by the ingestion of unpasteurized dairy products in endemic countries, whereas in developed countries infection occurs mostly due to occupational exposure [3-5]**.** In Kazakhstan (20000 *cases of brucellosis,* 1986-1994 y.), the contact route of transmission of the infection still prevails (79-86%), which over time is becoming increasingly less important in favor of the nutritional route. By the end of 9th decade of the 20th century, an alimentary route of infection is much less common (0.1–9.1%) [6]

The disease spreads to humans by the ingestion of raw dairy products, the consumption of infected meat from domestic livestock (sheep, goats, cattle, water buffalo, camels and pigs) and close contact with their secretions and carcasses [2].

Alimentary infection is caused by using raw and not sufficiently thermally processed livestock products (milk, dairy products, especially goat milk and feta cheese, barbecue, etc.). The long stay of brucella in milk determines its epidemiological role especially goat milk. There are known cases of human disease that has been caused by consuming unboiled milk. Brucella lives in meat and minced meat for 14 to 40 days, depending on storage temperature and salt concentration. This factor is of particular importance for workers in the meat processing industry and for the consumer [16].

In some epidemiologic studies from Turkey (*1028 cases of brucellosis)*, a history of raw dairy product consumption has been reported for between 62.6% and 94.6% of cases [2]. The consumption of raw dairy products in other studies has been reported as occurring in 23.6% of cases in Spain by Colmenero et al. (*530 cases)*,[7] 69% in Kuwait by Mousa et al. (379 cases),[8] 34.7% in the Balkan Peninsula by Bosilkovski et al. (418 cases), [9] and 22.4% in Iran by Roushan et al. (469 cases) [10]. A history of a local traditional food in Turkey – raw meat ball – consumption was reported in 55% in the series of Gu¨ r et al. (*283 cases)* [11]. High-risk occupations for the disease are shephards, butchery, farming, and people associated with veterinary medicine [3,4].

Although it is seen widely throughout the world, it is hyperendemic in the Mediterranean Basin and Arabian Peninsula, India, Mexico, and Central and South America. Brucellosis has been eradicated in England, in many northern European countries, and in Australia, New Zealand, and Canada [13,14]. The increase in the incidence of brucellosis of people in Kazakhstan is a direct consequence of the sharp deterioration of the epizootic situation: a direct link has been established between the infection of livestock and the incidence of people [6].

According to reports on the MEDinform website, which contains official statistics of the Ministry of Health of Kazakhstan, in 2000, 1918 cases were recorded (incidence rate of 12.9 / 100,000), and in 2004 their number increased to 3596 (incidence rate of 23.95 / 100,000). Interestingly, despite the improvement in the diagnosis and verification of brucellosis in 2018, 998 new cases were recorded, the incidence rate decreased to 5.46 per 100,000 population [17]. However, these figures do not fully reflect the actual situation in our country, because the high incidence of brucellosis in people does not always agree with the official statistics of the

veterinary service. In Kazakhstan, the following pattern remains: the predominance of small cattle as a source of infection, and in recent years it has been expressed more and more. Accordingly, there is a slight decrease in the value of cattle in infecting people. In almost all zones of Kazakhstan, except the western, small cattle are of primary importance in infecting people. In the western regions of Kazakhstan, the role of small and cattle is approximately the same (43% and 50%, respectively, and the rest is other ways of infection) [6]. There is a lot of speculation about reducing the incidence of brucellosis by 3.5 times over the last 10 years. Firstly, incomplete laboratory diagnosis in suspected brucellosis. According to the rules of the standard definition of the case of a particularly dangerous infectious disease, the following laboratory tests are necessary to confirm the diagnosis of "brucellosis": the Hadlson reaction, agglutination reaction, ELISA, passive hemagglutination reactions, antigen neutralization reactions, Coombs reaction, complement fixation reaction, method of detecting antigen-binding brucellous specificity lymphocytes (diagnostic value 95% in acute brucellosis), polymerase chain reaction using blood serum , blood cells, bone marrow, lymph node biopsy and other biomaterials, as well as bacteriological blood tests for brucellosis. But unfortunately, most cases use only screening methods to determine brucellous infection: the Hudlson reaction and agglutination test, which have low diagnostic value. Secondly, the low caution of infectious doctors and general practitioners. This may be due to the distinctive feature of modern brucellosis - the increase in morbidity among unprofessional groups, including children, along with persons associated with livestock production and processing of livestock products. Thirdly, the prevalence of the alimentary route of infection when the agent enters the body when the infected food is consumed (dairy, less often meat products). The alimentary route of infection is carried out when raw and insufficiently thermally processed livestock products (milk, dairy products, especially goat milk and feta cheese, barbecue, etc.) are consumed. This leads to an erroneous interpretation of epidemiological history. Thus, the decline in morbidity in Kazakhstan is surprising at a time when there are no epidemiological prerequisites for this phenomenon. All the above-mentioned reasons are still hypotheses that need further study.

Because brucellosis is one of the great imitators in the world of infectious diseases, it can mimic various multisystem diseases, showing wide clinical polymorphism, which frequently leads to misdiagnosis and treatment delays, further increasing the complication rates [3,4]. Clinically it may progress as a subclinical, acute, subacute or chronic infection. Since Brucella spp. are intracellular bacteria, relapse is often seen [3, 4, 5, 22].

Brucelles can persevere in the host 's body for a long time. Most commonly, the brucella reservoir is lymph nodes, bone marrow, and spleen. They play the role of "microbial depot," from where the infection is re-generalized: the patient after a long period of well-being, when he seems to have recovered, in supercooling, trauma, cold, stress, getting physiotherapeutic procedures, symptoms of the disease again appear. Centers of infection can be a source of another endogenous reinfection even after a significant period of time (months and years). Chronic inflammation can follow an acute, and sometimes the inflammatory process from the very beginning has the features of a chronic one. When acute clinical manifestations of brucellosis die away, focal manifestations come to the forefront (damage to individual organs - for example arthritis, spondylitis), followed by degenerative-dystrophic changes (after arthritis - arthrosis, osteochondrosis).

Clinical manifestations are the basis for the diagnosis of brucellosis. After an initial physical examination, we use serological tests [Wright test and 2-mercaptoethanol (2-ME)], cultivation and imaging methods to verify the diagnosis. To definitely diagnose brucellosis, the organism needs to be isolated from blood, bone marrow, wounds, purulent discharge or other body tissues and fluids, with culture or molecular/histological assessment [19]. The major pathological feature of Brucella spondylitis is nodular lesions consisting of epithelioid cells, which can be seen in the nidus under a light microscope. Affected areas may show histiocytosis, proliferative nodules, and granuloma, as well as large numbers of neutrophils, lymphocytes, monocytes, and eosinophils. The typical mechanism of brucellosis infection is direct contact with the skin or mucosa, although infection can also occur via inhalation of airborne droplets into the respiratory tract. Brucellosis can also invade the spine; this occurs in 2–53% of cases [20-22]. An important aspect in the pathogenesis of Brucella, apart from its virulence factors and the environmental factors contributing to infection, is host genetic background, which is crucial in determining the susceptibility or resistance to brucellosis [23]. Cell-mediated and humoral immune responses, in which several cytokines are involved, play pivotal roles in protection against

brucellosis [*1*]. Production and release of cytokines rely mostly on human genetic factors, so variations in the regulatory sequences of the cytokine genes can greatly affect the cytokine balance. A growing number of studies report higher prevalence of single nucleotide polymorphisms (SNPs) in the cytokine-encoding genes of patients with brucellosis. These SNPs are possibly the agents responsible for susceptibility to brucellosis and can be important in the clinical course and prognosis of the disease *[24-27]*. However, the extent to which these genetic variations can influence the development, progression, and outcome of brucellosis is yet to be known [*1*]. These nucleotide polymorphisms in the genes encoding the cytokines of patients with brucellosis are not excluded; they cause a systemic clinical manifestation [28].

The most common clinical presentations of human brucellosis are fever, sweating, musculoskeletal pains, lymphadenopathy or hepatosplenomegaly. The musculoskeletal system is particularly involved. Presentations of brucellosis are variable, deceptive and often non-specific, and they can mimic other infectious and non-infectious diseases [2].

Osteoarticular disease is the most common complication of brucellosis and has been described in 10%–85% of patients [3, 4]. Osteoarticular involvement rates of between 58.8% and 79.5% have been reported, [11, 41-43] but lower rates of between 9.3% and 22.8% have also been reported [40, 44-47]. In the T. Buzgan et al. study (*1028 cases*, Turkey) osteoarticular involvement was observed in 21.8% of acute cases, 34.7% of subacute cases, 25.7% of chronic cases, and in 27.3% of relapsed cases, with an overall rate of 25.3%. The enormous range between reports in the literature may be due to characteristics of the study populations, the radio-diagnostic methods used, and the different diagnostic criteria employed [2]. According to research Gu¨ r et al. (*283 cases,* Turkey) osteoarticular complications were the most frequent, found in 195 (69%) cases, followed by cutaneous (17%), genitourinary (8%), nervous (7%), respiratory (5%) and hematological (4%) complications. Cutaneous, hematological and respiratory complications in childhood; osteoarticular and cardiac complications in adults; and genitourinary, neurological and gastrointestinal complications in middle aged were more prominent [11].

Table 1 – The incidence of osteoarticular manifestation in patients with a diagnosis of chronic brucellosis according to different authors

The authors	Osteoarticular manifestations	Sacroiliitis	Spondylitis	Spondylarthrosis	Spondylodiscitis	Spondylosis	Osteochondrosis	Arthritis	Arthralgia
Esmaeilnejad-Ganji SM et al. (Iran, 2019)[19]	10-85%	80%	54%		6-85%			14-26%	
Kasatkina I. L. et al. (Kazakhstan, 1976) [83]	45-92%	-	10,2%	12,2%	5,8%	8,6%	37,6%	15,1%	42,2-86%
Solera et al. (35 Cases, Spain) [29]	10-85%	-	100%	-	-	-	-	-	54%
V.kh. Fazylov et al.(26 patients, Tatarstan [30]	65,4%	65,4%		80,8%				34,6%	
Tu L. et al. (72 Cases China) [28]	-	-	2-53%	-	-	-	-	-	-
Jiang et al. (850 Cases China)[46]	69,8	-	13,1%	-	2,2%	-	-	26%	65%
K.B.Kurmanova et al. (45 Cases, Kazakhstan) [16]	100%	-	3%	-	0,5%	-	-	-	100%
G.M. Kurmanova et all (186 Cases, Kazakhstan) [60]	79,4%	46,7%	6,5%			-	-	-	30,8%

According to the prof. Amireeva S.A. (2500 Cases, Kazakhstan, 1991-1994) 46.8% of patients have persistent involvement of large joints The preferential damage of the bone-joint system in brucellosis was the most frequent cause of the erroneous rheumatological diagnosis [6]. At the same time, there was no incomplete targeted collection of epidemiological history and analysis of clinical manifestation, as well as late use of laboratory methods of research in each suspected case of brucellosis.

Spinal brucellosis. The spine is one of the most common organs involved in brucellosis infection with a rate varying from 2%-54%, and the lumbar vertebrae are the most frequently affected [31, 32]. It mainly manifests as spondylitis, spondylodiscitis and/or discitis. Back pain is the most common compliant in spinal brucellosis and reported by about half of the patients [33, 34]. In patients with acute brucellosis, the morphology of the infected vertebrae is normal. The endplates, which have a rich blood supply, are the first vertebral bodies to be affected. Inflammation eventually spreads to the entire vertebral body, accompanied by early vertebral infections wherein inflammatory congestion and edema are the principal pathological changes, in addition to increased amounts of water in the vertebral bodies.

However, (at first) no obvious spinal deformities or bone destruction attributable to changes in the vertebral morphology are evident. When the disease enters its subacute and chronic stages, immune cells interact with the infected foci and bone destruction occurs. Infected vertebral bodies undergo complex changes, including hyperosteogenesis and sclerosis. Thus, the signal intensities of vertebral bodies are uneven, even when osteoporosis in diseased vertebrae and obvious changes in vertebral body morphology are absent [28]. The clinical and imaging manifestations are very similar to those of spinal tuberculosis, including narrowing of vertebral gaps, destruction of vertebral bodies, formation of bony bridges, and widening of the shadow of the vertebral column [43-44]. Cases with delayed or aggravated illness caused by early clinical misdiagnosis are frequent [45]. One of the targeted studies regarding Brucellosis spondylitis is described in the article by Solera et al., In which there are reliable data on the polymorphism of clinical manifestations. Thirty-five patients aged 14–74 years (average, 54 years) who had brucellar spondylitis were treated between January 1991 and December 1997. The time from onset of symptoms to diagnosis of spondylitis ranged from 1 week to 8 months (median, 9 weeks). Back or neck pain (100% of patients), fever (66%), and constitutional symptoms (57%) were the most common symptoms. Cultures of blood specimens from 26 patients (74%) were positive for *Brucella melitensis*. The duration of antimicrobial therapy (median, 120 days; range, 45–535 days) varied according to clinical response and the presence of epidural and paravertebral masses. One of the 35 patients underwent surgical treatment of a spinal epidural abscess. Therapy failed for 9 patients, and 5 had a relapse. There were no deaths or severe sequelae in this study. Brucellar spondylitis causes considerable suffering and absenteeism from work, but long-term clinical responses are favorable [29].

Spondylitis. Spondylitis or vertebral osteomyelitis is inflammation and infection of vertebrae which has a prevalence rate of 2%-60% and mostly observed in men aged > 40 years Old [14, 19]. According to study Jiang et al, arthralgia was detected in 69.8% of patients and spondylitis was found in 111 of 850 patients. According to this study, lumbar spine involvement was observed in 105 patients, the cervical spine was affected in 9 patients, and the thoracic spine was involved in 6 patients [46]. Lumbar (60%), sacral (19%) and cervical (12%) vertebrae were the most common affected sites, respectively, in a survey by Bozgeyik *et al* (*152 cases, Turkey)*, [47]. There are two types of spinal brucellosis, focal and diffuse. In focal involvement, osteomyelitis is localized in the anterior aspect of an endplate at the discovertebral junction, but in the diffuse type, osteomyelitis affects the entire vertebral endplate or the whole vertebral body [47, 48]. Spondylitis is the dangerous complication of brucellosis, due to its association with epidural, paravertebral and psoas abscess and potential (in causing nerve compression.)In one report, rapidly progressive spinal epidural abscess was observed following brucellar spondylitis, which was primarily misdiagnosed as a lumbar disc herniation [49]; delay in diagnosis and treatment were responsible for rapid progression of the disease.

Spondylodiscitis. Spondylodiscitis is an inflammatory disease of vertebral structures involving intervertebral discs and adjacent vertebral bodies and joints. It is the most severe form of osteoarticular involvement of brucellosis, and can have single or multi-focal involvement. The main complaint is back pain that is known to be the most prevalent complaint in the general population. Diagnosis of spondylodiscitis is difficult and is often characterized by delay from the debut of symptoms. Granulomatous spondylodiscitis may be caused mycobacterium tuberculosis, be a complication

of brucellosis, sometimes have a fungal origin, especially in patients with immunodeficiency [50]. It is the most severe form of osteoarticular involvement of brucellosis, because it makes a high rate of skeletal and neurological sequels despite therapy [19]**.** It is stated that 6%-85% of brucellosis osteoarticular involvements are related to brucellar spondylodiscitis. Lumbar (60%-69%), thoracic (19%) and cervical segments (6%-12%) are reported to be more involved in the spinal area [51-53]. Spondylodiscitis can be seen as single-focal and/or contiguous or non-contiguous multi-focal involvements. Multi-focal skeletal involvement in the spinal system was seen in 3%-14% of patients [53, 54].

Sacroiliitis. Large joints, like sacroiliac, are the most common regions of musculoskeletal involvement of brucellosis. Sacroiliitis, inflammation of sacroiliac joint, has been observed in nearly 80% of patients with focal complications and more frequently in adults [48]. It is reported that the rate of sacroiliitis is high in those patients who are infected with *B. melitensis* spp. [56, 57].

Sacroiloiits with brucellosis is(unilateral or bilateral)and is manifested by severe pain in the sacral region, aggravated by movement, especially when walking and when the body is tilted forward; in severe cases, patients lie motionless on their backs, afraid to move, so as not to cause increased pain [16]**.** Sacroiliitis was also simultaneously seen with dactylitis, olecranon bursitis, humerus osteomyelitis and iliac muscle abscess, and with other systemic diseases, like endocarditis, pyelonephritis and thyroiditis. A study showed that high-resolution MRI has a higher sensitivity than scintigraphy in the diagnosis of brucellar sacroiliitis [19].

Peripheral joints. Brucellosis with peripheral skeleton involvement is less prevalent compared with vertebral features. It can manifest as arthralgia, enthesopathy, osteomyelitis, arthritis, bursitis, tendonitis and tenosynovitis [19]. Arthritis occurs in 14%-26% of the patients suffering from acute, sub-acute or chronic brucellosis [58-59]. Articular Syndrome is significantly more often observed in secondary-chronic brucellosis 79.4%) as compared with primary chronic brucellosis 47 (59.6%, P <0.01) in the form of arthritis, arthrosis arthritis, bursitis, tenosynovitis, periostitis, perichondritis with characteristic symptoms. Knee, hip and ankle joints are among the most common peripheral regions affected by brucellosis and these patients present with arthritis. Shoulders, wrists, elbows, interphalangeal and sternoclavicular joints may also be involved [19]. Multiple joint arthritis caused by brucellosis was reported in 17% of patients in a study. In 44.3% with primary chronic brucellosis and in 41.2% with secondary chronic brucellosis small joints of the hands and feet were affected [60].

According to *T. Buzgan et al.* (*1028 cases, Turkey)*, study, the most common symptoms of brucellosis were arthralgia (73.7%), fever (72.2%) and fatigue (71.2%) and peripheral arthritis (14.3%), when in children arthralgia was detected in 85.9% of patients, and peripheral arthritis was found in 21.8% of children. Peripheral arthritis occurred more frequently than in the adult group (21.4% vs. 14.3%), while sacroiliitis was less frequent (2.6% vs. 6.2%) and spondylitis was not seen [61]. Brucellosis can involve the peripheral joints through septic (with presence of pathogen) and reactive (lack of the pathogen) mechanisms [62, 65]. Septic arthritis caused by brucellosis has been reported in the literature and it has been recommended that patients with septic arthritis living in the endemic areas, be examined in terms of brucellosis [64, 66]. Septic arthritis in brucellosis progresses slowly and starts with small pericapsular erosions. Blood culture is positive in 20%–70% of such patients. Although synovial fluid assessment is the most useful diagnostic method, the isolation of the pathogen from synovial fluid is not easy [67]. Knee arthritis has obvious symptoms and is less difficult to diagnose and treat due to easy access. However, the diagnosis and treatment of hip arthritis is more difficult and delay in diagnosis and treatment may lead to serious and (irreversible) complications, such as dislocation and necrosis of the femoral head [63, 68]. Brucellosis should be considered in the differential diagnosis for a patient presenting with knee or hip arthritis symptoms in endemic regions to prevent misdiagnosis and serious complications. Due to the synovial involvement of the disease, pathological evidence may not be found on radiograph in the early phase of infection.

Other Articular manifestations and complications. One of the clinical manifestations of infection is the development of osteoarthritis. In the study of G.M. Kurmanova et al. ((186 Cases, Kazakhstan), changes in the joints radiography were revealed, indicating that in patients with primary chronic brucellosis (21.5 ± 4.6%), with secondary chronic brucellosis (46.7 ± 4, 8), a progressive process was detected up to deforming osteoarthritis with osteophytosis of the knee joints (21.5 ± 4.6%). %); hip deforming arthritis was found in patients with primary chronic brucellosis (20.3 ± 4.5%), with secondary chronic brucellosis (41.1 ± 4.8%); In patients with primary

chronic brucellosis (19.0 ± 4.4%) and secondary chronic brucellosis (30.8 ± 4.5%), humroacular periarthritis was confirmed[60]. In a study by Ebrahimpour et al.[59], brucellosis was attributed to sternoclavicular (4.5%), wrist (2.4%), elbow (1.07%) and shoulder (0.6%) arthritis.

Table 2 – The frequency of manifestations of articular syndrome

The joints/the authors	G.M. Kurmanova et all [60]	V.kh. Fazylov et al. [30]
Humeral	18.7%	27%
Elbow	13.1%	
Wrist band	15%	30.8%
Small joints of the hands	17.8%	
Hip	13.1%	34.6%
Knee	45.8%	46.1%
Ankle	15.9%	
Small joints of the feet	23.4	11.5%

Delay in the diagnosis of brucellosis result in prolong disease duration which can lead to osteomyelitis or osteolytic lesions. Brucellar osteomyelitis has been observed in closed femur fracture and a pathologic fracture of humeru [69,70]. It was also seen in association with extra-articular prosthetic hardware[81]. It was reported the first case of brucellar osteomyelitis of pubic symphysis, who was symptom free within two-year follow-up despite inappropriate initial antibiotherapy [72].

Diagnosis of brucellosis.

The main issue in the fight against brucellosis remains the timely and complete identification of farm animals suffering from brucellosis. However, existing generally accepted laboratory methods do not always allow to determine the real epidemic and epizootic picture in our country.

Currently, the most common methods for detection of Brucella include culture techniques, serological tests and PCR-based assays. Real-time PCR seems to be highly reproducible, rapid, sensitive and specific. Additionally, this assay is easily standardized and minimises the risk of infection in laboratory workers. It is therefore a useful method for both the initial diagnosis of human brucellosis and the differentiation among inactive, seropositive, and active states. Queipo-Ortuño *et al*. reported that the sensitivities of a SYBR Green I LightCycler-based real-time PCR assay with serum samples was 93.3%, which is higher than 90% and 65% obtained by PCR-ELISA with whole blood samples and blood cultures, respectively . This group further developed a Light Cycler-based real-time PCR assay to detect *Brucella* DNA in serum samples. This assay was found to be 91.9% sensitive and 95.4% specific when tested with 65 negative control samples and 62 serum samples from patients with active brucellosis. Isolation of Brucella spp. is considered the gold standard technology, but it is lengthy, and requires high-level biosafety laboratories and certificated personnel [74,75].

Serological testing is widely used in the clinical diagnosis of Brucellosis, but serological tests can yield false negatives when detecting the early course of Brucellosis, and it can only indirectly diagnose Brucellosis based on a high antibody titre [73]. According to research, when “brucellosis” was diagnosed, the results of serological studies were unreliable. The result of SAT (Wright ‘s reaction) was negative in patients with diagnosis “Primary-chronic brucellosis” in 41.5% cases and “Secondary-chronic brucellosis” in 32.7% cases. Regarding the results of the Roz Bengal antigen test, which has great sensitivity, the ability to detect specific brucellosis antibodies at short notice after infection, more than half of patients (51.3%) with primary-chronic brucellosis and slightly less than one third of patients (28.6%) with secondary-chronic brucellosis were negative. ELISA for brucellosis were positive only in 40-50% of patients. Blood culture isolation in about 2.4-4% of patients, which once again proves the instability of laboratory diagnostics [76].

PCR-based assays are highly sensitive, specific, and rapid, and have been applied for the detection of Brucellosis in humans and other animals, and identification of Brucella in animal products and the environment [78,79]. However, PCR-based assays require expensive thermal cycling instruments and can take more than 1 h, which limit their application in point-of-care detection of Brucella, especially in undeveloped rural areas.

Recombinase polymerase amplification (RPA) offers a new approach to achieve rapid and point-of-care detection of Brucella [77]. A total of 52 Brucella field strains were detected by real-time PCR and RPA in parallel, and compared with real-time PCR, the sensitivity of the RPA assay was 94%. Thus, this RPA assay may be a rapid, sensitive, and specific tool for the prevention and control of Brucellosis [80].

Despite the availability of advanced laboratory research methods in the world sometimes these methods may not be reliable or some developing countries like Kazakhstan these new high-sensitivity types of polymerase valuable reaction may be absent. In that case a radionuclide scan can be a useful tool to verify the diagnosis.MRI may be the best method to diagnosis and localize the cause of spondylodiscitis, epidural abscess, or compression on the spine and spinal nerves related to brucellosis. Epidural abscess is a rare complication of spinal brucellosis but can lead to severe outcomes, such as permanent neurological deficits, or even death if not treated timely [19]. Imaging issues in the diagnosis of brucellosis spondylitis is fundamental and there are several scientists who have investigated this aspect to improve our understanding of the disease and minimize the erroneous diagnosis. They used data from x-ray, CT, and MRI 72 brucella patients with spondylitis who received treatment from 2010 to 2017 were subjected to a retrospective analysis; diagnoses were made by evaluating laboratory and pathological data. The results of this study showed the following features: X-ray films revealed changes in intervertebral space heights, the number of lateral osteophytes, and bone destruction, which were more severe in the following order: lumbosacral vertebrae (56 cases, 77.8%), cervical spine (6 cases, 8.3%), thoracic spine (5 cases, 6.9%), and multi-segmental mixed vertebrae (5 cases, 6.9%). CT revealed osteolytic destruction attributable to early-stage *Brucella* spondylitis (endplate and vertebral lamellar osteolysis), usually associated with multiple vertebral involvement, with the middle and late disease stages being characterized by osteophytes in the vertebral margins and bony bridges, endplate sclerosis, and vertebral osteosynthesis. *Tu L. et al.* encountered 54 cases (75%) with endplate lamellar osteolysis, 37 (51.4%) with vertebral lamellar osteolysis, 59 (81.9%) with marginal osteophytes, 10 (13.9%) with bony bridges, 25 (34.7%) with vertebral laminar sclerosis, and 17 (23.6%) with vertebral osteosynthesis. MRI revealed early, low-intensity, differential T1WI vertebral and intervertebral signals, with occasional iso-signals, T2WI iso-signals or high-intensity signals; and T2WI-FS vertebral and intervertebral high-intensity signals, commonly from vertebral soft tissues and rarely from paravertebral abscesses [28]. As MRI can detect early abnormal signals from vertebral bodies, intervertebral discs, and soft tissue, this is the first-choice imaging when evaluating patients with spinal brucellosis, and enhanced MRI scans improve diagnostic accuracy. The imaging features of spinal brucellosis need to be distinguished from those of spinal tuberculosis. The incidence of spinal tuberculosis can attain 40–50%, being the most common manifestation of pulmonary tuberculosis, often triggering vertebral body destruction and other serious complications. The clinical and imaging manifestations are very similar to those of brucellosis spondylitis, making misdiagnosis easy. The typical manifestations of spinal tuberculosis are bone destruction, dead bone, narrow intervertebral spaces, paraspinal abscesses, and deformities of the spinal posterior process [28]. Radionuclide bone scintigraphy is an important technique in determination of musculoskeletal region of brucellosis. Increased uptake of the involved region on bone scintigraphy is more in favor of brucellar spondylodiscitis than tuberculous spondylodiscitis [34, 35]. MRI is the choice for diagnosis of spondylodiscitis, epidural abscess and cord or root compression relevant to brucellosis [*22, 36, 37*]. In MRI, the lesion is found as destructive appearance (Pedro Pons'sign) at antero-superior corner of vertebrae accompanied by prominent osteosclerosis, which is a pathognomonic finding [38,39]. Spinal spondylitic brucellosis often involves the endplates of the junctions between the vertebral bodies and the intervertebral discs. The shape of the vertebral body is not affected, the posterior process does not exhibit compression or deformity, no bony hyperplasia is evident at the edges of vertebral bodies, bone death is rare, the intervertebral spaces are not obviously narrowed in those with early-stage disease, abscesses in the vertebrae and the psoas major muscle are rare, and abscess heterogeneity is limited. In general, only adjacent vertebrae are

affected, the vertebral bodies suffer only minor destruction, and adjacent organs are not involved [81]. Differential diagnosis requires the evaluation of biopsy samples. Furthermore, brucellosis titer test positivity and anti-brucellosis positivity are useful diagnostic criteria [82].

Diagnostic difficulties. Sacroiloiits with brucellosis is(unilateral or bilateral)and is manifested by severe pain in the sacral region, aggravated by movement, especially when walking and when the body is tilted forward; in severe cases, patients lie motionless on their backs, afraid to move, so as not to cause increased pain. In patients with≥ 3months back and age at onset ≤45 years should differentiate it from Brucellor back pain. AS and SpA is inflammatory type which is worse in morning, prolong period of inactivity and decreases with physical activity and exercise. In such cases, clinicians, especially orthopaedic surgeons, must understand the disease, especially imaging features, to ensure accurate diagnosis through a combination of epidemiological history, clinical manifestations, and laboratory data. The polymorphism of the clinical manifestation and the variety of osteoarticular manifestations greatly complicates the timely diagnosis and treatment of brucellosis. It is known that brucellosis is prone to a chronic recurrent course with frequent disability, which determines the social significance of the infection. The low diagnostic value of serological tests, which are used by many clinicians as screening methods for detecting brucellosis, complicates early diagnosis more and more. The low alertness of brucellosis infection, not only among therapists and other specialties, but also among infectious disease doctors, is a big problem due to the lack of awareness of doctors about all the clinical manifestations of this infection against the background of incomplete laboratory diagnosis, which leads to an erroneous diagnosis.

A characteristic feature of brucellous infection is the prolonged wave-like course of the disease with repeated relapse and remission. It should be remembered that in chronic brucellosis there is suppression of antibody formation and the value of serological methods decreases and this increasingly devalues serological methods of study. In Kazakhstan, despite changes in the population of patients with brucellosis over the last 10 years due to the increase in the share of urban residents among patients, A large number of patients still live in rural areas where it is not possible to fully examine, including the use of the method of detecting antigen-binding lymphocytes of brucellosis specificity and polymerase chain reaction, Especially the bacteriological examination with waiting for the results of the tests up to 40 days. The organization requires modern laboratories equipped with expensive analyzers, but the rural hospital cannot afford such costs. It is necessary to note the fact that there are no infectious doctors in rural hospitals who can correctly interpret the results of laboratory studies and given the epidimological history, knowing the full range of clinical manifestations will be able to verify the diagnosis in a timely manner. All these factors are the main problems of early correct diagnosis of brucellosis, which can eventually lead to partial or complete loss of working capacity of the patient.

Conclusion

Thus, brucellosis occupies a special position among other infectious diseases due to the peculiarity of the pathogen: high contagiousness or infectious ability of brucella; their resistance to non-specific factors of body protection; the ability to survive (and for years) even multiply within immunocompetent cells (macrophages); negligible protective role of anti-brucellosis antibodies, more precisely the formation of only relative immunity and the presence of re-infection in an endemic zone. Brucellosis is an important health problem in Kazakhstan. The disease has a significant morbidity and mortality. Additionally, since the disease primarily affects persons in their productive age, it causes important work-power losses. Eradication of the disease in humans can only be achieved by the control of the disease in animals; this necessitates a multidisciplinary approach involving both humans and animals. In addition to isolation and serological tests, non-specific tests such as CRP and ESR should also be used in treatment follow-up. In summary, brucellosis is easily misdiagnosed, although it is important to achieve an early diagnosis to prevent further complications. Blood cultures and Brucella spondylitis serology tests are required when patients with spinal lesions do not respond to standard treatment. The features of Brucella spondylitis in X-ray, CT, and MR images must also be better understood to minimize misdiagnosis and to use in combination with epidemiological and laboratory data. A high level of chronic infection and polymorphism of osteoarticular manifestations of brucellosis complicates differential diagnosis with inflammatory diseases of the joints and spine, which negatively affects the process of timely diagnosis and treatment, which ultimately affects the effectiveness of treatment and the further quality of life of patients.

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Section 2
Original research

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R.B. Issayeva [1], G.T. Tashenova[1]
Laimute Vaideliene[2], A.Zh. Ahenbekova[1], R.Z. Boranbaeva[3]

[1]Kazakh National University, Kazakhstan, Almaty, e-mail talipovna68@gmail.com
[2]Lithuanian University of Health Sciences,Vilnius,
[3]Research Center for Pediatrics and Pediatric Surgery, Kazakhstan, Almaty,

AUTONOMIC DYSFUNCTION IN PRESCHOOL CHILDREN

High prevalence of autonomic dysfunction syndrome in schoolchildren was found, the specifics of its clinical presentation with identification of the most salient symptoms are given. The purpose of the work was to find the occurrence of NS (nervous system) functional disorders in various age groups, with gender differences noted, among schoolchildren of secondary schools in Almaty. The NS dysfunction was assessed using questionnaires in 1827 schoolchildren (966 girls –52.87%, 861 boys –47.12%) 7–17 years old, attending the secondary schools in Almaty. As a result, we found numerous NS functional disorders among 56,8% of adolescents. Manifestations of vegetative instability were expressed as headaches in 44.5% of children, drowsiness in 53.8% of cases, complaints of fatigue and weakness in 56.8% of children. Complaints of sleep disturbance were recorded in 32% of schoolchildren, a greater number of complaints of syncope were received in the tenth grade from girls - 22%. Cardialgia, as a manifestation of NDC and adaptive-adaptive mechanisms of the body, occurred in 20.4% of cases.

Key words: autonomic dysfunction, nervous system, schoolchildren, forms (grades).

Relevance

Though demographic indicators have somewhat evened out recently, deterioration of health of children and adolescents attending educational institutions has become apparent [1,2]. It is reported elsewhere [3,4] that only 14-23% of schoolchildren are practically healthy, another 50% have functional disorders, and the rest have chronic diseases. Health survey data are indicative of significant deterioration of the health status of children and adolescents during the period of schooling. By the time they finish school, one in three graduates has myopia and impaired posture; one in four has cardiovascular pathology [5]. The leading cause for that, according to authors, is low physical activity and high educational burden [6,7].

The Kazakhstan Ministry of Health data [8] evidence that 53.8% of Kazakh schoolchildren have various health problems. Health check data suggest that every seventh schoolboy has digestive and musculoskeletal system diseases, every ninth would suffer from nervous system diseases, and every tenth, from diseases of respiratory tract and endocrine system.

The questionnaire findings show high prevalence of risk factors for the development of 'school-derived' diseases: lack of sleep, low physical activity, shortened walking time, visual overload, unhealthy dietary patterns, dull forms of leisure.

During the schooling period, the number of children with the musculoskeletal system disorders increases 1.5-2 times, with nervous disorders – 2 times, with allergic diseases – 3 times, with myopia – 5 times [9,10].

Therewithal, the published studies [10,11] provide scarce data on dynamic detection of the most

significant "school" pathology at various stages (grades) of education. Moreover, the bulk of studies on this topic primarily have focused on new type schools (lyceums, gymnasiums, private schools) rather than general education schools.

All the above imparts particular importance to the study and assessment of the health of pupils attending the general education schools in their relation to educational environment and lifestyle factors.

Objective of the study:

To assess the health status of students of secondary schools in Almaty, using the questionnaire survey method.

Material and methods

To achieve the above goal, we developed a screening questionnaire detecting the nervous system pathology. A descriptive epidemiological study was carried out to study the prevalence of these diseases in children. We interviewed on-site (at the place of study) 1824 schoolchildren of 1st through 11th grades, 6 to 17 years old, in general education schools of Almaty. Pupils in grades 1-4 were surveyed through questions asked from their parents, while in grades 5-11 the questionnaires were filled out by the students themselves. Pupils were taught according to standard curricula, with teachers imposing almost similar requirements on them. After being duly instructed on completing the questionnaire, both children and their parents checked the respective "yes" or "no" boxes.

The questionnaire data were fed in a database using the MS Access and MS Excel software, with the primary somatometric parameters values established. The average value of the (M) indicator, its error (m), and the mean squared deviation (δ) were calculated. The databases were statistically processed using the SPSS software. The correlation coefficient was calculated using the Eviews 8.0 statistical package. We also performed a hypothesis testing based on sample fraction (relative value) data. We observed methodical flawlessness and thoroughness in material collection and processing, used unified methods to ensure comparability of the results.

Results and Discussion

Our questionnaire-based research of junior and senior grade schoolchildren in Almaty showed prevalence of autonomic dysfunction syndrome in children, clinical presentation specifics were described and the most significant symptoms identified.

An average of 44.5% of all interviewed schoolchildren complained of headache: 52.9% of girls and 47.2% of boys. Figures 1 and 2 show the number of headache complaints in girls vs. boys start differing dramatically from the sixth grade ($p \leq .0.01$) ($p \leq .0.05$). In grades 7 and 8, the difference in complaints by sex is as high as 20%, while in grades 9 it is 25%.

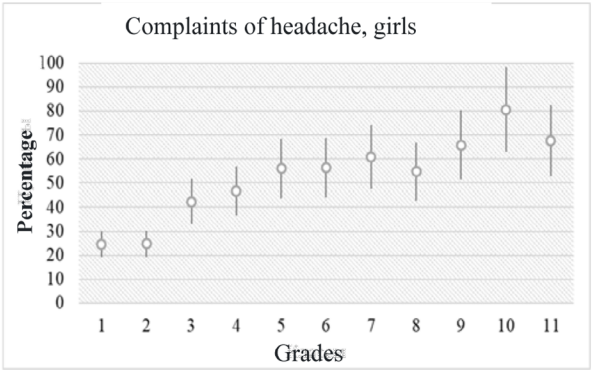

Figure 1 – Confidence intervals in girls complaining of headache, by grades, %

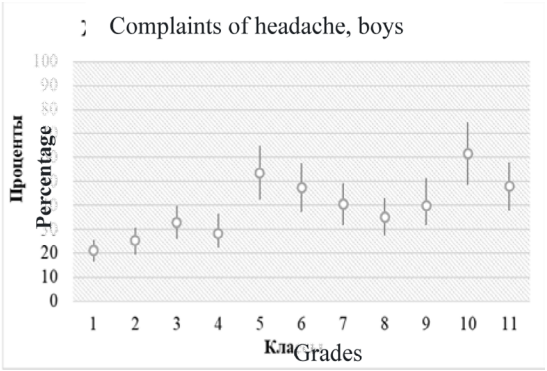

Figure 2. Confidence intervals in boys complaining of headache, by grades, %

Complaints of drowsiness were recorded in 53.8% of cases. Similar to headache complaints, girls are more likely to complain of drowsiness than boys (Figures 3,4). Starting from the fourth grade, the results reported for drowsiness are significant at one per cent ($p \leq .0.01$) and five per cent ($p \leq .0.05$) level. In the ninth grade, the difference in complaints by sex is as high as 37.5%. We can conclude that in the ninth to tenth grades, due to the increasing load of fundamental subjects, uptake of information by girls

becomes longer than by boys. Figures 3 and 4 show that from the first to the eleventh grades, drowsiness complaints would increase 2.2 times for girls and 2.0 times for boys. We also calculated correlation coefficients for autonomic dysfunction symptoms for girls and boys (Tables 1 and 2).

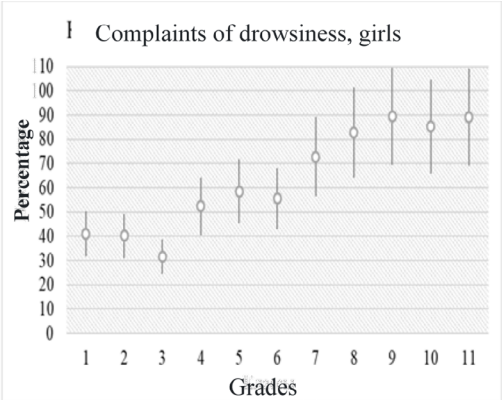

Figure 3 – Confidence intervals in girls complaining of drowsiness, by grades, %

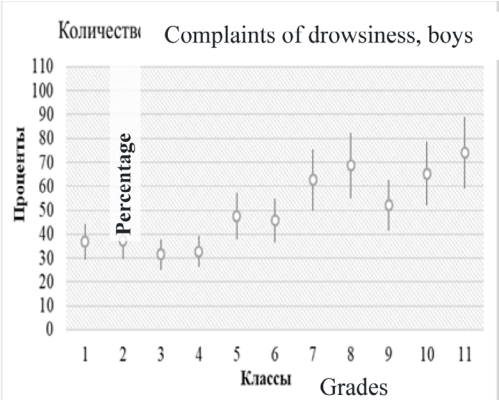

Figure 4 – Confidence intervals in boys complaining of drowsiness, by grades, %

«Drowsiness» and «Headaches» have demonstrated close correlation (0.84) at the one percent significance level, i.e. the two symptoms are closely correlated with each other. The correlation coefficient between the variables «Drowsiness» and «Weakness» in girls equaled 0.92, this value is significant at one percent level ($p \leq .0.01$). Table 1 shows very close correlation.

Table 1 – Values of correlation coefficients by symptoms of autonomic dysfunction in girls

Covariance analysis					
Correlation coefficient					
t-statistics					
Probability	Headaches	Weakness	Drowsiness	Sleep disturbance	Sweatiness
Headaches	1.000000				

Weakness	**0.887004**	1.000000			
	5.762747	-----			
	0.0003	-----			
Drowsiness	**0.837122**	**0.923608**	1.000000		
	4.591020	*7.228117*	-----		
	0.0013	*0.0000*	-----		
Sleep disturbance	**0.939186**	**0.927571**	**0.959549**	1.000000	
	8.204640	*7.447467*	*10.22464*	-----	
	0.0000	*0.0000*	*0.0000*	-----	
Sweatiness	**0.635733**	**0.785574**	**0.898679**	**0.838907**	1.000000
	2.470756	*3.808737*	*6.146823*	*4.623988*	-----
	0.0355	*0.0042*	*0.0002*	*0.0012*	-----

Table 2 – Values of correlation coefficients by symptoms of autonomic dysfunction in boys

Covariance analysis					
Correlation coefficient					
t-statistics					
Probability	Headaches	Weakness	Drowsiness	Sleep disturbance	Sweatiness
Headaches	1.000000				

Weakness	**0.693087**	1.000000			
	2.884439	-----			
	0.0180	-----			
Drowsiness	**0.602005**	**0.774417**	1.000000		
	2.261780	*3.672102*	-----		
	0.0500	*0.0051*	-----		
Sleep disturbance	0.387117	**0.671753**	**0.734579**	1.000000	
	1.259558	*2.720475*	*3.247840*	-----	
	0.2395	*0.0236*	*0.0100*	-----	
Sweatiness	0.044357	0.507542	0.340585	0.668301	1.000000
	0.133202	*1.767150*	*1.086727*	*2.695159*	-----
	0.8970	*0.1110*	*0.3054*	*0.0246*	-----

Complaints of fatigue and weakness were found in 56.8% of children. Figure 5 clearly shows an increase in complaints of weakness among girls, with no similar increase in complaints from boys and, on the contrary, a fluctuation in the number of complaints in one range (30-60%) can be seen. In tenth grade compared to the first grade, the schoolgirls' complaints rate increased by 2.3 times, while boys demonstrated only a 1.3 times increase over the same period of time. The variation in the number of complaints among boys did not significantly differ over the 1st to 11th grade span, as can be clearly seen in Figure 6. In girls, the number of complaints of weakness has predictably doubled by the eleventh grade, while the maximum value of 2.26 times hit in the tenth grade.

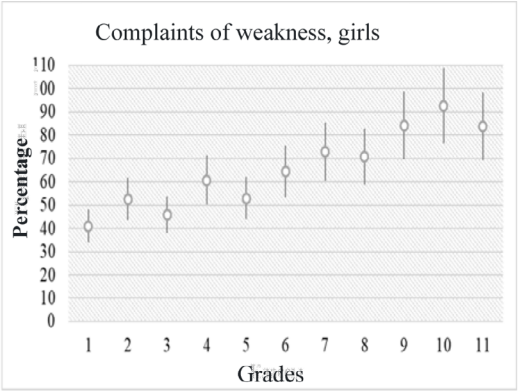

Figure 5 – Confidence intervals in girls complaining of weakness, by grades, %

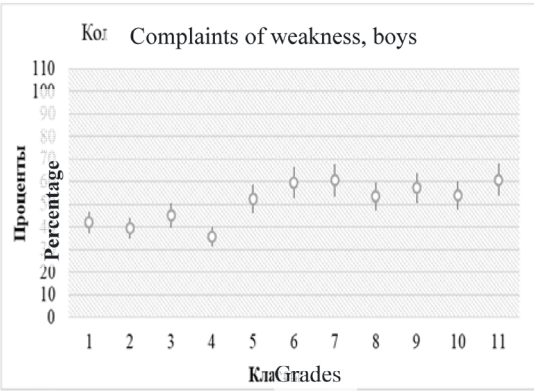

Figure 6 – Confidence intervals in boys complaining of weakness, by grades, %

In a multitude of neurological symptoms, complaints of sleep disturbance were the most common, reported in 32% of schoolchildren. From the first grade onward, both boys and girls demonstrate an increase in the number of complaints by 3.3 and 4.5 times, respectively (Table 3).

It's obvious that «Sleep disturbance» and «Sleepiness» shall correlate very closely as evidenced by calculations in Tables 1 and 2. While the number of complaints of sleep disturbance among girls has been steadily increasing from grade to grade, in the eleventh grade this increase, as percentage of complaints among boys, climbed 2.6 times compared to the tenth grade, although no sharp fluctuations had been observed before that. Most likely, this is due to the forthcoming Unified National Testing (UNT), with no additional calculations in support of this argument needed.

The «Sleep disturbance» variable also correlates with all other neurological symptoms (Table 2). For the first time, the number of complaints of the symptom in question from boys has exceeded, although not much, the figures for girls in the eleventh grade: 60.9% vs. 59.5% of girls. One asterisk corresponds to a 10% value (p>0.10).

Table 3 – Testing hypotheses about equality of percentage of sleep disturbance complaints for boys and girls by grade,%

Grades	Girls (N=966) av.value (CI)	Boys (N=861) av.value (CI)	Boys / Girls
1st Grade	13.1 (9.2–17.1)	18.4 (13.2–23.7)	*t = –0.84, p≤.100*
2nd Grade	13.4** (9.4–17.5)	23.1** (16.5–29.7)	*t = –1.72, p≤.021*
3rd Grade	20.7 (14.5–27.0)	20.0 (14.3–25.7)	*t = 0.13, p≤.224*
4th Grade	31.1*** (21.7–40.6)	17.4*** (12.4–22.4)	*t = 2.29, p≤.006*
5th Grade	36.6* (25.5–47.6)	28.6* (20.4–36.7)	*t = 1.20, p≤.058*
6th Grade	37.9 (26.5–49.4)	34.2 (24.4–44.0)	*t = 0.59, p≤.139*
7th Grade	48.9*** (34.1–63.7)	27.3*** (19.5–35.1)	*t = 3.08, p≤.001*
8th Grade	52.4** (36.6–68.3)	38.4** (27.4–49.3)	*t = 1.83, p≤.017*
9th Grade	53.9*** (37.7–70.2)	29.3*** (21.0–37.7)	*t = 3.07, p≤.001*
10th Grade	58.5*** (40.9–76.2)	23.1*** (16.5–29.7)	*t = 2.84, p≤.001*
11th Grade	59.5 (41.5–77.4)	60.9(43.5–78.2)	*t = –0.11, p≤.228*

Note: *, **, *** - significant at 0.1; 0.05;0.01

The number of complaints of sweating as percentage of total pupils is the lowest (15.6%) compared to the other symptoms examined (Table 4).

Table 4 – Testing hypotheses of equal percentage of sweat complaints for boys and girls by grade,%

Grades	Girls (N=966) av.value (CI)	Boys (N=861) av.value (CI)	Boys / Girls
1st Grade	13,1 (9,7–16,6)	15,8 (12,1–19,4)	*t = –0.44, p≤.165*
2nd Grade	9,3 (6,8–11,7)	7,7 (5,9–9,5)	*t = 0.39, p≤.174*
3rd Grade	9,0** (6,6–11,4)	15,8** (12,1–19,4)	*t = –1.49, p≤.034*
4th Grade	18,9*** (13,9–23,8)	8,7*** (6,7–10,7)	*t = 2.09, p≤.009*
5th Grade	11,4* (8,4–14,4)	14,3* (11,0–17,6)	*t = –0.62, p≤.058*

6th Grade	16,1 (11,9–20,4)	15,8 (12,1–19,4)	*t = 0.59, p≤.139*
7th Grade	20,7*** (15,2–26,1)	11,1*** (8,5–13,7)	*t = 3.08, p≤.001*
8th Grade	28,0** (20,6–35,5)	18,6** (14,3–22,9)	*t = 1.83, p≤.017*
9th Grade	27,6*** (20,3–34,9)	20,0*** (15,4–24,6)	*t = 3.07, p≤.001*
10th Grade	19,5*** (14,4–24,7)	7,7*** (5,9–9,5)	*t = 2.84, p≤.001*
11th Grade	27,0 (19,9–34,2)	21,7(16,7–26,8)	*t = –0.11, p≤.228*

*Note: *,**, *** - significant at 0.1; 0.05;0.01*

This is also corroborated by the calculations presented in Table 2. Sweatiness correlates slightly weaker with the rest of the variables. We expected boys to complain of sweating more often as they are more active physically, but this did not come true, and girls, again, complained more often, which, among other things, may stem from change in the hormonal background in high school.

Differences in sweating complaint rates between male and female students were verified for grades 3 and 8 at a 5% significance level, that is, with a 95% probability, for grades 4, 7, 9 and 10 with a 99% probability, and for grades 5 with a 90% probability. No statistically significant differences were found for the remaining grades (first, second and eleventh grades).

We reviewed another questionnaire survey data, such as dizziness or orthostatic intolerance experienced by schoolchildren when changing their body position, and found these complaints to build up steadily among schoolchildren from the 4th to 11th grades: from 10.3% to a maximum of 41.7% in the 11th grade. In general, this symptom was observed in 16.4% of students, which is quite a large number. These symptoms were more often registered in girls. In most cases, the above symptoms probably come as a result of incipient puberty (11 to 12 years of age in girls and 13 to 14 years of age in boys and an increased study load of middle and high school students, especially in the 10th (31.3%) and 11th (41.7%) grade in anticipation of the forthcoming unified national test: both boys and girls are experiencing enormous mental and physical stress, as seen in Figures 7 and 8 for the eleventh grade. The confidence interval in Figures 1 and 2 shows us quantitative range in which dizziness complaints will be detected. Starting from the seventh grade, the percentage of complaints among girls is increasing, while among boys it is, conversely, decreasing to reach almost a convergence point in the eleventh grade; this corroborates our hypothesis that the number of complaints is equal for both sexes.

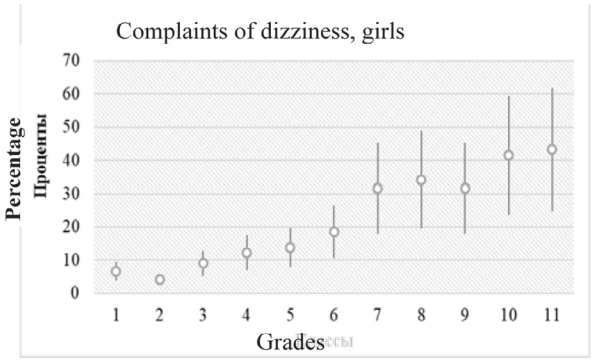

Figure 7 – Confidence intervals of number of dizziness in girls, by grades, %

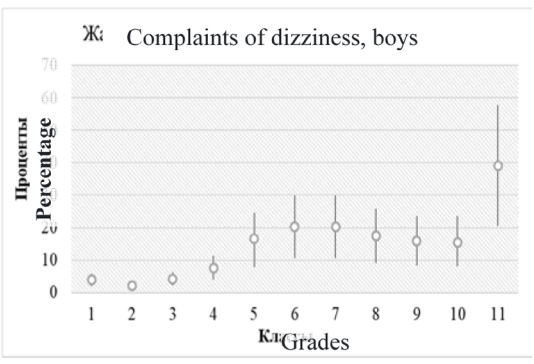

Figure 8 – Confidence intervals of number of dizziness in boys, by grades, %

Thus, the results we obtained from the questionnaire data on autonomic stability in the interviewed students of general education schools are consistent with the published data [12,13]. These results reflect the degree of mastery of general education subjects. Newcomers to school, who have

to study for at least 3-4 hours with short breaks, will find the first two years of study the most difficult in terms of getting used to this pace of life. So, it is natural to see the number of vertigoes in this group above the average for grade one to four schoolchildren. The results obtained for the fifth grades also seem natural, as additional general subjects are being introduced at this point of schooling, with a separate teacher for each subject, which may also add stress in the beginning. This situation will be resolved by Grade 6, when pupils get used to the way each teacher teaches and the amount of homework. The ninth and tenth grades are known to introduce more hours of workload in core curriculum (mathematics, physics, chemistry, geography, etc.) in view of impending single national test, which may also have a negative impact on well-being. The results of the eleventh grade are in agreement with the logic of research. In this case, the main hypothesis was that, on average, no more than 27 pupils would experience dizziness due to the stressful study load, and given the number of children surveyed in the 11th grade, this number would be nearly half (27/60=0.45) of total pupils count, i.e. 45% of the surveyed cohort complained of dizziness.

Fainting is a sudden short-term loss of consciousness, which may be preceded by a prodromal signs and symptoms: a sense of discomfort, nausea, yawning, diaphoresis, leg muscle weakness, darkened vision, flickering «flies» before the eyes, surging dizziness, buzzing or tinnitus in the ears, numbness of the extremities. Autonomic dysfunction is a frequent cause of fainting in schoolchildren [14].

Frank manifestation of vascular dysfunction, such as fainting, was fortunately less common: 4.6% of cases in both schools. In these two schools, girls had fainting in 5.6% and boys in 3.5% of cases.

Table 5 shows the hypothesis of fainting equality between boys and girls by grade, as percentage.

Table 5 – Testing hypotheses of equal percentage of fainting in boys and girls by grade, %

	Girls (N=966) av.value (CI)	Boys (N=861) av.value (CI)	Boys / Girls
1st Grade	3.3 (1.4–5.2)	3.9 (2.4–5.5)	t = –1.69, p<.001
2nd Grade	1.0 (0.4–1.6)	3.3 (2.0–4.6)	t = –10.23, p<.000
3rd Grade	4.5 (1.9–7.1)	0.0 (0.0–0.0)	t = 21.80, p<.000
4th Grade	4.9 (2.0–7.8)	2.2 (1.3–3.0)	t = 10.92, p<.000
5th Grade	2.4 (1.0–3.9)	4.8 (2.9–6.6)	t = –8.80, p<.000
6th Grade	6.5 (2.7–10.2)	4.4 (2.6–6.1)	t = 7.46, p<.000
7th Grade	6.5 (2.7–10.3)	5.1 (3.0–7.1)	t = 4.13, p<.001
8th Grade	2.4 (1.0–3.9)	4.7 (2.8–6.5)	t = –6.98, p<.000
9th Grade	10.5 (4.4–16.7)	1.3 (0.8–1.9)	t = 20.16, p<.001
10th Grade	22 (9.1–34.8)	3.8 (2.3–5.4)	t = 11.66, p<.004
11th Grade	10.8 (4.5–17.1)	8.7 (5.3–12.1)	t = 1.40, p<.003

Table 2 data precludes us from rejecting the null hypothesis that the number of fainting complaints among boys and girls in the first and eleventh grades are equal, which is also clearly illustrated in Figures 3 and 4. For all other grades, this hypothesis is rejected at 5 percent significance. Herewith, the processed computed values of the questionnaires for girls and boys yielded the opposite result for the second to tenth grades: in the second grade, boys complained of fainting more often than girls, while in the third girls fainted more often, in the fourth grade, again boys, and so on (Figure 9, 10). The highest number of complaints was reported in the tenth grade girls: 22 per cent, which figure really stands out compared with other grades, where percentage of fainting was in the range of one to eleven per cent.

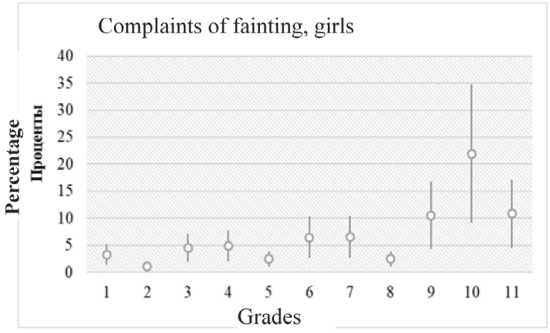

Figure 9 – Confidence intervals of number of fainting in girls, by grades, %

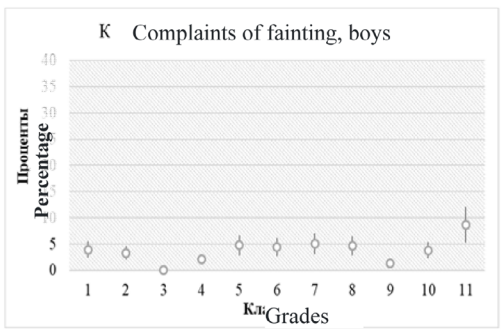

Figure 10 – Confidence intervals of number of fainting in boys, by grades, %

The results are also consistent with the logic of research. It is clear that the number of dizziness is observed more often in any age category in contrast to fainting, as supported by the z-statistics values. The main hypothesis for the first to fourth grades is that the average number of fainting will not exceed six cases, for fifth to eighth grades it will not exceed 9 cases, and for ninth to eleventh grades the number of fainting will not exceed 8 cases. Thus, we can state with 95 per cent probability that in similar secondary schools, i.e. schools with approximately the same study load, the number of fainting due to the stressful learning process will not exceed 6-9 cases per year on average.

The cardiovascular system is the one that reacts most promptly to changes in the body-environment balance and gets actively involved in all adaptive responses [15]. The cardiovascular system is regarded as a universal indicator of all pathological processes, that reflects the level of regulatory mechanisms and adaptive capacity of the body [14,15].

Neurocirculatory dystonia (NCD) is a functional disorder of the cardiovascular system in children most commonly seen in adolescence at puberty, when the body is subjected to alteration and all regulatory processes, including the function of the cardiovascular system, undergo significant changes. There are also gender differences: in girls, the NCD is registered much more often [12]. Psycho-emotional stresses, which often accompany the puberty period, also play an important role [13].

Cardialgia (pain in or near the heart) occurred in 20.4% of interviewees, equally as often in boys and girls, also were reported in school No.15 (17.7%), and more often in school No.16 (20.3%).

Table 6 tests the hypothesis that the average number of complaints of heart pain among schoolchildren will not exceed 19 for primary schoolchildren, 51 complaints for schoolchildren in grades 5 to 8, and 32 complaints for high schoolchildren.

Table 6 – Testing the hypothesis that percentage of complaints of heart pain in boys and girls by grade are equal, %

	Girls (N=966) av.value (CI)	*Boys (N=861) av.value (CI)*	*Boys / Girls*
1st Grade	8.2 (4.6–11.8)	0.0 (0.0–0.0)	*t = 19.50, p<.001*
2nd Grade	9.3 (5.2–13.4)	8.8 (5.6–12.0)	*t = 1.08, p<.001*
3rd Grade	9.9 (5.5–14.3)	14.7 (9.3–20.2)	*t = –9.99, p<.001*
4th Grade	16.4 (9.1–23.7)	7.6 (4.8–10.4)	*t = 19.01, p<.001*
5th Grade	17.1 (9.5–24.7)	28.6 (18.0–39.1)	*t = –17.32, p<.002*
6th Grade	15.3 (8.5–22.1)	21.1 (13.3–28.8)	*t = –11.30, p<.002*
7th Grade	42.4 (23.6–61.2)	24.2 (15.3–33.2)	*t = 21.26, p<.003*
8th Grade	37.8 (21.0–54.6)	23.3 (14.7–31.8)	*t = 15.66, p<.004*

9th Grade	31.6 (17.6–45.6)	20 (12.6–27.4)	*t = 12.19, p<.003*
10th Grade	51.2 (28.5–74.0)	34.6 (21.9–47.4)	*t = 5.89, p<.013*
11th Grade	56.8 (31.6–81.9)	30.4 (19.2–41.6)	*t = 8.28, p<.015*

With regard to the equality of complaints of heart pain, we can accept the null hypothesis for the second grade, that is, there is no significant difference in the number of complaints from girls and boys. In the other cases, the null hypothesis is rejected, as we clearly see in Figures 11 and 12. As in all previous cases, the number of complaints received from girls is almost twice as high as the number of complaints of heart pain from boys.

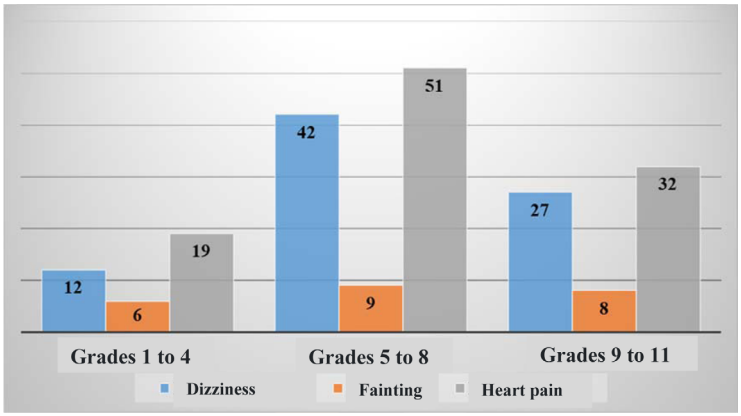

Figure 11 – Confidence intervals of number of heart pain in girls, by grades, %

Figure 12 – Confidence intervals of number of heart pain in boys, by grades, %

Our initial research hypothesis has been confirmed for most grades. In Figure 13, we showed tangible result: the number of complaints of dizziness, fainting, and heart pain, and we can clearly see that most students complained of heart pain.

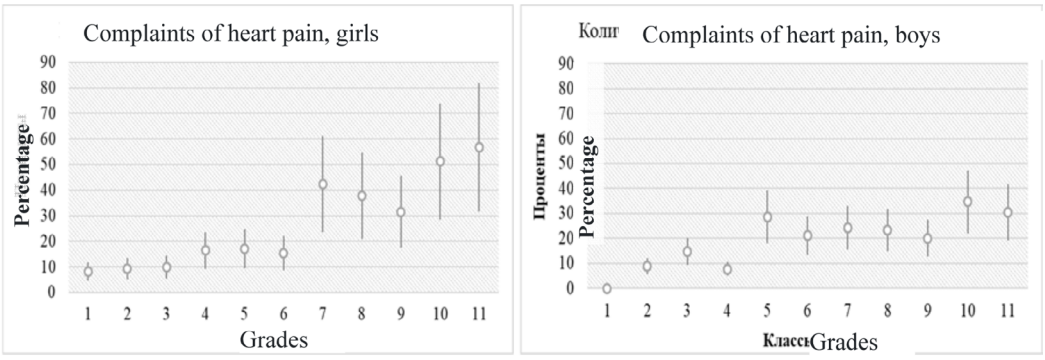

Figure 13 – Occurrence of complaints of dizziness, fainting and heart pain,%

The results we obtained from the questionnaire data on autonomic stability in the interviewed students of general education schools are consistent with the published data [11,12,13]. Girls complained of dizziness, heart pain 2-3 times more often than boys, and fainting was much less common in comparison with dizziness and heart pain in both girls and boys. The highest number of fainting

complaints was received in the tenth grade from girls: 22% (*t = 4.13, p<.001*). Dizziness is reported more often in any age category in contrast to fainting, as corroborated by the z-statistics. The number of complaints of heart pain by girls is almost twice as high as the number of complaints of heart pain by boys. Of three complaints studied: heart pain, dizziness, and fainting, the majority of students complained of heart pain.

Conclusion

The health survey data is indicative of numerous functional disorders in children's organs and systems detectible at early stages of the educational process. The nervous system disorders lead the list (56.8%). The data obtained suggests that adolescents of both sexes present autonomic instability symptoms.

An imbalanced autonomic nervous system manifested as headaches in 44.5% of children, statistically more often in girls than boys, becoming obvious from the sixth grade onward ($p \leq .0.01$ and $p \leq .0.05$). In the seventh and eighth grades, the difference in complaints by gender was as high as 20%, while in the ninth grade it was 25%.

Drowsiness was reported in 53.8% of cases, with a reliable 1 per cent and 5 per cent significance for girls from the 4th grade onward to reach a gender difference of 37.5% by the 9th grade. Starting from the fourth grade, the results reported for drowsiness are significant at one per cent ($p \leq .0.01$) and five per cent ($p \leq .0.05$) level. In the ninth grade, the difference in complaints by sex is as high as 37.5%.

Complaints of fatigue and weakness occurred in 56.8% of children. There is a clear upward trend in occurrence of fatigue and weakness among pupils of both sexes from the first grade: a 2.3 times increase in girls, and a 1.3 times increase in boys by the tenth grade.

The most distinctive of all neurological symptoms are sleep disturbance complaints, which were reported in 32% of schoolchildren and correlated with all other neurological symptoms. The largest number of fainting complaints were received in the tenth grade from girls, 22% (*t = 4.13, p<.001*). Cardialgia as a manifestation of NCD and adaptative mechanisms of the body was found in 20.4% of cases.

We believe the combination of cephalgia with fatigue and sleep disorders deserves closer attention, as this would have a serious impact on schoolchildren's performance, interpersonal relations and how well they would digest the learning material.

Teenagers belong to the risk group for the potential development of psychosomatic disorders and hence need regular medical checkups and preventive care.

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Aigerim Mullen[1], Kuat Abzaliyev[1], Ghazwan Butrous[2]

[1]al-Farabi Kazakh national university,
Kazakhstan, Almaty, e-mail aigerimmullen@gmail.com
[2]University of Kent, Canterbury, UK

THE PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH VENTRICULAR SEPTAL DEFECTS: A SINGLE-CENTRE EXPERIENCE IN THE REPUBLIC OF KAZAKHSTAN

Abstract. The aim of this study was to evaluate the impact of pulmonary arterial hypertension on outcomes following surgical or transcatheter repair of isolated ventricular septal defect in the Republic of Kazakhstan.

Echocardiography and catheterisation reports of children with isolated ventricular septal defect complicated pulmonary arterial hypertension surgical or transcatheter repair between 2012 and 2016.

Amongst 38 children ventricular septal defect mean size was 10.92 ± 6.38mm. The mean systolic pressure in the right ventricle on Echocardiography was 55.42 ± 18.47 mmHg. Mean pulmonary arterial pressure by right heart catheterisation was 52.12 ± 29.44 mmHg. The mean end diastolic index for all children was registered as 76.78±19.58ml. Cardiac output was preserved in all children. In the preoperative period, 9 of these children were treated with sildenafil.

One week after the operation, mean right ventricle systolic pressure decreased as for children who did not receive preoperative sildenafil (from 55.5±14.8mmHg to 32.2±14.4mmHg) ($p < 0.01$), as for children who did (from 81.4±10.3mmHg. to 48.1±12.4mmHg (p value < 0.01)). End diastolic index normalized in 92.5% of cases. Right ventricle systolic pressure decreased >40% in all children a month after the surgery.

In our study prescription of specific drug therapy of pulmonary arterial hypertension with the purpose of preparing for surgery has no effect on the effectiveness of surgical treatment of ventricular septal defect. We had had no early postoperative mortality.

Key words: ventricular septal defect, pulmonary arterial hypertension, children, cardiac surgery, outcomes.

Introduction

Pulmonary arterial hypertension in children with congenital heart defects is a common consequence of left-to-right shunts, known as associated pulmonary arterial hypertension. As reported by Denise van Der Linde at al. in 2011 [1] over the last decades, number of newborns born with congenital heart defects every year is over 1.35 million worldwide. However significant geographical differences were found. Asia reported the highest congenital heart defects birth incidence, with 9.3 per 1,000 live births (95% CI: 8.9 - 9.7). Republic of Kazakhstan is a Central Asian country with the total population over 17 million [2]. There is a significant increase in the detection of congenital heart defects in the Republic of Kazakhstan from 4.4 per 1,000 live births in 2003 to 8.9 per 1,000 live births in 2012 [3].

Amongst congenital heart defects lesions which cause pulmonary arterial hypertension, ventricular septal defects is leading in frequency, with pulmonary arterial hypertension in betweet 18% [4]and 41.4% [5] in western countries. Previous experience of surgical repair of ventricular septal defect in children shows importance of preoperative hemodynamic assessment of pulmonary circulation. Data, including mean pulmonary arterial pressure and pulmonary vascular resistance have a strong impact on outcomes following surgery[6-8]. However, the risk of repair may be significantly ameliorated by the use of preoperative specific drug treatment to modify pulmonary vascular resistance [9,10].

The Scientific Centre of Paediatrics and Paediatric Surgery of the Ministry of Health of the Republic of Kazakhstan is a multidisciplinary national centre of excellence in child health. Since 2011, Scientific Centre of Paediatrics and Paediatric Surgery provides cardiac surgery and intervention cardiology care for children with pulmonary arterial

hypertension-congenital heart defects. This study was to analyse, in a single centre, the influence of pulmonary arterial hypertension on outcome following cardiac surgery or transcatheter repair of ventricular septal defect in children, between 6 months and 16 years of age, with isolated ventricular septal defect.

Materials and methods: We conducted a retrospective analysis of 38 hospital records of children with pulmonary arterial hypertension associated with ventricular septal defect from 2012 to 2016.

Inclusion criteria: 1. age between 6 months and 16 years old, both sexes; 2. isolated ventricular septal defect; 3. pulmonary arterial hypertension defined by tricuspid regurgitation velocity on Echocardiogrephy >36 mmHg., and confirmed by Catheterization or intraoperative measurements of mean pulmonary arterial pressure >25 mmHg.

Exclusion criteria: 1. Age under 6-month-old and over 16 years old; 2. additional left-to-right shunts as patent ductus arteriosus or arterial septal defect; 3. Pulmonary stenosis or right ventricle outflow tract obstruction; 4. presence of the other causes of pulmonary arterial hypertension, such a lung disease, connective tissues disease; 5. No follow up data; 6. Improper or lack of measurements.

Accordingly the retrospective data, in the preoperative period 23 patients were assessed by the echocardiographic examination alone, while 15 had had continious echocardiographic assessment (high right ventricle systolic pressure with bidirectional or right-to-left shunt) and underwent additional right heart catheterization measurement to determine the pulmonary arterial hypertension status.

Echocardiographic assessment.

Patients were assessed at baseline clinically and echocardiographically and followed up for a minimum of one month after discharge from the hospital. The echocardiographic measurements of the size and function of the heart structures and ventricular septal defect features were made in the subcostal view, apical four-chamber view, the apical five-chamber view, the parasternal long axis view, the parasternal short axis view of the left ventricle at the aortic root level, mitral valve, papillary muscles and apical level. To optimize the calculations, we used left ventricle end diastolic index greater than 75, for defining left ventricle dilatation, right ventricle/left ventricle ratio greater than 0.7 to define right ventricle dilatation. For pulmonary artery and aorta dilatation we used calculations of z score >2.0 [11,12]. And for ventricular septal defect, the largest defect diameter was indexed to the size of the aortic root recorded from the parasternal long axis view in systole. Thus, the ratio of the maximum size of the ventricular septal defect (mm) to the diameter of the aortic valve in systole (mm) as a representation of the shunt's size (ventricular septal defect/aorta), or the ventricular septal defect index. When analysing the data, the ventricular septal defect index from 0 to 0.3 was interpreted as a minor or small defect, 0.3 to 0.7 moderate, and greater than 0.7 as a large defect. For primary evaluation tricuspid regurgitation velocity was assessed and right ventricle systolic pressure was calculated as a sum of tricuspid regurgitation gradient and right atrium pressure (defined by inferior vena cava collapsing during the breathing). Right ventricle systolic pressure >36mmHg. accepted as a sign of pulmonary arterial hypertension associated wth congenital heart defects. For secondary pulmonary arterial hypertension assessment the mean systemic arterial pressure to mean pulmonary arterial pressure ratio was calculated. The mean pulmonary arterial pressure / mean systemic arterial pressure >0.3 defined as pulmonary arterial hypertension, >0.75 children were registered as a high mortality risk [13].

Right heart catheterization.

The mean pulmonary artery pressure was measured by right heart catheterization or during the surgical operation. In case of preoperative right heart catheterization the full protocol for the procedure with measurement of cardiac output, mean pulmonary arterial pressure, mean pressure in right ventricle, right atrium with the blood samples for sO_2 taken from inferior vena cava, superior vena cava, right atrium was performed. Pulmonary vascular resistance index was calculated using the Fick formula. After acute vasoreactivity test (nebulised iloprost inhalation; 2 mcg/kg during 3-5 min) the same measurements were repeated. A positive test was defined as a PVRI decline >20% with the stable cardiac output.

Postoperative data.

For assessment of surgery or transcatheter closure outcome the following criteria were analysed: clinical status; (1) oxygen saturation, haemoglobin's levels, (2) Echocardiographic indices (end diastolic index, cardiac index, ventricular septal defect index), right ventricle systolic pressure in pre- and postoperative period, right ventricle to left ventricle ratio. Furthermore, duration of staying in intensive care unit and bed days were analysed.

Statistical analysis.

The variables are quantitative and continuous. Shapiro-Wilk criterion was calculated for verification of the normal distribution of a small number of variables. To exclude false results for a small number of variables, we used the Wilcoxon test to determine the statistical significance of the differences in the repeated measurements (right ventricular systolic pressure before and after the operation). This nonparametric test does not require a normal distribution as a mandatory condition. For all calculations we used the R studio statistical software. Continuous variables were expressed as mean ± standard deviation and analysed by R studio. P value more than 0.05 was considered non-significant.

Results:

Demographic data.

We identified 38 children, 22 boys and 16 girls; age 6 - 12 months 10 children, 1-3 years 9 children, 3-7 years 10 patients, 7-11years 5 children and 11-16 years 4, with a diagnosis of isolated ventricular septal defect complicated by pulmonary arterial hypertension. Body mass index among the boys were between 50^{th} and 5^{th} percentiles and girls were between 25^{th} and 5^{th}.

Preoperative data.

The mean sO_2 for all children was 92.17±4.7%; sO_2 less than 90% was in 6 children, 90-95% in 21 children and >95% in 8. Red blood cells mean amount was normal in all children $4.6±0.57*10^{12}$/l, and mean haemoglobin's level was 119.4±15.45g/l.

The mean size of the ventricular septal defect was 10.92 ± 6.38 mm. Mean ventricular septal defect index was 0.72 ± 0.49. It was interpreted as small ventricular septal defect in 8 children (0.188± 0.119), as moderate in 13 (0.49±0.1) and as large ventricular septal defect in 17 children (1.2±0.44). The mean systolic pressure in the right ventricle on Echocardiography was 55.42 ± 18.47 mmHg. In children who underwent cardiac catheterisation (N = 15) mean pulmonary arterial pressure by right heart catheterization was 52.12 ± 29.44 mmHg. Systolic and diastolic systemic blood pressure were registered respectively 92.6+11.04 and 57.19±8.99mmHg. For the mean pulmonary arterial pressure to mean systemic arterial pressure ratio mean level was 0.63±0.22. 27 children had have mean systemic arterial pressure to mean pulmonary arterial pressure ratio <0.75. and 11 children were >0.75.

The mean end diastolic index for all children was registered as 76.78±19.58ml. Cardiac output was preserved in all children. Dilatation of the left ventricle was recorded in 23 patients, for them basic drug treatment including diuretics (spironolactone 2mg/kg/dose 2 t/day per os); and afterload reduction with low-doses of angiotensin converting enzyme inhibitors (captopril 0.1mg/kg/dose 3 t/day per os) was prescribed.

Mean z score for pulmonary artery size was 1.4±1.3. In 11 children pulmonary artery dilation was registered. In 9 children a acute vasoreactivity test with inhaled iloprost was performed. A positive response, with a reduction in pulmonary vascular resistance index >20% was noted in 8 children. In the pre-operative period, all 9 of these children were, subsequently, treated with sildenafil in a dosage of 1.5 mg/kg 3 times a day (weight of up to 20 kg) and 20 mg 3 t/day (weight over 20 kg)

Of the 38 children 36 had ventricular septal defect surgical repair and 2 underwent transcatheter device closure. There were no deaths. In 8 children with positive acute vasoreactivity test specific pulmonary arterial hypertension medical treatment with sildenafil was prescribed before surgery. 1 patient who did not have a positive response during acute vasoreactivity test also underwent surgery with prescription of sildenafil in preoperative period.

Post-operative findings.

We had had no early postoperative mortality.

In the postoperative period 2 children experienced pulmonary hypertensive crisis. Both cases were soon after the transferring the patient to the ward. As treatment intravenous nitroglycerin and Iloprost inhalations were used with the prolongation of the basic diuretic therapy. However pulmonary hypertensive crisis was a single event for these children, after stabilisation, no recurrence of pulmonary hypertensive crisis was registered. They stayed with the sildenafil prescription for the next 6 months.

One week after the operation a decrease in left ventricle dilatation with preserved function was noted on echo in all operated patients. In children who did not receive specific therapy the mean right ventricle systolic pressure decreased from 55.5±14.8mmHg to 40.8±12.6 mmHg ($p < 0.01$). In 1 month mean right ventricle systolic pressure decreased to 32.2±14.4mmHg ($p<0.01$) (Figure 1).

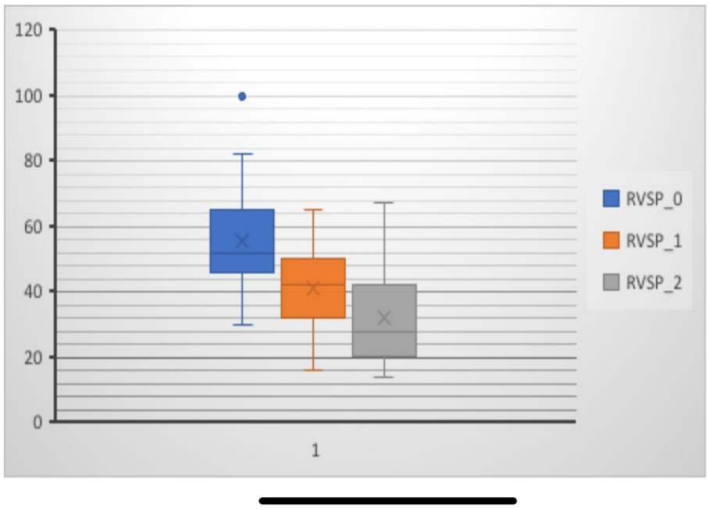

Figure 1 – Difference between pre- and post-operative right ventricular systolic pressure in children after surgery and after catheterisation

RVSP_0 – preoperative right ventricle systolic pressure, RVSP_1 –right ventricle systolic pressure 1 week after operation, RVSP_2 –right ventricle systolic pressure 1 month after operation

One month after the operation the echocardiographic assessment showed that the right ventricle systolic pressure was improved in all children. Persistant pulmonary arterial hypertension was registered in 4 patients who continued sildenafil therapy.

In children who received specific therapy in the preoperative period, the right ventricle systolic pressure also decreased >40%, from 81.4±10.3mmHg. to 48.1±12.4mmHg in a month after the surgery (p value 0.01), which was not different from that in children without medical preparations for surgery (mean preoperative right ventricle systolic pressure 55.1±15.9 mmHg, 1 month after operation 32.4±15.3 mmHg, $p > 0.05$) (Figure 2).

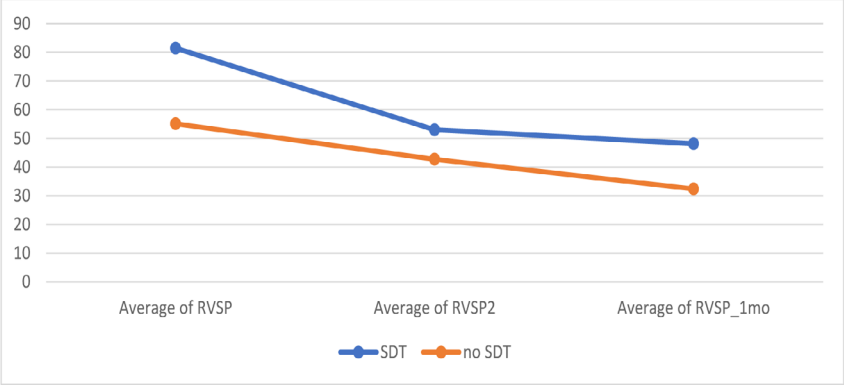

Figure 2 – Comparison of mean right ventricle systolic pressure's dynamic in children who received specific PAH therapy in preoperative period and in children without specific PAH therapy.

SDT – specific drug therapy, RVSP – preoperative right ventricular systolic pressure, RVSP2 - right ventricular systolic pressure 1 week after operation, RVSP_1mo – right ventricular systolic pressure 1 month after operation.

In the postoperative period, 7 children who were operated showed rising of right ventricle systolic pressure above 40 mm.Hg. which resulted in prescription of sildenafil treatment. The volume of the left ventricle cavity normalized in 92.5% of cases (end diastolic index decrease, p value < 0.05).

The mean length of stay in the intensive care unit was 3.02±4.6 days. The mean length of hospitalization was 17.6±12.9 days. In the group

of children without preoperative sildenafil therapy, the length of ICU staying was 3.7±4.8 days and the period of hospitalization was 19.1±13.9 days. In contrast in children with specific drug treatment the mean length of stay in the intensive care unit for was 5.6±6.8 days and the mean length of hospitalization was 24.1±16.7 days.

Discussion: This study is the first to systematically evaluate the outcome from ventricular septal defect repair of children in Kazakhstan. We have demonstrated excellent outcomes with no mortality in 38 patients who underwent surgical or transcatheter repair of a ventricular septal defect complicated by pulmonary arterial hypertension.

From demographic data, we found that 50% of children were 1-7 years old with the slight prevalence of boys vs girls. Surgery outcomes were similar for all children: no heart rhythm complications, zero mortality, de-escalation of pulmonary arterial hypertension progression. Secondary changes such as left ventricle and pulmonary artery dilatation are reversible and controllable after surgery in patients with pulmonary arterial hypertension associated with ventricular septal defect.

Patients who took sildenafil as preoperative specific drug therapy showed the same results with those who didn't. What is controversial to publications, demonstrated the efficacy of sildenafil to prevent and control the pulmonary hypertensive crisis[6,9.10.14]. Surgical treatment was obvious way to decrease mean pulmonary arterial pressure in a short-time, however for the midterm result complex treatment as specific drug therapy after ventricular septal defect repair is more effective for management of pulmonary arterial hypertension in postoperative period. In 1-month period, we registered significant decreasing of right ventricle systolic pressure in patients with residual pulmonary arterial hypertension after ventricular septal defect repair who received sildenafil as specific drug therapy. Our results endorse the previous trials of sildenafil efficacy for pulmonary arterial hypertension associated with congenital heart defects [6,9,10,14-19].

Pulmonary arterial hypertension is an important indicator for operability of ventricular septal defect in children. Nowadays cardiac surgery tends to early operative management of the defect what could prevent pulmonary arterial hypertension development. Most of the patients demonstrated good response for complex approach to treatment. Basic therapy with potassium-sparing diuretics and ACE-inhibitors in the preoperative period with the prescription of the specific drug therapy after the radical correction showed high efficacy for management of pulmonary arterial hypertension. Residual pulmonary arterial hypertension after the ventricular septal defect repair potentially could cause opposite surgery result with the right ventricle failure, pulmonary hypertensive crisis and increase the risk of mortality. Therefore, moderate and large ventricular septal defect have to be closed in the age under 1 year old. In the presence of ventricular septal defect complicated by pulmonary arterial hypertension the medicaments management of volume overload due to left-to-right shunting is a key for positive outcome of cardiac surgery or intervention.

Study limitations. The major limitation of this study that in the Republic of Kazakhstan there were absence of the electronic database for echocardiographic and catheterisation records what is crucial for long-term follow up of the patients in most of the hospital. We have tried to overcome this limitation by studying one centre that keep the record over 5 years, however the sample size is small due to single centre. We are reporting here this experience and we plan to follow up with most report electronic database in the future.

Conclusion: We have demonstrated excellent outcomes with no mortality in 38 patients who underwent surgical or transcatheter repair of a ventricular septal defect complicated by pulmonary arterial hypertension. Accordingly to this study, the prescription of specific drug therapy of pulmonary arterial hypertension with the purpose of preparing for surgery has no effect on the effectiveness of surgical treatment of ventricular septal defect. Thus, further studies are needed for clarifying the rationality of specific drug therapy prescription in the preoperative period in this category of patients.

Conflicts of interest: none

Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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M.U. Mukanov[1], A.M. Mukanov [2]

[1]al-Farabi Kazakh national university,
Kazakhstan, Almaty, e-mail Mukanov-m@mail.ru
[2]Polyclinic №20 Health Department of Almaty

PREVENTION OF POSTOPERATIVE COMPLICATIONS IN PURULENT PERITONITIS

Objective of the study is to improve the efficiency of surgical treatment of peritonitis by introducing new methods of prevention of postoperative complications.

In this paper, we presented the results of clinical studies of 180 patients operated on various forms of diffuse peritonitis.

We developed the "Drainage device" consisting of coaxially placed tubes, optimal for draining the irregularly shaped cavities, and applied it in clinic.

Anolyte solution, which is an aqueous solution of diluted sodium chloride solution passed through the electrochemical reactor, has been used to cleanse the abdominal cavity. The bactericidal effect of the solution has been clearly demonstrated by the results of bacteriological studies.

We have validated that viscero-parietal adhesions play pathogenetic role in the mechanism of acute adhesive intestinal obstruction, the latter being the result of fixation of two multifunctional organs, small bowel and anterior abdominal wall, which leads to continuous traction with accompanying ischemia, pain syndrome and impaired passage of intestinal contents.

In order to prevent viscero-parietal adhesions in peritonitis and acute adhesive small bowel obstruction, we proposed a novel Method for the prevention of acute adhesive bowel obstruction".

The introduction of these preventive methods into clinical practice resulted in a threefold decrease in the number of postoperative complications.

Key words: Peritonitis, postoperative complications, visceroparietal adhesions, prevention of adhesions, acute adhesive intestinal obstruction, peritoneal lavage.

Introduction

G.M. Wegner, a renowned surgeon of the 19th century, is believed to utter a catch phrase in 1876, 'Me and my generation have been brought up in awe of God and peritonitis.'

In 1971, K.S. Simonyan [1] in his seminal book Peritonitis, remarked, 'One hundred years have passed since these words were said, and alas, we have no awe of God now, though are still fearful of peritonitis.' Nowadays, surgeons [2,3,4,5] claim the awe of God is back, with awe of peritonitis in place as before.'

Indeed, in spite of achievements of modern surgery, diffuse peritonitis is still the greatest challenge faced by emergency abdominal surgery.

Lead Russian and foreign clinics failed to report any downward trend in mortality rate associated with this condition over the past decades: it ranges from 20-30% to 50-70% plus, being the highest in postoperative peritonitis, with established multiorgan failure and septic shock [6,7,8].

The incidence of postoperative complications in peritonitis varies from 10 to 23%, with no noticeable dramatic change in recent years [9].

Most common encountered complications are: wound infection, 12.5%; progressive peritonitis, 22%; abdominal cavity abscesses, 9.7%; eventration, 7.5%; early adhesive small bowel obstruction, 12.2%. [10,11].

Diffuse peritonitis creates particularly favorable conditions for the development of adhesions in the abdominal cavity: fibrin deposits on the intestinal loops, intestinal paresis.

According to T.T. Daurova and S.D. Andreev [12], abdominal adhesive disease (AAD) occurs in 83-92% of patients, with acute adhesive small bowel obstruction (ASBO) developing in 30% to 67% of patients with this disorder.

The aim of the study is to develop and introduce efficient ways of prevention of both early and late postoperative complications of peritonitis.

Patients and methods. We analyzed the results of operations performed on 180 patients with various forms of diffuse peritonitis in the clinic during the period of 2000 to 2019. The age of patients ranged from 15 to 92 years.

The main group included 42 patients who were given surgical treatment using the methods of prevention of postoperative complications developed by us, vs. the control group of 138 people treated by conventional methods.

By etiology of peritonitis, both groups were similar in terms of underlying diseases, with equal incidence and severity of the disease. The etiological factors were: acute appendicitis (21%), acute cholecystitis (26%), perforated peptic ulcer, both duodenal and gastric (5%), adhesive bowel obstruction (10%), pancreonecrosis (12%), abdominal injuries (12%), and a number of gynecological diseases (5%).

We evaluated the peritonitis prognosis using the APACHE scoring system and the Mannheim Peritonitis Index. The extent of surgical treatment in patients depended on the cause of peritonitis and aimed at eliminating the source of the disease (Table 1).

Table 1 – Surgical treatment of peritonitis

Type of operation	Main group (n=42)			Control group (n=138)		
	Total	RL*	ELC*	Total	RL*	ELC*
Appendectomy	9	-	-	46	5	2
Cholecystectomy	11	1	1	43	4	2
Simple oversewing of the gastric and duodenal peptic ulcer	1	-	-	7	1	1
Resection of the ulcer plus pyloroplasty	-	-	-	2	-	-
Gastric resection	1	-	-	2	-	-
Adhesiolysis	3	-	-	10	2	-
Division of adhesions + small bowel resection	1	1	-	-	-	-
Herniotomy	2	-	-	5	-	-
Herniotomy + small bowel resection	1	-	-	3	-	1
Suture closure of traumatic rupture of the intestine	3	-	-	6	1	-
Resection of the site of traumatic rupture of the intestine	1	-	-	3	-	1
Double barrel colostomy in colonic disruption	1	-	-	2	-	-
Drainage of the omental bursa	5	-	-	1	-	-
Salpingo-oophorectomy	2	-	-	7	-	-
Uterine amputation	1	-	-	2	-	-
Total:	42	2	2	138	12	7

Abbreviations: RL, relaparotomy; ELC, elective laparo-cleansing;

A total of 203 operations, including RL and ELC, were performed on 180 patients.

We retrospectively reviewed the results of surgical treatment of patients in control group and found the following postoperative complications:

Wound-related complications: wound infection (48), anterior abdominal wall phlegmon (8), eventrations (3). The incidence of these complications varied from 0.7 to 19.6% and was proportionate to the length of stay.

Extra-abdominal complications: pneumonia (21), others (7) 1.5% to 6.5%.

Intraperitoneal complications: abdominal abscesses (up to 5.1%), progressive peritonitis (up to 7.3%), early acute adhesive ileus (up to 4.3%).

Radical removal of the source of peritonitis and thorough cleansing of the abdominal cavity intraoperatively are the two key elements of therapeutic efforts largely determining the further course and outcome of the disease.

In peritoneal lavage, the primary task is to mechanically cleanse the peritoneal cavity, and secondly, exercise antibacterial effect on intra-abdominal infection.

The first task, in advanced forms of peritonitis with non-removable fibrinous-purulent deposits firmly accreted to visceral peritoneum, is quite a challenge and not always feasible. The second task is also problematic, because sanitizing solutions, including antibiotics, often fail to achieve complete positive effect. Therefore, there is a constant search for more effective means of sanitizing the abdominal cavity.

For this purpose, we use anolyte solution in our clinical practice. Anolyte is an aqueous solution of dilute sodium chloride solution passed through the electrochemical reactor that produces chlorine oxygen and hydroperoxide oxidants (hypochloric acid, hypochlorite ion, active oxygen compounds). The solution is non-toxic, displays high reactive and catalytic activity at low concentration of active substances, possesses disinfectant and anti-inflammatory properties.

The bactericidal effect of the solution is clearly demonstrated by the results of a bacteriological study (Table 2). A quantitative study of microflora in 1 ml of peritoneal exudate was carried out as a gauge for sanitizing effect. Samples were taken (from the drainage tube) before sanitizing the abdominal cavity, upon completion of the procedure, and while in progress, on different days after the operation.

Table 2 – Bacteriological study

Group	Duration of treatment (days)			
	1	3	5	7
Controls	$7.96\pm0.14 \times 10^7$	$7.1\pm0.21 \times 10^7$	$6.5\pm0.19 \times 10^6$	$5.7\pm0.23 \times 10^5$
Main	$7.1\pm0.20 \times 10^7$	$4.74\pm0.16 \times 10^3$ $p < 0.05$	Not isolated	Not isolated

Efficiency of the surgical intervention largely depends on how adequate are the applied abdominal cavity drainage methods.

Conventional methods for draining the abdominal cavity in generalized purulent peritonitis entail insertion of drain tubes through individual punctures on the anterior abdominal wall and into the lesser pelvic cavity (right and left), subphrenic space (bilaterally) and subhepatic space.

However, specifics of anatomical structure of the abdominal cavity, such as attachment sites for the mesentery, spatial orientation of pouches and recesses of the peritoneum and its bursae, especially amid peritonitis, preclude an adequate drainage of pathological exudate from each and every cavity formed by the peritoneum by means of conventional drains.

We have proposed and used in our clinical practice a *Drainage Device* (Inventor's Certificate #1813457) consisting of coaxially mounted tubes, installed movably relative to each other. The device is optimal for draining the irregularly shaped cavities (Fig.1).

This is how the device works: through a puncture in the abdominal wall, a small diameter tube (1) is threaded from within the abdominal cavity outward, with tubes 2 and 3 in its lumen; then from within the lumen of tube 1, tube 2 is threaded through the inlet holes, further on, tube 3 is threaded from within the lumen of tube 2 through the inlet holes. From the abdominal side of the drainage system, tubes 2 and 3 are placed in advance. Then, by sliding the inner tubes relative to the outer ones, the target sections of the abdominal cavity are drained. The inlet openings are sealed. Postoperatively, different compartments of the abdominal cavity are independently suctioned through tubes 1 – 3. Moreover, each of the tubes can be used for peritoneal lavage, with no risk of contagion through the drains from one source of infection to another.

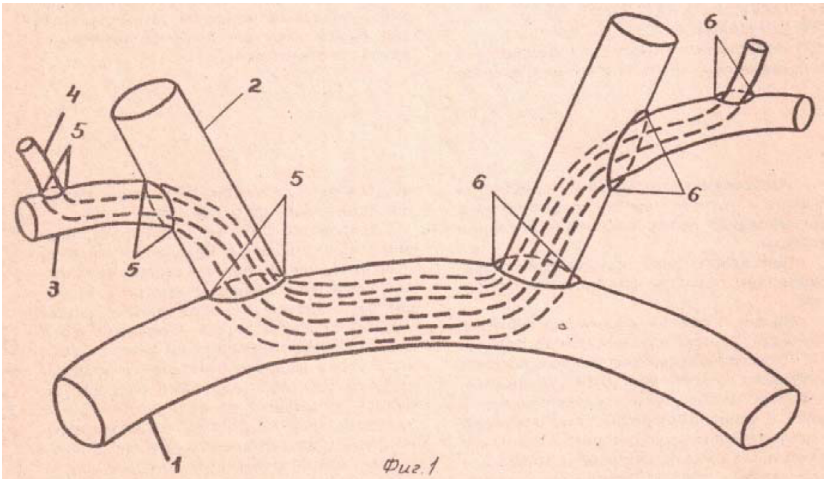

Figure 1 – Drainage device. 1. Principal drain. 2,3,4. Internal drains. 5. Openings in the proximal end of drains. 6. Distal end openings.

Diffuse peritonitis with fibrin deposits on intestinal loops, non-sliding relative to each other (largely due to intestinal paresis) presents an excellent environment favoring the development of adhesions in the abdominal cavity and its ominous complication: acute adhesive ileus, both in early and late postoperative period.

We retrospectively reviewed the patients in the control group (138) and found early adhesive intestinal obstruction in 12 cases (8.7%), and late one in 28 cases (20.3%).

In developing our methods of prophylaxis of acute adhesive intestinal obstruction in the wake of peritonitis, we abided by the following tenets:

Intraperitoneal adhesions per se are recognized as the primary cause of acute adhesive small bowel obstruction (ASBO). Of practical importance, both in terms of incidence and probability of ASBO onset, are adhesions between the parietal peritoneum of the anterior abdominal wall and intestine, categorized in D.I.Balatsenko's classification (1957) as viscero-parietal adhesions (VPA), or traction adhesions according to A.O.Vereshchinsky' s classification (1925).

The high probability of ASBO formation in the presence of VPA is due to the fact that:

1. The anterior abdominal wall – an integral part of respiration process and contributor to abdominal muscles – will cause impaired intestinal motility when restricted in its excursion by tenacious accreted adhesions.

2. Let's regard the parietal peritoneum and intestinal loops as two parallel planes. Then, the adhesions formed between these two planes run perpendicularly or at an angle, which naturally may lead to an inflection of the bowel loop.

3. With every movement of the anterior abdominal wall, the traction of the bowel loops firmly attached to the mesentery posteriorly and to VPS anteriorly, will strain the mesentery and distort its vessels and nerves, with resultant compromised blood flow through the mesenteric vessels, pain syndrome and hindered passage of intestinal contents.

Thus, the pathogenetic role played by viscero-parietal adhesions in the mechanism of acute adhesive intestinal obstruction can be reduced to the following: the two differently functioning organs – the intestine and the anterior abdominal wall – attach to each other. Moreover, the inflected and stretched intestinal tube will make the mesentery strain with resultant ischemia, pain syndrome and hindered passage of intestinal contents.

In order to prevent adhesion and its complications in peritonitis we proposed the following Method of Prevention of Acute Adhesive Intestinal Obstruction (Patent #13124): Before the operation, we prepare an airtight 30 by 40 cm sized polyethylene bag (Fig. 2). Multiple microperforations are made in the back of the bag. The upper corners of the bag are snipped away to make two holes. Through these holes the tube is threaded, with its perforations collocated within the bag and tube openings outside it.

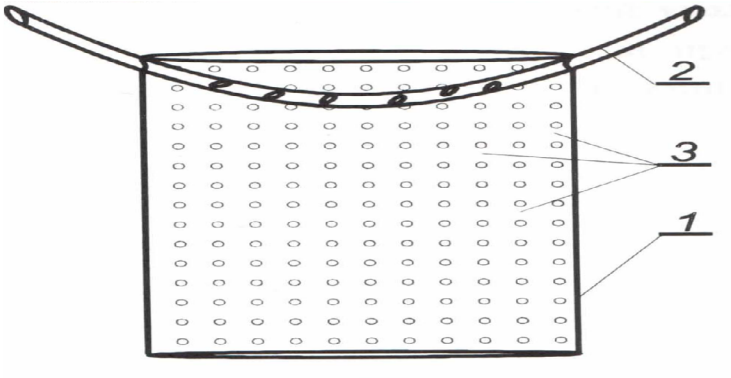

Figure 2. 1– polyethylene bag 2– drainage tube within the bag cavity. 3– microperforations in the back of the bag.

During the operation, upon control of the source of infection and abdominal cleansing, the plastic bag is placed into the abdominal cavity with its multiperforated rear aspect facing the bowel loops. Through the counterpunctures in both subcostals, both ends of the drain tube are exteriorized from the bag's cavity and fixed to the skin. In the iliac region, a small incision is made through all layers of the abdominal wall, about 2.5 cm long, through which the lower corner of the bag is exteriorized. Through the same counterpuncture, a separate drainage tube is placed into the small pelvic cavity to drain the abdominal cavity. The laparotomy wound is suture closed in a layered fashion.

After the operation, the peritoneal lavage is delivered by jet injection of antiseptic solutions through both ends of the drainage tube of the polyethylene bag. Effectively, the liquid is sprayed to all areas of the abdominal cavity through the microperforations in the bag's lower wall, mostly between the loops, in a 'shower' fashion, thus ensuring complete sanitation of the abdominal cavity. At the same time, the presence of the bag itself made of inert material (polyethylene) separates the intestines off the parietal peritoneum of the anterior abdominal wall. The peritoneal lavage is to be stopped when clean return from the small pelvis cavity is obtained and intestinal peristalsis is restored postoperatively. On day 5 or 7 post-op, as indicated, the tube is removed first from within the bag, then the bag itself is easily pulled out if firmly grasped by its exteriorized end in the iliac region. The drain tube from the small pelvis cavity is removed the next day.

Results of the study

The above described innovative methods and technical approaches we employed in surgical treatment of peritonitis, such as anolyte solution as an abdominal cavity detergent, peritoneal lavage for both optimal cleansing of the abdominal cavity postoperatively, separating the intestinal loops off the anterior parietal peritoneum, drainage device, helped us achieve an almost three-fold decrease in the number of postoperative complications: wound complications 9.5% vs. 30.4%, intraperitoneal complications 7.1% vs. 19.6%, and extraperitoneal complications 11.9% vs. 16.7%. Postoperative mortality in the main group was 6% (3) vs. 29% (21) in the control one.

We hope our limited experience with the above novel technology will help practical surgeons to better treat this complex and dangerous pathology.

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A.M. Kurmanova[1*], B.K. Amanzholova[1],

N.V. Kravtsova[2]

[1]Al-Farabi Kazakh National University, 050040, Almaty, Kazakhstan
e-mail: alm_kurmanova@mail.ru
[2]QLaboratory LLP, Almaty, Kazakhstan

THE ACTIVITY OF CYTOTOXIC LYMPHOCYTES IN PATIENTS WITH PREECLAMPSIA

With preeclampsia, the average levels of biochemical parameters in mild and severe form did not differ significantly from those in the group with uncomplicated preeclampsia of pregnancy. There is a tendency to a decrease in total protein and an increase in bilirubin, creatinine, urea, and blood transferases as it becomes heavier. In the hemostatic system, there was also a tendency toward a decrease in fibrinogen and platelet count as gestosis worsened. The average hemostasis in the groups with preeclampsia did not differ from the group with uncomplicated pregnancy. However, thrombocytopenia was observed in 28% and 32% of cases with mild and severe forms of preeclampsia. Moreover, a pronounced decrease in platelet count (almost 10 times) was recorded in 5.4% of patients with severe preeclampsia. In patients with preeclampsia, the production of intracellular perforin in the regulatory cells - CD4 + Perf + lymphocytes was significantly reduced and increased - in natural killers CD16 + Perf + and CD56 + Perf + .

Key words: preeclampsia, cytotoxic lymphocytes, perforin.

Introduction

Preeclampsia is a leading obstetric pathology that determines the level of reproductive loss and perinatal complications [1]. The frequency of preeclampsia in the general population of pregnant women is 5-10% and is one of the main causes of maternal mortality - 12-30% [2]. The frequency of preeclampsia in the Republic of Kazakhstan ranges from 14.5-35%.

According to modern concepts, pre-eclampsia is considered as a "disease of adaptation" to pregnancy with all stages inherent in the general adaptation syndrome. Indicators of developing dysfunction in the body of a pregnant woman are changes in the immune, neurohumoral and other systems responsible for the regulation of vascular tone and the state of microcirculation [3]. The pathogenesis of preeclampsia is based on imperfect adaptation, in which insufficient release of Th1 cytokines, proteolytic enzymes, and free radicals causes a small invasion of the spiral arteries by cytotrophoblast and systemic dysfunction of endothelial cells [4]. Hypertension developing in the III trimester is a compensatory response with adequate placental perfusion for fetal growth [5].

Physiological pregnancy is characterized by the activation of an inflammatory cellular response, which was demonstrated by the analysis of inflammatory markers (CD11b, CD64, CD62L, HLA-DR and intracellular types of reactive oxygen). The leukocytes of healthy pregnant women showed significantly higher levels of CD11b +, CD64 + cells and oxygen radicals compared with samples from non-pregnant. At the same time, women with preeclampsia showed lower expression of CD62L and significantly higher levels of production of reactive oxygen species compared to healthy pregnant women, indicating generalized changes in circulating leukocytes, however, there were differences in many respects between pregnant women with preeclampsia and gestosis smaller than those between the control groups of pregnant and non-pregnant women [6].

The most obvious changes in gestosis were noted in the level of lymphocytes with a phenotype characteristic of cells with cytotoxic activity [3]. It was shown that in the peripheral blood of women with this pathology, the contents of CD16 +, CD8 + HLA-DR + and CD8 + CD16 + lymphocytes were higher than during normal pregnancy [7]. Analysis of cellular immunity indices showed an increase in natural killers of CD16 + CD56 + in the peripheral blood during preclampsia [8]. It is known that, upon activation of natural killers, perforin production increases [9]. Therefore, the level of intracellular

production of perforin in effector lymphocytes can be regarded as a marker indicating the cytotoxic potential of killer cells, and as a possible predictor of the development of preeclampsia.

In this regard, we conducted a study evaluating the cytotoxic potential of peripheral blood lymphocytes in patients with preeclampsia.

Methodology

We examined 25 patients with mild preeclampsia, 37 patients with severe preeclampsia and 15 patients with uncomplicated preeclampsia during pregnancy with a gestational age of 34-38 weeks (III trimester). All patients underwent a comprehensive examination, including determination of hemoglobin level, biochemical tests (ALT, AST, bilirubin, total protein), platelet count, hemostasiogram indicators, protein level in urine analysis. A subpopulation analysis of peripheral blood lymphocytes was performed by flow cytometry on a FacsCalibur instrument (Becton Dickenson / USA) in the CellQuest program using monoclonal antibodies to surface lymphocyte antigens (NPO Sorbent / Moscow, Russian Federation): mature T-lymphocytes – CD3 +, T helper cells – CD4 +, cytotoxic lymphocytes CD8 +, natural killers CD16 +, CD56 + stained with phycoerythrin. The level of intracellular perforin in the cytotoxic cells was evaluated, and the expression of Perf + stained with FITC was evaluated.

Discussion and results

It was found that the average levels of biochemical parameters in mild and severe form did not differ significantly from those in the group with uncomplicated pre-eclampsia of pregnancy (table 1).

Table 1 – Blood biochemical parameters in patients with preeclampsia (PE)

Indicators	Control, n = 15	Light PE group, n = 25	Heavy E group, n = 37
Total protein, g / l	66,5±2,9	67,2±5,4	63,5±5,1
Bilirubin, mmol /l	6,2±0,7	8,7±3,8	9,0±2,6
Creatinine, mmol /l	57,3±5,0	70,3±13,7	65,2±13,3
Urea, mmol /l	3,1±0,5	4,1±1,2	7,2±4,8
Glucose, mmol /l	6,3±2,4	4,5±0,4	4,8±0,6
ALT, Units /l	16,4±6,4	11,5±4,5	14,6±7,4
AST, Units /l	15,4±7,6	16,9±7,1	18,9±7,8

Despite the tendency for a decrease in total protein and an increase in bilirubin, creatinine, urea with preeclampsia, there was a pronounced scatter of indicators (there were both reduced and increased indicators). The level of blood transferases also showed a tendency to increase them. In patients with uncomplicated pre-eclampsia pregnancy, a 2-fold increase in ALT was recorded in 10% of cases, while in patients with a mild form of preeclampsia, an increase in ALT and AST by 2 norms was detected in 8% and 12% of cases, respectively, and in patients with a severe form of preeclampsia in 21% and 19% of cases, respectively.

In the hemostasis system (table 2), a tendency toward a decrease in fibrinogen and platelet count as gestosis worsened was also recorded.

Table 2 – Hemostasis in patients with preeclampsia (PE)

Indicators	Control, n = 15	Light PE group, n = 25	Heavy PE group, n = 37
Fibrinogen, g / l	4,3±0,1	4,0±0,1	3,4±0,5
Prothrombin time, sec	16,2±2,4	17,4±1,1	16,7±0,8
Prothrombin index	90±4,8	90,6±5,8	94,1±3,7
Platelets, x 10^9 g/l	235,2±55,0	221,2±56,9	224,5±73,8

However, the average hemostasis in the groups with preeclampsia did not differ from the group with uncomplicated pregnancy. However, thrombocytopenia was observed in 28% and 32% of cases with mild and severe forms of preeclampsia. Moreover, a pronounced decrease in platelet count (almost 10 times) was recorded in 5.4% of patients with severe preeclampsia.

Data characterizing the characteristics of the population composition of peripheral blood lymphocytes with a mild form of preeclampsia are presented in table 3.

Table 3 – Relative content of lymphocyte's subpopulations in patients with light PE

Indicators, %	Control, n = 10	PE, n=10	P < 0,05
CD3+Perf-	64,7±2,7	67,3±2,8	
CD4+Perf-	37,8±1,6	34,3±8,3	
CD8+ Perf-	31,4±1,0	24,9±6,3	
CD16+Perf-	0,61±0,3	4,07±3,4	
CD56+Perf-	0,7±0,1	3,2±1,4	

It should be noted that according to the average values of the lymphocyte subpopulations, there were no significant differences in comparison with the control group. Although there was a downward trend in CD4 + lymphocytes and an increase in CD16 + and CD56 + lymphocytes.

We also studied the production of perforin by cytotoxic cells of peripheral blood (table 4).

Table 4 – The relative content of perforin-positive lymphocytes in patients with PE

Indicators, %	Control, n = 10	PE, n=10	
CD3+Perf+	9,1±0,9	10,5±1,3	
CD4+Perf+	9,6±0,5	4,9±1,2	P < 0,05
CD8+Perf+	6,8±0,4	13,3±7,1	
CD16+Perf+	1,0±0,02	9,1±0,7	P < 0,05
CD56+Perf+	0,6±0,03	9,8±2,4	P < 0,05

Conclusion

In patients with preeclampsia, the production of intracellular perforin in the regulatory cells - CD4+Perf+ lymphocytes was significantly reduced and increased - in natural killers CD16+Perf+ and CD56+Perf+. The content of CD3+Perf+ and CD8+Perf+ in patients with preeclampsia did not differ from those in the group with uncomplicated preeclampsia pregnancy. From the second half of physiological pregnancy, a second wave of trophoblast invasion into the muscle segment of the spiral arteries of the uterus is observed, and activation of regulatory T-helpers is necessary [10]. It would expect an increase in the level of cytotoxic lymphocytes - CD4+, CD8+ lymphocytes and natural killers that limit trophoblast invasion. However, in the pathological course of pregnancy, in our study, significant differences were found only in the level of perforin-positive natural killers. Apparently, during preeclampsia, the functional properties of cytotoxic cells are redistributed, therefore, their study must be carried out with the study of the intracellular cytokine content.

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K.Z. Saduakasova[1], G.S. Svyatova[2]

[1]Al Farabi Kazakh National University, e-mailkasy-haus@mail.ru
[2]Scientific Center of Obstetrics, Gynecology and Perinatology,
NMGC (National Medical Genetic Counselling Center).

SEROTONINERGIC SYSTEM CONTRIBUTION TO THE DEVELOPMENT OF EARLY ONSET CHILDHOOD SCHIZOPHRENIA

Relevance. In recent years, active research on the relation rs6313 polymorphism with response and side effects of taking antipsychotics and antidepressants - established ability of these receptors to bind some antipsychotic drugs, in particular, slowing down the development of negative symptoms in patients with schizophrenia. Thus, when studying the antipsychotic effect of clozapine, its relationship to 5NTR2A receptors was found, therefore, the functional variability of the gene encoding these receptors may affect the clinical effect of clozapine. It was shown that the frequency of rs6313 5NT2A is higher in the group of patients who are resistant to treatment with atypical antipsychotic drugs [17,18,19]. The article does not cover the history of studying the genetic polymorphism 5NT2A, hypotheses "for" and "against" its participation in the pathogenesis of mental diseases. Analysis of the current available scientific literature has shown that our study on the search for associations of the rs6313 genetic polymorphism of the 5NTR2A gene with the development of schizophrenia is the first conducted not in an adult, but in a child population. Clinical and psychopathological features were studied and the genetic contribution of the 102t/S polymorphism of the 5NTR2A gene to the development of child and adolescent schizophrenia was determined.

Key words: serotonin receptor gene 5HTR2A, rs6313 of 5HT2A gene, association with schizophrenia, A2A2 genotype frequency, early onset childhood schizophrenia, schizophrenic dysontogenesis, pseudo-oligophrenic deficit.

Introduction

Study of schizophrenia has been historically emphasizing the role of heredity in the development of schizophrenia and searching for potential precursors and genetic markers of the disease. The development of molecular genetics gave ample opportunities to search for genetic input of various polymorphisms of so-called *candidate genes* to the risk of schizophrenia. Although the important role of the genetic component in the etiology of schizophrenia is now well established, the mechanism of hereditary transmission remains unclear, and the pathological genes predisposing to the disease have not yet been identified. It is known that each gene can be represented in many forms, they are called polymorphic variants of the gene, and the phenomenon itself is termed molecular-genetic polymorphism. Serotonin receptors type 2a (5HTR2A) are believed to be one of the candidate genes in the origin of schizophrenia and play a lead role in the emergence and development of endogenous mental diseases [1,2,3].

The studies in neurochemical effects of modern atypical antipsychotics have supported the hypothesis of their positive impact on the schizophrenia symptomatology, probably through combined effect on serotoninergic and dopaminergic receptors [3,4,5,6,7,8]. Still, some scientists believe that an increase in dopaminergic activity is not a direct cause of schizophrenia, and its symptoms appear as a result of a decrease in modulating effect on the dopaminergic system of other neurotransmission systems, in particular serotoninergic and glutamatergic ones [9].

Serotonin synthesis starts with tryptophan which successively, via the hydroxylation and decarboxylation reactions, turns into 5-hydroxytryptophan and then into the final product of 5-hydroxytryptophan or serotonin (5HT). The 5-HT2A (5-HT2, HTR2A) gene encodes the 5-hydroxy-tryptamine (serotonin) receptor coupled with G-protein (GPCR) and is responsible for post-synaptic serotonin signal transduction. Serotonin-sensitive neurons mature in the deep structures of the middle lobe of the brain and then migrate to the cortex, frontal lobes and other areas of the cortex,

participate in the regulation of emotions, behavior and circadian rhythms, influence sleep, and coregulate somatic functions of the body and the activity of the autonomic nervous system [10,11].

The association of polymorphism of the HTR2A (102C> T) rs6313 gene with the development of mental disorders (depression, suicides, bipolar disorders, etc.) has been found in many populations, but the results of these studies are not unequivocal and are contradictory at times. Currently available data suggest that 5HTR2A dysfunction is also observed in affective disorders. R. Joober [12] noted an earlier age of manifestation in patients with the rs6313 of 5HTR2A gene schizophrenia and alcoholism. In her studies, N. G. Mityushina et al. showed much higher frequency of A2A2 genotype in the group of schizophrenic patients (Russian population) with pronounced negative symptomatology (decreased personality level) and hereditary burden as opposed to the group of patients with minor personality disorders [13,14,15,16].

In spite of contradictory results of research into serotonin blood, liquor and brain structure levels, serotonin concentration in schizophrenia was found to be directly related to total brain mass. Postmortem studies of the brain revealed a decrease in the number of 5HTR2A receptors in the prefrontal region [1].

In recent years, the association of rs6313 polymorphism with the response and side effects of antipsychotic drugs and antidepressants has been actively studied. These receptors were found to bind some antipsychotic drugs, in particular, those hindering the development of negative symptoms in schizophrenic patients. For example, a study of the antipsychotic effect of clozapine revealed its affinity to 5HTR2A receptors, therefore, the functional variability of the gene encoding these receptors may influence the clinical effect of clozapine. Frequency of rs6313 5HT2A was found to be higher in the group of patients who were resistant to atypical antipsychotic drug medication [17,18,19].

This paper does not aim to cover the history of the study of 5HT2A genetic polymorphism, nor any pro and con hypotheses that it is involved in pathogenesis of mental diseases. There were quite a few publications on this topic in the early 2000s. We have reviewed the currently available scientific literature and found our research into presumable association of genetic polymorphism of rs6313 of gene 5HTR2A with development of schizophrenia to be a pioneering study of children population, not adults. Clinical and psychopathological patterns of 102T/C of 5HTR2A gene have been studied and genetic contribution of its polymorphism to development of childhood-onset and adolescent schizophrenia has been identified.

Material and methods of research

In our studies, we recruited a sample of 112 probands and 104 donors (deemed mentally healthy persons) aiming to see if the allelic polymorphism of 5HT2A gene is associated with schizophrenia, and particularly, if this gene is involved in overall susceptibility to the disease, and if allelic polymorphism has an impact on the clinical diversity of the endogenous process. The accuracy of the results was assessed and confidence intervals for relative values were calculated in distribution of serotonin receptor of 5HTR2A gene types in selected clinical groups [20,21].

The age of onset of initial manifestations and age of schizophrenia debut in childhood and adolescence were taken as a basis for recruitment of proband groups into this study. Two groups were formed according to these criteria: early-onset childhood schizophrenia (code ICD-10 - F20.xx3) – 58 (51.79%). Abiding by the core principle in psychiatry, that is clinical and psychopathological analysis, we categorized the group of children with ECS into its two known clinical variants: continuous ECS (malignant and sluggish) and paroxysmal ECS (with malignant and sluggish course), 58 probands. The second group includes probands with the process onset at the age of 14 years and older, 54 (48.21%) probands. In line with the quantitative requirements for statistical sampling, we singled out paranoid schizophrenia, F-20.0, and episodic schizophrenia with stable and progressive deficit: F-20.x1; F-20.2 according to ICD-10.

Inclusion criteria for controls (104 persons) were: vocational school or university graduates; no ancestors with schizophrenia and schizoaffective psychosis, epilepsy, behavioral disorders of unidentified etiology; age 18 to 50 years [20].

To determine the statistical significance of frequencies in the control and study samples, Pearson's criterion was used, with the p value < 0.05.

Discussion: First, we conducted an analysis to see if the differences in frequency distribution of allelic polymorphism of serotonin receptor 5HTR2A gene in the study vs. control groups are not random (Table 1).

It should be noted that the data we obtained are in agreement with the results of similar studies in the Russian population [1,11,13], obtained on Caucasian and ethnic white schizophrenic patients in the

United Kingdom [2], as well as studies conducted in Canada [15,16], where the frequency of the adverse homozygous A2A2 (χ^2) genotype carrier status [2] in these populations was significantly higher than in healthy individuals: χ^2 = 7,9; 6,26 и 6,54, respectively, vs. χ^2 = 11,25 (p<0,05) in our studies of the Kazakh population. The results of our studies showed that the odds ratio (OR) in homozygous adverse A2A2 genotype carriers increases the risk of schizophrenia in the Russian population by 1.9, in the UK population by 1.7, in the Kazakh population we studied - by 2.82 times.

Table 1 – Distribution of allele and genotypes frequencies of the serotonin 5HTR2A receptor gene in the studied groups, %

Groups	N	Genotype Frequency						Allele frequency	
		A1A1		A1A2		A2A2		pA1	pA2
		N	%	N	%	N	%	%	%
Cases	112	8	7.14 ±	59	52.68 ±	45	40.18* ±	33.48 ±	66.52* ±
Healthy	104	10	9.62 ±	74	71.15 ±	20	19.23 ±	45.19 ±	54.81 ±
Note: *- the differences are statistically significant in relation to the compared group (p < 0.05)									

The association of the adverse A2A2 genotype carriership of the 5HTR2A gene with schizophrenia determined by us gave rise to a number of studies related to clinical and psychopathological peculiarities of different clinical forms of ECS and genetic polymorphism of the gene under study. Thus, the risk of empirical development of schizophrenia for the adverse A2A2 genotype carriers in the ECS group as a whole, and for female patients in the ECS proband group could not be detected, while for male patients it equaled 2.38 (no association with the disease is assumed at OR=1).

However, it should be noted that similar studies of the Chinese, Irish, Swedish and Italian populations [22,23,24] have found no association with the rs6313 polymorphism of the 5HTR2A gene with the risk of schizophrenia. It is assumed that frequency variability of alleles and genotypes in different ethnic populations, as well as extreme clinical and genetic heterogeneity of mental diseases could be responsible for such contradictory results [1].

As presented in Table 1, the frequency of carrying a homozygous A2 minor allele in the main group was 40.18 ± 4.6%, significantly higher than the similar frequency in the healthy individuals group, 19.23 ± 3.9% (p<0.05), suggesting its possible association with the development of schizophrenia in the Kazakh population.

Apparent gender differences in schizophrenia found by researchers made them seek rationale for this, more based on clinical observations. Some researchers believe the clinical differences between schizophrenic patients of different sexes reflect a different balance of etiological factors or different frequency of subtypes (i.e. strong genetic influence in women and greater environmental dependence in men). V.M. Bashina [25], an ECS researcher, has found male predominance among patients with continuous sluggish schizophrenia and Kanner's non-progredient autism syndrome (2.9:1), and higher proportion of females among paroxysmal schizophrenia patients with low level of progredience (2.1:1) vs. 1.6:1 and 2:1, respectively, in our studies (Table 2).

The rs6313 carriers of 5HTR2A gene of malignant form of continuous schizophrenia display the disease odds ratio (OR) 2.5 times higher than controls.

The distribution of allelic polymorphism genotypes of the serotonin 5HTR2A receptor gene in the group of studied probands with continuous malignant ECS was as follows: A1A1 genotype could not be detected; A1A2 genotype identified in 21 (75%) and A2A2 genotype in 7 (25%) probands.

Table 2 – Distribution of allele and genotypes frequencies of the serotonin 5HTR2A receptor gene by gender and ESC course type, %

Genotype	Continuous ECS								Total	
	malignant				sluggish					
	m		f		m		F			
	n	%	n	%	n	%	n	%	n	%
A1A1	-		-		1	1.72±	-		1	1.72±
A1A2	15	25.86±	6	10.34±	4	6.89 0.6	1	1.72±	26	44.82±
A2A2	6	**10.34***±	1	1.72±	3	5.17 0.65	4	6.89±	14	**24.13***±
N	21	36.21±	7	12.06±	8	13.79±	5	8.62±	41	70.68±
	Paroxysmal ECS									
	malignant				sluggish				Total	
A1A1	-		2	3.44±	-		2	3.44±	4	6.89±
A1A2	1	1.72±	8	66.67±	-		-	-	9	52.94±
A2A2	2	3.44±	2	3.44±	-		-	-	4	6.89*±
N	3	5.17±	12	20.68±			2	3.44±	17	29.31±
Total	24	41.37±	19	32.756.16	8	13.79±	7	12.06±	58	51.784.72
Note: m – male; f – female; * – the differences are statistically significant in relation to the compared group ($p < 0.05$)										

The frequency of the adverse A2A2 genotype of the 5HTR2A gene was found highest in males as evidenced by a statistically significant excess of this genotype frequency in the ECS group boys when the rs6313 frequencies were compared in pairs with those of the male control group: χ^2=10,13 (p<0,05). This may indicate the possible impact of this genotype on a number of insidiously evolving negative symptoms which in early childhood would have, instead of typical presentation, the schizophrenic dysontogenesis symptomatology (in essence, these are negative symptoms), intertwined with age-related ontogenesis.

Drawing on available scientific data on the heterogeneous distribution of genders in different forms of schizophrenia, we completed a comparative analysis in the proband group based on gender differences.

Distribution of patients by age of onset of initial manifestations of schizophrenia depending on the diagnosed carriership of the serotonin 5HTR2A receptor gene genotypes is indicative of differences related to the carriership of a particular genotype (see Table 3).

For rs6313 carriers, the mean age of overt signs of schizophrenic dysontogenesis was 3±0.26 years. Proband children under study displayed reduced activity at this stage, most noticeably, listless indifferent attitude to feeding, dysontogenesis of play and speech activity, denial of games and communication, slowly breaking family ties, unresponsiveness to caress, lack of initiative in establishing communication, privatism, loss of acquired skills of speech and game activity: all negative symptomatology. The mean period of non-overt (negative symptomatology) to full blown signs of the disease equaled 4.25±0.35 years for rs6313 vs. 4.66±0.33 years for A1A2 genotype.

At the full-blown signs stage (mean age 5.5±0.43 years), the main characteristics of proband's mental state were pronounced autistic behavior, primarily its negativistic variant, unpronounced affective, neurosis-like and catatonic disorders, with symptoms of terminal states in the form of oligophreniform deficit.

It was interesting to know whether there are age differences in different variants of the ECS for rs6313 carriers. When comparing the frequency

distribution of the serotonin 5HTR2A receptor gene genotypes in continuous malignant and paroxysmal ECS for rs6313 carriers, we identified significant differences in their distribution depending on the age of probands. The age of probands, in both initial and manifest stages of development, was younger in the continuous malignant ECS, the t-criterion was 2.89 and 2.60, respectively, with 95% CI ($p<0.05$).

Table 3 – Average age and frequency distribution of the serotonin 5HTR2A receptor gene genotypes

Genotype	Continuous ECS			
	sluggish		malignant	
	i	m	i	m
A1A1	10±4.0	15±2	-	-
A1A2	6.25±1.49	11.25±2.39	3.27±0.21	6.05±0.45
A2A2	8.29±1.41	14.57±1.04	3.00±0.26	5.5±0.43
Note: i – initial period; m – manifest period				

It should be noted that clinical presentation of malignant continuous ECS has been most thoroughly described by clinical scientists, and its description in our probands did not differ much from that in children in other populations. The most common symptoms were: early on presentation of initial catatonic disorders, more often in the form of catatonic excitation (prolonged repetitive monotonous movements: rocking, bumping against objects, continuously knocking one's head against a wall, brandishing objects and monotonous unprovoked long crying, mutism), less often as stupor (in the form of «withdrawal «, «freezing») and rapidly evolving terminal state as oligophreniform deficit.

Conclusion

So, in Kazakh population we established association of the rs6313 5HT2A genetic polymorphism with ECS. In malignant form of continuous disease, we found the rs6313 5HT2A to be associated with the following: negative symptoms manifesting at the initial stage in the course of the disease; with significant predominance of males in malignant course; with younger age of probands in both initial, and manifest stages of ECS course; and with rapidly developing oligophreniform deficit in the malignant continuous ECS.

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S. Kamenova[1], A. Kondybayeva[2], J. Krupinski[3],
Zh. Dyusembaeva[4], G. Umutbaeva[4]
N. Buyrakulova[4], O. Antonyuk[4], M. Arshidinova[4], G. Karimov[4]

[1]al-Farabi Kazakh national university, Kazakhstan, Almaty, e-mail: dr.kamenova@mail.ru
[2]Asfendiyarov Kazakh national medical university,
[3]Neurology Department, Mutua de Terrassa Hospital, Terrassa, Barcelona, Spain
[4]City Clinical Hospital No7, Stroke Unit No1

CLINICAL FEATURES AND REASONS FOR THE PROGRESSION OF ISCHEMIC STROKE IN THE ACUTE PERIOD

We examined 663 patients who were admitted to the clinic by ambulance, for determine the factors of clinical deterioration and progression of ischemic stroke in the acute period of the first 24-72 hours. Among the patients received in the acute period, a fatal out come occurred in 7.23% (48) patients, men - 45.8% and women - 54.2%.

At the time of admission to the hospital, almost 96.7% of patients with acute ischemic stroke had a disorder of consciousness from stunning to coma. The most significant risk factors for the development of ischemic stroke among 663 patients were arterial hypertension - 80.1%, chronic heartfailure - 57.9%, coronary heart disease - 25.5%, atrial fibrillation - 19.5%, type 2 diabetesmellitus 12.5%. In accordance with the international criteria of TOAST (1993), pathogenetic mechanisms of the development of ischemic stroke have been determined in patients. Atherothrombotic stroke developed in 303 (45.7%), cardioembolic stroke in 185 (27.9%) patients, lacunar stroke in 167 (25.2%) patients, undefined genesis stroke in 8 (1.2%) patients.

The progression of neurological deficiency in ischemic stroke is a bad prognostic factor.

Key words: Stroke, acute period, clinical features, risk factors, aggravating factors of progression, pathogenetic subtypes of ischemic stroke.

Stroke ranks second among deaths [1-4], is the main cause of morbidity in old age [2,3] and persistent disability leading to disability [3,4].

Many researchers suggest that the frequency of stroke increases rapidly with age and doubles in each decade after the age of 55 [3,4].

The literature shows that the incidence increases in older age groups, amounting to 670-970 cases per 100,000 people per year among persons aged 65-74 [3.4.5]. In this case, ischemic stroke under 35 years of age is more common in men than in women, and in older age groups, higher incidence is observed in women [3].

The problem of a stroke is one of priority the direction ˇ social ˇ politicians in Kazakhstan. According to official statistics of the Ministry of Health of the Republic of Kazakhstan, every year more than 40 thousand cases of stroke are registered in our country, of which 5 thousand die in the acute period of 1-7 days and another 5 thousand within 30 days after discharge home [7.8].

According to Akshulakov S.K. et all. (2018) [8] The mortality rate in hospital for treated cases with ONMK (hemorrhagic ischemic strokes) in the Republic of Kazakhstan for 12 months of 2017 amounted to 13.3%, there is an increase of 0.7% compared to 2016 data. Analysis of the sex and age structure of all deaths in hospital showed that men were 54% and women were 46%. The high level of fatality is observed in the age group from 41 to 70 years of age at 60% [8].

In randomized and prospective controlled clinical studies comparing hospital treatment of stroke with alternative service, it has been proved that treatment of stroke in specialized departments improves the end result-survival [9,10]. Progression of symptoms after arrival in hospital is a serious problem for the outcome of the disease [11,12,13]. Acute stroke refers to urgent, often critical conditions requiring urgent medical care, and priority actions taken by the first hours, which are fundamental for further repair of damaged brain tissue and favorable prognosis for the patient [13]. Positive dynamics are believed to be achieved by careful monitoring and maintenance of physiological homeostasis [13,14]. Early neurological deterioration is associated with

increased mortality within 7 days of stroke onset [15,16].

It should be noted that a number of physiological functions usually involved in cerebral metabolism (control of blood pressure, heart rate, temperature, glycemia) play a key role in the development of the ischemic process, and can also exacerbate the process of brain damage during the first hours of ischemic stroke [15,16].

On the basis of the above, we focused our study on neurological deterioration during the first 24-72 hours in patients with acute ischemic stroke admitted to hospital after the onset of the first symptoms, because this time is crucial for the possible progression of brain infarction.

This work is due to the lack of research in our country related to hospital fatality and the influence of factors on the early deterioration and progression of ischemic stroke in the acute period.

Research objective is:determining clinical deterioration and progression of ischemic stroke in the acute period of the first 24-72 hours.

Our tasks included identifying possible mechanisms and causes leading to ischemic stroke, as well as studying factors associated with progression and early neurological deterioration in the acute stroke phase.

Material and methods:

This prospective study was conducted for 10 months and included 663 patients with acute ischemic stroke who were hospitalized in the city clinical hospital № 7 of Almaty.

We compared two groups of patients with ischemic stroke: group-1 (n = 615) with a favorable prognosis, and group-2 with an unfavourable fatal outcome (n = 48) in the acute stroke period. Detailed clinical, laboratory and instrumental examination were carried out according to clinical protocols of the Republican Center for Health Development of the Ministry of Health of the Republic of Kazakhstan from 2016, as well as algorithms of actions and diagnostic criteria at the stage of reception rest, intensive care unit, neuroreanimation department.

We compared demographic characteristics, risk predictors, laboratory-instrumental examination data, comorbid diseases in patients diagnosed with ischemic stroke in the acute period of both groups.

The study was approved by an ethical committee. The diagnosis of stroke was based on ICD-10, WHO 1992.

Criteria for inclusion in the study

Age of patients more than 25 years

For the first time the arisen ischemic stroke aterotromboticheskу, kardioembolicheskу or lacunary (the 1st day), confirmed with neurovisualization methods.

the informed consent to a research was signed by All patients or their lawful representatives.

Criteria for exclusion from study

the Ischemic stroke with hemorrhagic treatment;

Subarakhnoidalny hemorrhage.

System diseases of connecting fabric;

Existence in the anamnesis of oncological diseases,

Existence in the anamnesis of tuberculosis,

Existence in the anamnesis of alcohol or drug addiction, mental diseases;

Thromboses of deep veins.

Hereditary trombofiliya;

Absence with own hand signed (or other independent witness in the absence of physical capacity of signing by the patient) forms of the informed consent.

Among our patients, only 1.04% of patients received treatment with recombinant tissue plasminogen activator (rtPA), of which a positive result was observed in only 3 cases. These patients were excluded from the study to ensure homogeneity of the group.

The diagnostic process was organized as much as possible in the reception department and included the following elements: collection of complaints and history, general physical examination, neurological examination with auxiliary evaluation scales, emergency laboratory (clinical, biochemical analyses, coagulogram) examinations, electrocardiogram (ECG) and X-ray examination of the chest, if necessary, consultations of specialists. Mandatory emergency specific studies: CT or MRI, transcranial duplex Doppler study.

According to the clinical protocol, mandatory scheduled examinations were carried out during the first 24 hours of hospitalization, if necessary - in dynamics.

In the work we used the following estimated scales of neurological status of patients:

for assessment of level of consciousness used a scale of a coma of Glasgow,

the neurologic status with assessment of neurologic deficiency was estimated on NIHSS scale

the standardized screening testing of function of swallowing

the modified scale of Renkina-MRS

Early progression of symptoms was defined as increasing the NIHSS score by two or more points (or stroke-related fatality) between arrival and day 3. According to the internationally accepted definition, we investigated the deterioration within 24-72 hours after the arrival of one of the following NIHSS points: level of consciousness, swallowing, speech, movement of eyeballs, motor function of the arm and leg. Patients with early neurological impairment were compared to patients with unchanged or improved NIHSS scores [17].

Statistical methods.

Data processing was done using Microsoft ® Office 's Excel 2016 Tabular Processor Data Analysis Suite, IBM SPSS Statistics version 23 for Windows.

Results: In this study, we did not observe sexual differences among the hospitalized 663 patients due to ischemic stroke, there were 52.9% (351) of women and 47.1% (312) of men. The average age of patients was 62, 5 ± 5.6 years for men and 71, 4 ± 5.1 for women.

The diagram clearly shows the prevalence of ischemic stroke at the age of 60-80.

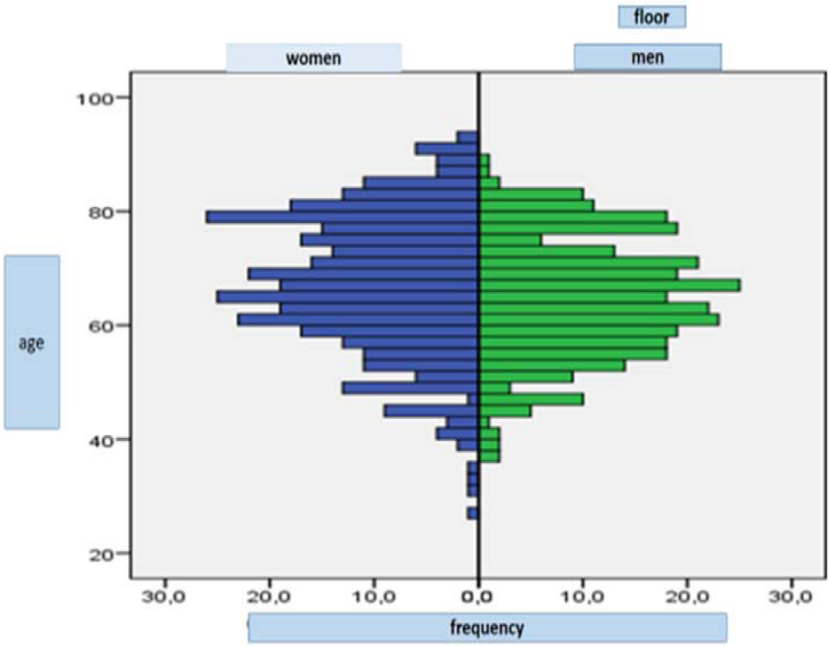

Figure 1 – Description of patients with ischemic stroke by sex and age. (Pareto's chart)

From the total number of patients with an ischemic stroke (663) almost at 7.23% (48) patients in the sharp period there came the lethal outcome, the number of men of 45.8% and women of 54.2%.

The most significant risk factors for ischemic stroke among 663 patients were arterial hypertension - 80.1%, chronic heart failure - 57.9%, ischemic heart disease - 25.5%, atrial fibrillation -19.5%, type 2 diabetes mellitus - 12.5%. In history, 10.8% of patients had a myocardial infarction. In 8.7% of patients with stroke development was preceded by transitionally ischemic attack. Chronic obstructive pulmonary disease was detected in 1.7% of patients, chronic kidney disease in 0.5%.

In accordance with the international criteria of TOAST (1993), pathogenetic mechanisms for the development of ischemic stroke have been determined in patients. Atherotrombotic stroke developed in 303 (45.7%), cardioembolic stroke in 185 (27.9%) patients, lacunar stroke or small vascular disease in 167 (25.2%) patients, undefined genesis stroke in 8 (1.2%) patients.

In the analysis of neurological status of patients, various degrees of expression of motor and sensitive disorders, brain nerve lesions, symptoms of oral automatism, bulbar and pseudobulbar syndrome, dysphonia, dysarthria, speech disorders, gnosis and praxis disorders, depression, etc.

At the time of admission to hospital, almost 96.7% of patients in acute ischemic stroke had a disorder of consciousness from deafening to coma. The average Glasgow coma score was 10.9 ± 2.6 (Table 1).

Table 1 – Assessment of consciousness level in patients with different pathogenetic subtypes of ischemic stroke.

subtypes of an ischemic stroke	n=663	Scale of a coma of Glasgow Points + Averagedeviation	Standarderror	95% ConfidenceInterval for Average
Aterotrombotic	303	10±0,656	0,038	9-12 points
Cardioembolic	185	8 ±0,813	0,060	4-10 points
Lacunar	167	14±0,459	0,036	12-14 points
Uncertaingenesis	8	9±0,354	0,125	4-10 points
Intotal	663	11±0,827	0,032	9-13 points

The most severe patients with consciousness suppression at admission were identified with cardioembolic stroke (8 0.813) and uncertain pathogenetic subtype (9 0.354) points.

The determination of the severity of ischemic stroke conducted on the NIHSS score scale showed that the severity of neurological symptoms averaged 12.0 ± 6.8 points when admitted. Of the total number of patients with ischemic stroke, a mild degree of severity on the NIHSS scale was found in 57 (8.6%) patients, an average degree in 460 (69.4%), a severe degree in 88 (13.3%), an extremely severe degree of severity was found in 58 (8.7%) patients.

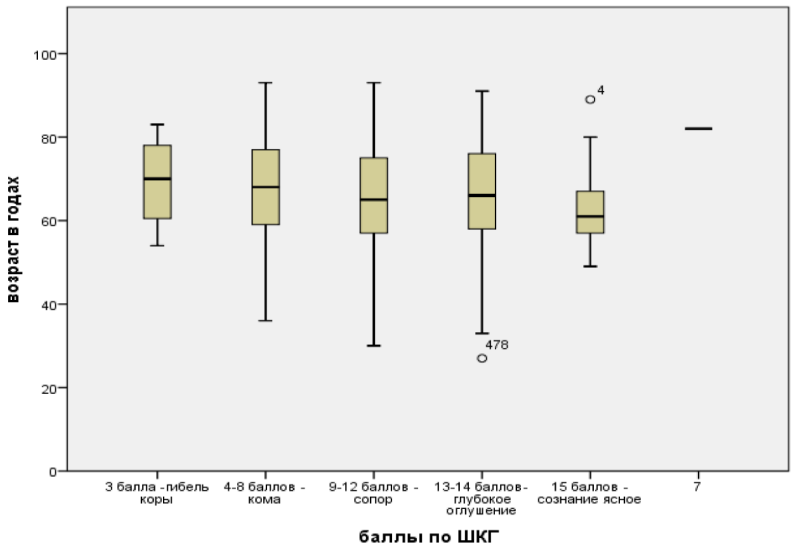

Figure 2 – Description of the level of consciousness of patients according to age (Drawer chart. IBM SPSS Statistics 23,0).

When admitted, patients with cardioembolic stroke were characterized by neurological disorders over the age of 65. Patients with lacunar stroke had less pronounced neurological disorders compared to patients in the other groups. But in lacunar stroke patients, motor aphasia was reliably more common, which exacerbated disability.

Analysis of early fatality showed that a statistically significant indicator in age characteristics among the examined group-2 patients was between 65 and 79 years of age ($p < 0.001$). Of these, 64.6% (31) died in the first day (up to 24 hours) of hospital stay. In 16.7% (8) patients mortality occurred in the following 3 days (72 hours), in 18.75% (9) during the first week. The average age of patients in group-2 with adverse mortality was 68, 3 ± 12.0, including in females 75, 6 ± 5.8 and in males 67, 6 ± 3.2.

At the time of admission, all patients in Group-2 with NIHSS mortality were rated as a severe stroke (21 to 42 points). We have obtained a statistically

significant difference in the NIHSS score when arriving in the groups being compared. It was in these patients in group-2 with an adverse outcome that the deterioration continued to increase.

Comparison of demographic and clinical data of both groups of patients shows that when comparing groups by age and sex were comparable. The median age of group-1 was 65.0 11.7 and group-2 was 68.3 12.0 years, respectively. Women in the 1-group had 53.8% in the second group 54.1%, men 46.1% and 45.8% respectively. In group 1, women under the age of 39 and over the age of 90 predominated.

Cardioembolicpathogenetic subtype of ischemic stroke occurred more frequently 56.3% (27) in group-2 with fatal outcome than in the first group - 25.7% (158), respectively ($p < 0.001$).

In group-2 with fatal outcome, atherotrombotic subtype of ischemic stroke was detected in 43.8% (21) and 45.9% (282) in the opposite group. Lacunar subtype 27.2% (167) and uncertain genesis 1.3% (8) is diagnosed in group-1 only.

Statistically significant progression of severity of neurological symptoms on Glasgow coma scale and NIHSS scale, and functional disorders on Rankin scale in the second group was revealed when comparing average values and standard deviations with the first ($p < 0.001$).

Higher scores of functional gross life disorders with a rating of 5 on the Rankin scale were mRS observed in 77.8% (35) of 2-group patients on admission, compared to 1-group where there were mild and moderate life limitations in 84.0% (517) patients. Only 15.9% (98) had a score of 4-5 ($p = 0.0001$).

An assessment of the severity of ischemic stroke on the NIHSS scale at admission, during the first hours after symptoms appeared, showed that the severity of neurological symptoms averaged 11.1 5.9 points in group-1 and 22.5 7.3 points in group-2s, respectively ($p = 0.0001$). The progression of neurological symptoms is more evident in the group with cardioembolic stroke and atherotromboticpathogenetic subtypes of ischemic stroke (Figure 3).

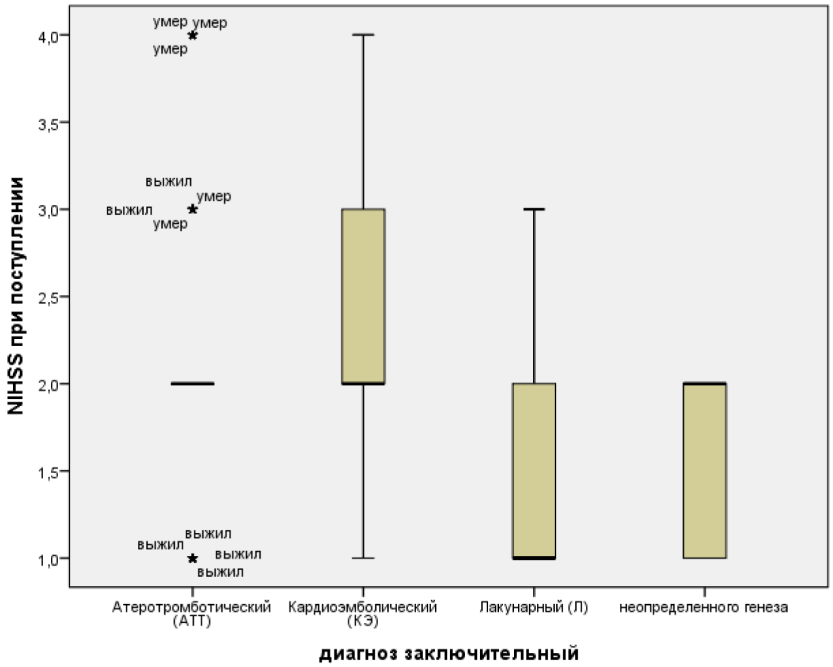

Figure 3 – Equalization of the degree of stroke severity on the NIHSS scale, in patients with different pathogenetic subtypes of ischemic stroke in both groups (Box diagram. IBM SPSS Statistics 23,0).

t seems essential to note that the results of our study confirmed the importance of assessing early neurological deterioration. After 24 hours in hospital, the NIHSS parameters increased to 11.5 5.6 and 26.5 7.0 points in the compared groups, respectively ($p < 0.001$).

The progressing course of a stroke which is followed by increase of neurologic symptomatology within 24-72 hours on NIHSS scale on ≥1 points was observed at 245 (36.8%), at 418 (63.1%) patients the neurologic status remained stabler in the same hours.

And among group-2 with a lethal outcome 42 (87.5%) patients had early neurologic deterioration (assessment of NIHSS of ≥1 point), within the first 24 hours after the beginning of a stroke, in opposite group 202 (32.8%) (p<0.001). The degree of progression on the NIHSS scale after 72 hours in hospital is significantly more often detected in the same group p < 0.001 (X ² = -8.035).

When assessing neurological status in group-2, speech disorder, paresis 7 and 12 of a pair of cranial nerves were more often detected. It has been found that impairment of swallowing function is most common in patients of group-2 in 75% (36), in the opposite group 0.7% (4) p < 0.001 * *

When assessing neurological symptoms after 24-72 hours in hospital. In the second group, there was a significant increase in focal and global symptoms, including a change in consciousness (to deep coma level) p < 0.001, X ² = -16.745 (equal).

Statistically significant indicators of adverse outcome were observed at delivery of patients later than 4 hours < 0.001. Late delivery of patients to hospital is associated with severe stroke, which is rated on the NIHSS scale as severe stroke (21 to 42 points).

Thus, the most important factors directly related to high mortality in acute ischemic stroke (24-72 hours) are (p < 0.001): the age of patients over 67 years. Later admission to hospital from the moment of stroke start 59.2% against 32.3% group with favorable outcome (p < 0.001).

Table 2 – Assessment of risk factors influence in acute period of ischemic stroke

RiskFactors	Group-1 (*n* = 615) *n* (%)	Group-2 (*n* =48) *n* (%)	X²	*p-value*
Arterialhypertension	491 (79.8)	40 (83.3)	0.157	0.692
Chronicheartfailure	355 (57,7%)	29(60,4%)	0.163	0.704
Myocardialinfarction	65 (10,5)	7 (14,5)	0.192	0.685
Fibrillationofauricles	107 (17.4)	22 (45.8)	21.194 X²	<0.001
Coronaryheartdisease	133 (21.6)	36 (75%)	64.004 X²	<0.001
Type 2 diabetesmellitus	67 (10.9)	16 (33.3)	18.473 X²	<0.001
Chronicobstructivepulmonarydisease	6 (1.0)	5 (10.4)		0.001**
Chronicdiseaseofkidneys	2 (0.3)	1 (2.1)		0.202**

* t-test
**Exact criterion of Fischer
Average - t-test comparison for independent groups (quantitative data), with variance inequality
Sharecomparison - X ² test

is important to note that atrial fibrillation, ischemic heart disease, type 2 diabetes mellitus, chronic obstructive pulmonary disease were significantly more common (p < 0.001), CBP (p = 0.202 * *) causes of deterioration resulting in death (Table 2).

When comparing the incidence of risk factors, diastolic blood pressure was equally encountered in both groups without a significant difference in the group of survivors of 91.7 9.5mHg. Article and in the opposite group 93.1 16.0

Systolic blood pressure was significantly higher in the group with a fatal average of 172.7 44.27 mmHg.

We have identified a link between severe stroke (NIHSS 16-42 points) and high systolic blood pressure of more than 180 mm Hg in almost 50% of patients with death in the acute stroke period. When admitted to hospital in the same group of patients in 18.6% (9) cases, severe stroke was associated with low systolic blood pressure less than 90 mm Hg and low diastolic blood pressure less than 60 mm Hg.

In group-1, the average systolic blood pressure in the patients was 167.1 31.12 and in 57.7% of the patients, the systolic blood pressure was below 180 mm Hg. We traced arterial hypertension in groups with different ischemic stroke subtypes to 95% confidence interval for mean value (Table 3).

Table 3 – Blood pressure at various pathogenetic subtypes of ischemic stroke

ABP	pathogenetic subtypes of ischemic stroke	n=663	BPmmHg. mean deviation ± standard error	(95%confidence interval)
CSBD	Aterotrombotic	303	158,45±26,387	155,47-161,43
	Cardioembolic	185	192,32±28,236	188,23-166,42
	Lacunar	166	201,57±17,649	198,86-204,27
	Uncertaingenesis	8	153,75±26,152	131,89-175,61
Intotal		663	167,49±31,950	165,05-169,93
ДДВР	Aterotrombotic	303	91,01±8,634	90,04-91,99
	Cardioembolic	185	89,43±13,056	87,54-91,33
	Lacunar	167	95,93±7,457	94,79-97,07
	Uncertaingenesis	8	92,50±8,864	85,09-99,91
Intotal		663	91,83±10,115	91,06-92,60

Patients with the highest and lowest blood pressure levels in the first 24 hours after a stroke were more likely to have early neurological impairment and lethal prognosis. Patients with systolic artery pressure at intake below 120 mm Hg had an increased risk of death compared to patients with AAD between 140-150 mm Hg.

There is also a link between high levels of systolic artel pressure at intake and mortality only in cardioembolic, and low numbers of systolic artel pressure at atherotrombotic subtypes of ischemic stroke.

According to the literature, the increase in blood pressure after ischemic stroke is assumed to be an adaptive response that helps to maintain cerebral blood flow and perfusion of the ischemic half, despite the loss of cerebral autoregulation. Conversely, it is believed that an excessive increase in blood pressure can lead to neurological deterioration from the hemorrhagic transformation, especially in the presence of a damaged blood-brain barrier [10,13,14].

Thus, the aggravating factors of progression in the acute period of ischemic stroke-related to early mortality are concomitant diseases: uncontrolled arterial hypertension, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease.

All patients in the first day of the disease to verify the diagnosis were subjected to CT or MRI of the brain, at the same time the localization and size of the focus were taken into account (Table 3). It was established that the severity of ischemic stroke of the patient was in direct statistically significant relation with the size of the focus of the injury ($p < 0.001$).

Table 4 – Size of the focus in the groups being compared

Focus size	group 1 n=615	group 2 n=48	X^2	p-value
No heart attack, but clinical symptoms persist < 24 hours	34 (5.5%)	0 (0.0%)		
Infarction< 1.5 cmindiameter	209 (34.0%)	2 (4.2%)		<0.001
Infarction up to 1/3 of the territory of the middle cerebral artery or 1.5-5 cm in diameter	313 (50.9%)	3 (6.3%)		<0.001
Infarction 1/3-2/3 middle cerebral artery or > 5 cm, without the effect of occupied area	44 (7.2%)	20 (41.7%)	212.7 (X^2)	<0.001
Infarction 2/3 of middle cerebral artery territory or > 5 cm in diameter plus area effect	15 (2.4%)	23 (47.9%)		<0.001

Intracranial hypertension syndrome, expression of brain edema and stroke were objectified for MRI or CT at admission (within 24 hours) or during admission to hospital in 102 patients. Intracranial hypertension was observed at extensive strokes (the diameter of the focus was more than 5 cm). The large centers with a diameter more than 5 cm are revealed in the first group in 9.6% (59) cases from them 2.4% (15) with perifocal hypostasis, in group-2 with a lethal outcome of 89.6% (43), and with perifocal hypostasis was 23 (47.9%) patients ($p < 0.001$). The centers of the average sizes also prevailed in the first group of 50.9% (313) against the second group of 6.3% (3). The lacunary centers <1.5 cm in the diameter are revealed in the first group in 34.0% (209). In the second group lacunar foci were found in 4.2% (2) both foci were dissected in the brain stem ($p < 0.001$).

Swelling of the brain, accompanied by compression of the brain stem, led to death.

Arterial hypertension and hemorrhagic transformation on MRI (in patients with cardioembolic stroke) contributed to the severity of the prognosis.

In the course of the study, we considered it important to carry out an analysis of the distribution of patients on the localization of the heart of infarction (MRI) and the localization of the affected arteries according to the UZDG, with the possibility to determine the dependence of the progression of neurological symptoms in the acute period of ischemic stroke. There were no significant differences in the degree of progression of neurological symptoms and localisation of the focus and basin of the affected arteries.

Cardioembolic stroke is a severe condition due to the large size of the heart attack, with a high level of intra-hospital fatality (56.3%) and significant neurological dysfunction with more severe life disorders with a rating of 5 on the Rankin mRS scale.

Brain swelling is the leading cause of early deterioration and death in patients with large heart attacks.

Our study found that dangerous for hospital mortality in acute period of ischemic stroke, brain swelling usually develops for the first seven days after hospitalization, but 37.5% (18) of patients died in the first 24 hours after symptoms appear.

As a result of the single-factor analysis, it was found that the most significant predictors of deterioration with an increased risk factor of hospital mortality in the acute period of ischemic stroke at admission are: impaired swallowing function, impaired breathing function (32 patients were on the spark ventilation of the lungs), depressed consciousness on the Glasgow coma scale up to 4-10 points. Patients with cardioembolic subtype under 67 years of age, with high systolic arderial pressure (above 160 mmHg), and patients with atherotrombotic ischemic stroke subtype over 65 years of age ($p < 0.000$) with low systolic blood pressure (below 118 mmHg).

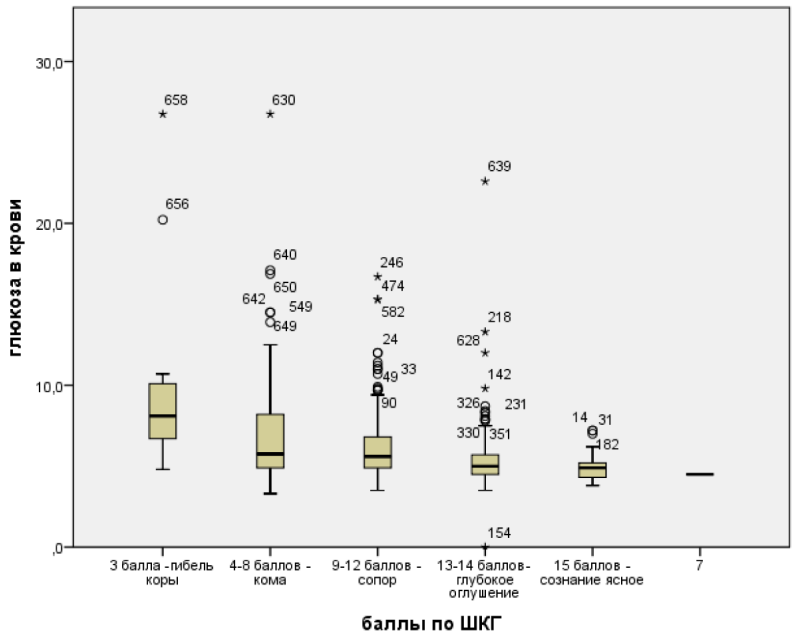

Figure 4 – Glucose levels in patients with different levels of consciousness (Drawer chart. IBM SPSS Statistics 23,0).

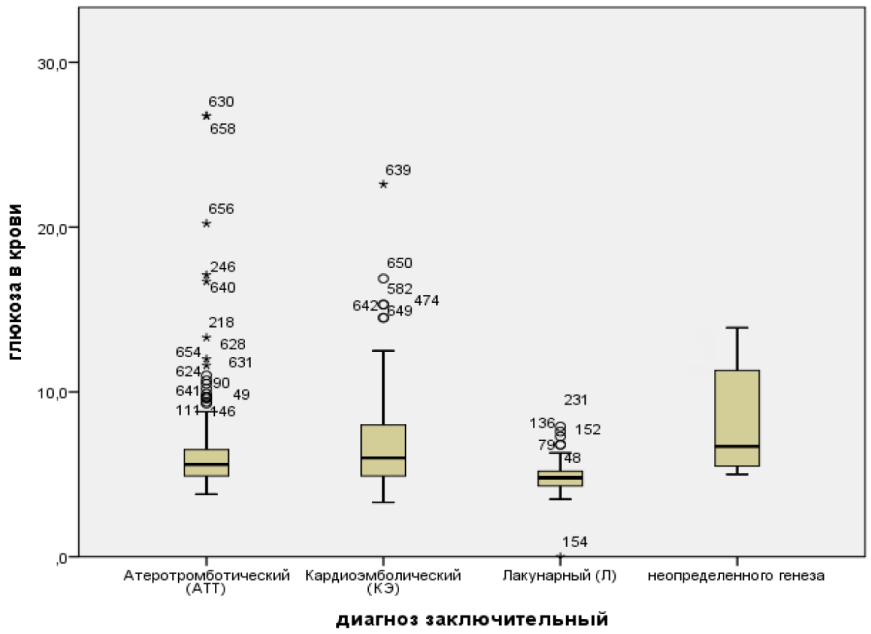

Figure 5 – Glucose levels in patients with different pathogenetic subtype of AI (Box diagram. IBM SPSS Statistics 23,0).

Data from laboratory indicators (general blood test, blood glucose and coagulogram) of patients of two observation groups showed that hyperglycemia was significantly more common in the second group than in the first group $p < 0.001$. Hyperglycemia is detected in acute period in patients with depressed consciousness by Glasgow coma scale up to 4-10 points, and reliably more often in patients with cardioembolic and atherotrombotic subtypes of ischemic stroke (Fig.4.5)

Thus, aggravating factors of progression in the acute period are: late delivery of patients to hospital, age over 65 years, swallowing disorders, concomitant diseases of atrial fibrylation, ischemic heart disease, chronic heart failure, chronic obstructive pulmonary disease, diabetes mellitus of the second type, chronic kidney disease, as well as hyperglycemia, size of infarction focus more than 5 cm in diameter with the effect of occupied area.

The progression of neurological deficiency in ischemic stroke is a poor prognostic factor. Worsening acute stroke in the early stages of its development 24-72 hours is common and has potentially serious consequences for the patient. Progression increases fatality and disability. Our study suggests that it is particularly important in the acute stroke period to draw the attention of medical staff to these factors in order to stabilize the progression of neurological symptoms.

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Abdugafarova Kibriyanur[2], Sultan Mussakhan[1], Dias Tastanbekov[1,2]

[1]al-Farabi Kazakh national university, Kazakhstan, Almaty
[2]Akyl-D LTD, Kazakhstan, Almaty, e-mail tastanbekovdb@gmail.com

DEVELOPING THE METHOD OF GENERATED OZONE AMOUNT REDUCTION IN DOMESTIC INDOOR AIR PURIFIERS

Air quality hugely affects human wellbeing, the fundamental wellsprings of contamination of which are strong suspended particles (of different sizes) and vaporous toxins (VOCs, NOx, SOx, scents). Many respiratory diseases are related to pollution of air, the heavy utilization of synthetic chemicals, the uncontrolled utilization of medications, different viral diseases, the development of new allergens and various different components. The use of indoor cleaning products and air fresheners can cause exposure to secondary air pollutants through inhalation of cleaning staff and building occupants. Because of Almaty air quality citizens often use devices for indoor air purification. Some of such devices remove VOCs with aid of catalytic organics decomposition under UV. Despite efficient organics decomposition, as side effect UV causes ozone formation which is harmful if exceeds certain concentration (ambient air standard).Ozone is usually present indoors due to external air intrusion. Thus, reduction of generated ozone concentration is an urgent task.

Key words: air quality, ozone removal, catalytic decomposition, photocatalysis, airborne disease.

Almaty air quality is shown in the table below [1]

Table 1 – Air pollution in Almaty (maximum single concentration)

Almaty districts	CO, mg/m_3	Lead, mg/m_3	NO_2, mg/m^3	NO, mg/m^3	O_3 mg/m^3	SO_2, mg/m^3
Almaly	4.61	0.00015	0.08	0.27	0.52	0.123
Zhetysu	5.2	0.004	0.07	0.26	0.52	0.23
Turksib	3.8	0.0005	0.014	0.17	0.46	0.16

Problem of air pollution caused increase of popularity of air purifiers. The photocatalytic oxidation (PCO) used in them is considered one of the economically feasible methods of purification from organic pollutants in comparison with other purification technologies, such as adsorption, biofiltration or thermocatalysis. FCO protects health in the long run by providing clean air that is almost completely free of pathogens and mold spores.

Since almost every existing air purifiers use UV-lamp as one of the many purification steps, problem of ozone generation is very important and needs to be taken into account.

Issue of air contamination caused increment of prominence of air purifiers. The photocatalytic oxidation (PCO) utilized in them is viewed as one of the financially attainable strategies for purging from natural poisons in examination with other cleansing advances, for example, adsorption, biofiltration or thermocatalysis. PCO ensures wellbeing over the long haul by giving clean air that is totally liberated from pathogens and shape spores.

Notwithstanding, air purifiers dependent on UV-lights produce ozone (O_3) during activity, either purposefully or as a side-effect of air ionization. This is a genuine concern, in light of the fact that O_3 is a criteria air poison managed by wellbeing related government and state benchmarks. Ozone-driven science is a wellspring of indoor auxiliary contaminations of potential wellbeing concern. This examination explores how measure of shaped ozone

can be wiped out utilizing CuO impetus in type of work under direct UV-light.

Since pretty much every current air purifiers use UV-light as one of the numerous decontamination steps, issue of ozone age is significant and should be considered.

Introduction

The use of indoor cleaning products and air fresheners can cause exposure to secondary air pollutants through inhalation of cleaning staff and building occupants.

Ozone is usually present indoors due to external air intrusion. There are also indoor sources of ozone for some office appliances and air purifiers. Indoor air purification has gained widespread popularity in recent years due to increasing air pollution issues in urban areas, with a broad variety of indoor air purifiers available to the public. Odorous volatile organic compounds (VOCs), dust, pollens, and airborne contaminants are the primary targets of indoor air purification, which are thought to intensify respiratory health problems. There are three main types of air purifiers, from an operational point of view:

(1) air filtration, (2) air ionization, and (3) ozonolysis of air impurities.

Household use of some air ionization and air purifiers for ozonolysis has raised serious concerns, as they emit ozone (O3), an air pollutant standard, either as a result of air ionization or deliberately. Depending on the configuration, some ionic air purifiers will transmit O3 per hour at a rate of a couple of milligrams of O3, which is virtually similar to the O3 measurement transmitted during continuous operation by dry-process scanners. Ozonolysis air purifiers usually generate several hundred milligrams of O3 per hour indoor air with a target of oxidizing VOCs. O3 interacts with most saturated VOCs extremely slowly though. Half-lives of popular VOCs found indoors are days at 100 ppb of O3, or even years. O3 reacts much more easily with VOCs containing unsaturated carbon-carbon bonds found in cooking oils, air fresheners, cleaning items, and so on than with other polycyclic aromatic compounds contained in household materials (e.g., pigment coloring in carpets). However, these reactions, as stable products, produce carboxylic acids, epoxides, organic peroxides, aldehydes, and ketones, some of which may have adverse health effects. This is why we had to decompose ozone to natural oxygen gas (dioxygen).

Ozone decomposition to dioxygen is a thermodynamically preferred cycle with a reaction heat of somewhere = -138 kJ / mol and a free reaction energy of somewhere = -163 kJ / mol. However, ozone is thermally stable up to 523 K, so it requires catalysts to decompose at lower temperatures.

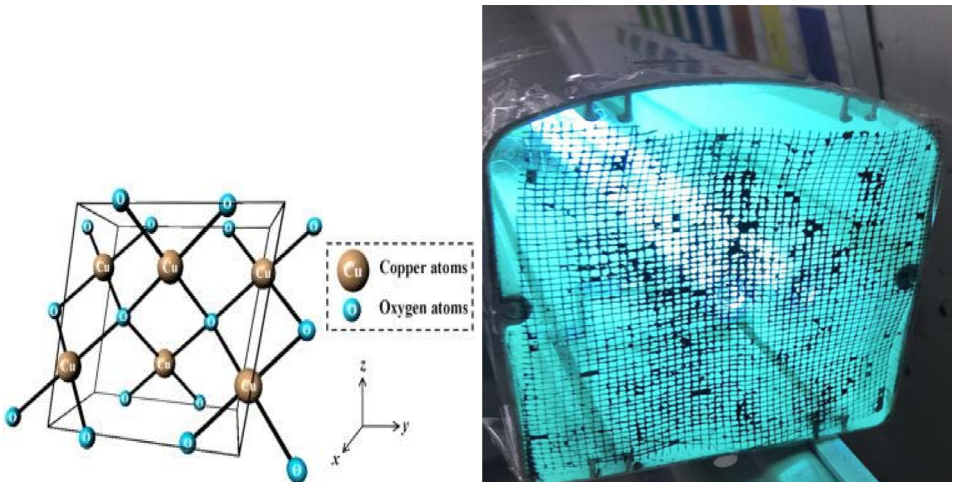
CuO is known to be catalyst for ozone decomposition under UV light. This property can be used to eliminate generated ozone. In order to increase contact surface and not to hinder air flow we used CuO immobilised on a mesh.

Goal of the project

The determination of concentrations of ozone in air in the range of a few parts per million has become an increasingly important problem as a result of current toxicological and air pollution studies. Ozone was producing as a by product, which is obviously was bad because our household air purifier must clean air and not produce waste products. At the beginning we needed to calculate the amount of ozone our equipment generated, and then recheck the difference with the equipment with presence of CuO catalyst.

The chemical iodide methods tended to be among the most effective, and therefore were chosen for investigation. Thanks to its relatively weak, pH-independent RedOx potential, and iodine / iodide reversibility reaction. Iodometry can be used to assess both the amount of reducing agents (by direct iodine titration) and the amount of oxidizing agents (by thiosulfate titration). The same simple and accurate end point detection system, based on the blue starch complex, can be used in all cases.

Many investigators have used iodometric methods for the determination of concentrations of ozone in the range of several percent by volume and higher. They have investigated the stoichiometry by comparison of the amounts of iodine liberated with the amounts of ozone determined by physical measurements of gas density or pressure change.



structure of CuO B) CuO mesh used as a catalyst for ozone decomposition

Ozone Procedures Reagents

1.Potassium iodide solution. Dissolve 10.0 grams KI into 100 mLs demineralized water. C = N/V= 10/(39+ 127)/0,1=0,6024 mole/l
2.the (65%) concentrated sulfuric acid reagent 3.Starch indicator.
4.Sodium thiosulfate solution (0.1N).
5.Sodium pyrophosphate (decahydrate), 5% solution.

Apparatus

1.Analytical balance (+/- 0.1 mg/L)
2.Small weighing bottle (< 5 mLs)
3.250 mL Erlenmeyer flask
4.50 mL buret
5.Conical flask for titration per 100 ml - 2 pcs.
6.Rubber pear or pipettor - 1 pc
7. 250-mL Beaker.
8.250-mL Graduated cylinder.
9.10 ml aliquot pipette - 1 pc.
10.Small funnel for a burette - 1 pc.
11.A glass under a burette of 50 - 100 ml - 1 pc.

MEASUREMENTS

Iodine liberated by the ozone was measured titrimetrically. Distilled water was used in the reference tube. Titrations were made with 0.1 N sodium thiosulfate in a semi-micro buret and using a visual endpoint with starch indicator.

PROCEDURE AND STANDARDIZATION

For the use with the alkaline reagent was prepared as follows: The strong stock solution of potassium iodate (0.2973 gram per liter) was diluted: with distilled water to give a dilute standard of which 1 ml was equivalent to 105.8 micrograms

I_2. Aliquots of 0.1 to 0.5 ml of this dilute standard were diluted to 10 ml , acidified via HCl.

STOICHIOMETRY

It thus seems evident that the actual reaction between the ozone and the iodide must have a different stoichiometry in alkaline solution.

The reactions :

$$(1)\ 0_3 + 2H^+ + 2I^- \rightarrow 40_2 + H_2O + I_2$$

In weak alkali, the equivalent reactions for the same stoichiometry are commonly given as:

$$(2)\ 30_3 + I^- \rightarrow 30_2 + I_2 + 0_3$$

followed upon acidification by:

$$(3)\ 0_3 + 6H^+ + 6I^- \rightarrow 3I_2 + 3H_20$$

We found experimental evidence to indicate that in strong alkali this pattern is not followed. When portions of samples in reagent I_2 were acidified to pH 6.2 with solid boric acid, the iodine released was approximately 50 % of that resulting from the usual acidification to pH 2. No iodine mas obtained from the reagent I_2 with added iodate, upon acidification with boric acid.

Reversible iodine/iodide reaction mentioned above is

$$2I^- \leftrightarrow I2 + 2e^-$$

and obviously whether it should be treated as oxidation with iodine or reduction with iodides depends on the other redox system involved.Second important reaction used in the iodometry is reduction of iodine with thiosulfate:

$$S_2O_3^{2-} + I_2 \rightarrow S_4O_6^{2-} + 2I^-$$

In the case of both reactions it is better to avoid low pH. Thiosulfate is unstable in the presence of acids, and iodides in low pH can be oxidized by air oxygen to iodine. Both processes can be source of titration errors. Iodine is very weakly soluble in the water, and can be easily lost from the solution due to its volatility. However, in the presence of excess iodides iodine creates I_3^- ions. This lowers free iodine concentration and such solutions are stable enough to be used in lab practice. Still, we should remember that their shelf life is relatively short (they should be kept tightly closed in dark brown bottles, and standardized every few weeks). Iodine solutions are prepared dissolving elemental iodine directly in the iodides solution. Elemental iodine can be prepared very pure through sublimation, but because of its high volatility it is difficult to weight. Thus use of iodine as a standard substance, although possible, is not easy nor recommended. Iodine solutions can be easily normalized against arsenic (III) oxide (As_2O_3) or sodium thiosulfate solution.

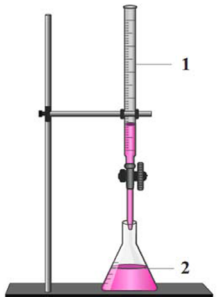
It is also possible to prepare iodine solutions mixing potassium iodide with potassium iodate in the presence of strong acid:

$$5I^- + IO_3^- + 6H+ \rightarrow 3I_2 + 3H_2O$$

Experimental Section

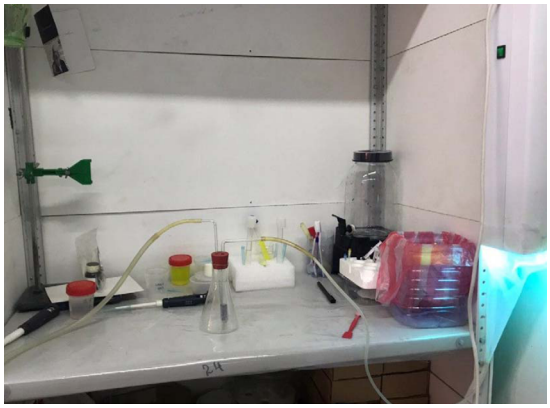
This section summarizes key features of the experimental methods.

Experimental Procedure.



1. $Na_2S_2O_3$ 0,1M

2. mixture of titrant with generated I_2



Design of experiment:

$$O_2 + O \rightarrow O_3 \text{ (under direct UV-LIGHT)}$$
$$O_3\ (g) + 2KI\ (aq) + H_2SO_4\ (aq) \rightarrow I_2\ (s) + K_2SO_4\ (s) + O_2\ (g) + H_2O\ (l)$$
$$3.\ I_2 + 2Na_2S_2O_3 \text{-> } 2NaI + Na_2S_4O_6$$

Results and Discussion

Equivalent weight of $Na_2S_2O_3$= 158/2=79 equivalent g/mole

$$C_1V_1=C_2V_2$$

Titration without CuO catalyst

v1= 4,60 ml
v2=4,,62 ml
v3=4,61 ml
v average=4,61 ml

Titration in the presence of CuO catalyst

v1=4,12 ml
v2=4,13 ml
v3=4,125ml
v average=4,125 ml

We calculated the mass of generated O_3 without the use of catalyst mesh

$m(O_3)=V(Na_2S_2O_3)*$ $C(Na_2S_2O_3)*Meq(O_3)*$ V volumetric flask/ V aliquot * 1000 = 0,1* 4,61 *24*100/1000*10=0,11 g in 1 dm^3
= 0,11 mg per 1 m^3

This amount is higher than maximum permissible concentration. Whereas, the maximum permissible concentration of ozone in the air of the working area is - 0.1 mg / m3.

However, when we used our CuO mesh catalyst, mass of generated O_3 significantly decreased

$m(O_3)=V(Na_2S_2O_3)*$ $C(Na_2S_2O_3)*Meq(O_3)*$ V volumetric flask/ V aliquot * 1000= 0,1*4,125*24*100/1000*10=0,099g in 1 dm^3
= 0,099 mg per 1 m^3

Our result fits the standards.

Conclusion

Everyone are at risk from air pollution indoors. Air pollution issue has caused increased use of air purifiers. In activity, however, air purifiers based on UV-lamps emit ozone (O3), either deliberately or as

an air ionization byproduct. This is a serious concern, because O3 is an air pollutant already governed by federal and state health-related regulations. Ozone-driven chemistry is a source of possible health concern in indoor secondary contaminants. This study investigated how to remove the amount of ozone produced using the CuO catalyst in the form of mesh under direct UV-light.

An overview of the patent literature discusses the structure, preparation methods, and efficiency of current ozone decomposition catalysts. Catalysts are found to consist of noble metals or metal oxides backed by a large supporting surface layer. We chose CuO as a catalyst, because it is considered to be a catalyst under UV light for ozone decomposition. This property is used to remove the ozone that is produced.

Without the use of CuO catalyst our household air purifier based on UV- light generated excess amount of ozone which exceeded the maximum permissible concentration standards. After performing experiments with CuO mesh we obtained permissible results.

Since practically every present air purifiers use UV-light as one of the various purification steps, issue of ozone is noteworthy and ought to be considered.

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Saidkhodjaeva Saida

PhD, Associate Professor, Department of Neurology
Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan
e-mail: dr.saida25@gmail.com

INNOVATIVE NEURO REHABILITATION OF AGGRESSIVE BEHAVIOR AND COGNITIVE ABILITIES OF CHILDREN WITH HIV-ENCEPHALOPATHY

The chronic medical conditions in the pediatric population pose a range of potential cognitive and emotional - behavioral challenges not only to the child, but also to the family members and health care providers. Neurological sequels and neurocognitive disorders in infected children are due to static or progressive encephalopathy that influences different domains such as speech and language, memory, learning, information processing and motor functioning. This paper comprehensively reviews the issues of personal observations and carried out modern psycho-neurological investigations of 170 children infected with HIV . The necessity of using the innovative NIRVANA neurorehabilitation system based on immersing the patient into virtual reality and game motivation, which contributed to a significant improvement in motor and emotional disorders, was shown. Virtual reality (VR) shows perspectives for healthcare applications because it provides patients with an exciting, often interesting, approach to achieving the goal of increasing productivity. Also, a persistent tendency to improve the intellectual level and quality of life of physical and emotional activity.

Key words: HIV infection , neurorehabilitation, HIV encephalopathy, children, NIRVANA, memantine.

Introduction

Worldwide, thirty five million people are infected with HIV, with approximately 3.2 million (9%) of them being under the age of 15 [1]. HIV (human immunodeficiency virus) infected children are at risk of growth failure and developmental disorders [2,3]. Severe neurodevelopmental, cognitive and motor dysfunctions have also been shown since the first reports of pediatric AIDS in the 1980s [3,4,6]. Growth failure is common in HIV-infected children; they are shorter and thinner than healthy counterparts [5]. HIV associated neurologic disease was demonstrated in 30% - 60% of infected children and adolescents [7]. Neurological sequels and neurocognitive disorders in infected children are due to static or progressive encephalopathy that influences different domains such as speech and language, memory, learning, information processing and motor functioning. Time of infection, viral load, CD4 count, antiretroviral medication, co-morbid diseases and environmental conditions are effective factors [8-10]. The prevalence of delay in cognition, motor function, speech and language was reported in 8% - 60% of HIV-infected children by Van Rie [5]. Ruel et al. also showed significant motor and cognitive disorders in 93 HIV-infected children with CD4 cell counts of 350 cells/μL and percentages of more than 15% [6]. Boyede et al. also demonstrated that RPM cognitive scores (nonverbal test of general intelligence) were lower for HIV-positive compared with HIV-negative children [10]. On the other hand, medical treatment including combination of antiretroviral therapy (ART) and supportive medications prolong survival and also promote rowth and developmental status [12]. Also, children with chronic illness, in general, are found to be at greater risk for psychiatric problems, including depression, anxiety, and feelings of isolation. Children with HIV/AIDS have additional factors in complexity of their illness and treatment as well as in the adverse psychological circumstances and poverty in which many live. Prevalence rates for psychiatric disorders in perinatally-infected children vary from 55% to 61%. The most common disorders found are anxiety disorders, followed by attention-deficit hyperactivity disorders, conduct disorders, oppositional defiant disorders, and mood disorders. [11].

Antiretroviral therapy alone is not enough to alter the neurocognitive effects of HIV infection. The stimulation techniques provided by caring people at home can lead to significant improvements in the neurocognitive status of HIV-infected children undergoing antiretroviral therapy [10]. Moreover, a wide range of potentially effective

methods have been identified to reduce the severity of inflammatory reactions connected HIV-associated neurocognitive disorder in adults. Many of these methods pass the second phase of testing. Nowadays, there are no unified recommendations for the use of these techniques in adults and no studies of efficacy in children have been conducted [12]. However, recent studies in this area demonstrate that the addition of special rehabilitation methods, such as virtual reality technologies, to safely correct cognitive and motor impairment in children with HIV encephalopathy is necessary to standard multidisciplinary rehabilitation. Virtual reality (VR) shows perspectives for healthcare applications because it provides patients with an exciting, often interesting, approach to achieving the goal of increasing productivity [13]. Virtual reality technology (VR) is quickly becoming a popular application for research in the field of physical rehabilitation and motor control [14]. Indeed, according to Dahdah et al., for the first time data show that semi-immersive virtual reality can be effective in improving performing functions and the processing speed of information in patients with brain injuries. In addition, VR increases motivation and pleasure in patients (important factors for successful rehabilitation), which also contributes to the restoration of behavioral and cognitive nature, which is also noted by Dvorkin et al. Other researchers point out that routine rehabilitation exercises may seem tedious because of their repetitive nature. Moreover, patient motivation is an important factor in the success of rehabilitation [15]. Computerized programs and the VE rehabilitation system during rehabilitation sessions increase patient motivation, provide flexibility and shorten the treatment period [16]. In addition, being a more high-tech intellectual method of treatment, it can be more maneuverable and easier to promote in rehabilitation and brings pleasure in the recovery of patients.

The most popular technologies are those with full immersion and without additional motion recognition devices, since the latter limit the range of movements and give negative influence due to the weight of the input device, causing the patient to prematurely fatigue during exercise.

Objective: to evaluate the effectiveness of neurorehabilitation in children with HIV encephalopathy using the interactive virtual reality NIRVANA system

Material and research methods.

The study included 170 children (92 boys – 59,74% and 78 girls – 40,6%) who were registered for HIV infection and receiving antiretroviral therapy (HAART). The average age of the patients was 14.53 ± 1.58 years (12-18 years), the time from the moment of HIV diagnosis was 7.05 ± 3.36 years (1-13 years), the duration of antiviral therapy was 6.41 ± 3.47 years (1-13 years old). In 43 patients (25.29%), the vertical route of infection was diagnosed, and in no case the mother took HAART during pregnancy. In other children, the infection pathway is identified as parenteral. The average virus concentration was 345.85 ± 181.45 copies / ml, while in 23 patients (14.94%) HIV RNA in the blood was not determined. The average number of CD4 + cells was 461.91 ± 230.32 in 1 mm3 of blood.

A neurological study included a standard neurological examination, including an assessment of consciousness and certain mental functions, speech, praxis, gnosis, functions of the cranial nerves, the state of the motor and sensory spheres, the autonomic nervous system, as well as functional and visualization methods (electroencephalography and magnetic resonance tomography).

Also, in the process of neurological research, the degree of neurological dysfunction was assessed using the screening scale for pyramidal extrapyramidal disorders for children older than 7 years, proposed by V.V. Glushchenko and P.B. Shabanov in 2013, according to which dysfunction was assessed according to a 6-point system (0 points - no violations - 5 points - severe violations) depending on the volume and strength and passive and active movements, the characteristics of tendon and periosteal reflexes, coordination and posture .

Neuropsychological screening included the identification of disorders of praxis, for which we used the assessment of kinesthetic (afferent), spatial, dynamic (kinetic) praxis by visual and tactile pattern. This patient, was asked to connect 1 and 2 fingers of the hand into a ring, squeeze fingers into a fist, leaving 2 and 3 fingers extended, raise a hand up, bending at the elbow (“voting”), touch the ear and eye with your hand. The assessment included the determination of the functional ability of the afferent basis of movement, the visual-spatial organization of movement, the perception of the body diagram, the arbitrary regulation of movements and the dynamic organization of movements. The result was presented in points, where 0 points corresponded to the absence of violations and 5 points to random movements and the inability to accept outside help.

All patients included in the study underwent testing aimed at studying the psychological and cognitive status of patients, including test methods: “Raven’s progressive matrix scale” (state of intelligence) and pediatric quality of life

questionnaire (PedsQL) for adolescents of 13-18 years old.

The Raven's test, proposed for the assessment of the level of intelligence, is based on the use of the ability to learn mainly on the generalization of one's own experience and the creation of schemes to handle complex events, logical thinking. This test is convenient in application and simplicity in interpretation, repeatedly confirms high indicators of validity and reliability. The test is not associated with linguistic abilities and skills and does not depend on the level of education. The Raven's matrix consists of 60 images combined into 5 matrices, in each it is necessary to select the missing fragment, using the identified patterns. In each matrix tasks are progressively complicated. Test tasks are performed without time limit, but it is noted how many tasks are completed correctly in the first 20 minutes. Thus, the Standard Progressive Raven Matrices test can be used both as a speed test (with time limits) and a performance test (without time limits). The choice of the test application regimen should be made depending on the purpose and conditions of the diagnosis (first of all, the possibility of the patient in long-term, continuous work with the test). Assessment is the percentage of correct answers, expressed in percent. Interpretation of the test allows us to distinguish 5 degrees of intellectual development: 1st degree - more than 95% - high intelligence; 2nd degree - 75-94% - intelligence is above average; 3rd degree - 25-74% - average intelligence; 4th degree - 5-24% - intelligence is below average; 5th degree is a defect.

Bass-Darki test, modified by G.V. Rezapkina, proposed in 2006, allows to diagnose various types of aggressive behavior. The test includes 35 statement questions. The test is suggested to the patient to apply the statement to himself. If he reacts in a similar way, the answer is given 1 point. During the interpretation, all issues are divided into 7 forms of aggression. The form that received more than 3 points is recognized as dominant in the patient. According to the test results, the following forms of aggressive behavior are distinguished: physical aggression (statements 1,8,15,22,29), indirect aggression (2,9,16,23,30), irritation (3,10,17,24,31) , negativism (4,11,18,25,32), resentment (5,12,19,26,33), suspiciousness (6,13,20,27,34), verbal aggression (7,14,21,28 , 35). The test is based on self-esteem. Its accuracy depends on the frankness of the patient. According to the results of the testing (increased level of aggression, inability to control emotions, etc.), it is not recommended to choose professions related to communication, maintenance, upbringing, training - that is, all professions related to people. Low values for this test testify to your delicacy, pliability and non-conflict. However, these indicators may prove a lack of perseverance in achieving their goals and defending their position.

The study of the quality of life of children is a new topical area of interdisciplinary research in domestic health care. The development of a methodology for studying the quality of life in pediatrics opens up the possibility of a comprehensive analysis of the physical, psychological and social functioning of children. For this, our study used the pediatric quality of life questionnaire PedsQL, version 4 (for children aged 13-18), published in 1998 and translated into Russian, includes 23 situations that describe physical, emotional, social activity and school life. The questionnaire is recommended for studying the quality of life of healthy and sick children, using these tools normative indicators of quality of life for the child population can be obtained. The use of the created tools in children with various diseases allows to expand knowledge about the attitude of children of a given age to their own health problems, treatment, degree of satisfaction with treatment; opens up new possibilities for assessing the impact of various diseases on the physical, psychological and social functioning of sick children. The test subject is asked to rate how each of these situations created difficulties over the past month. In this case, 0 points are assigned to a situation that has never created difficulties, 5 points - in the case of constant difficulties with the described action. Thus, the maximum score for each situation is 5 points (almost impossible activity), the minimum score is 0 (no difficulty. The maximum score in terms of physical activity is 32 points, emotional social and complex activity is 20 points, the total maximum score is 92 point.

All patients were randomly divided into two therapeutic groups: in the comparison group (85 patients), in addition to HAART, memantine hydrochloride was included in the treatment. The drug is a non-competitive antagonist of glutamate N-methyl-D-aspartate (NMDA) receptors, inhibits glutamatergic neurotransmission and the progression of neurodegenerative processes, has a neuromodulating effect. The mechanism of action is associated with the modulation of glutamatergic transmission, which mediates cortical-cortical and cortical-subcortical relationships in the brain. A series of controlled studies proved the ability of memantine to improve and stabilize cognitive functions, daily activity, and reduce behavioral disorders. It contributes to the normalization of mental activity (improves

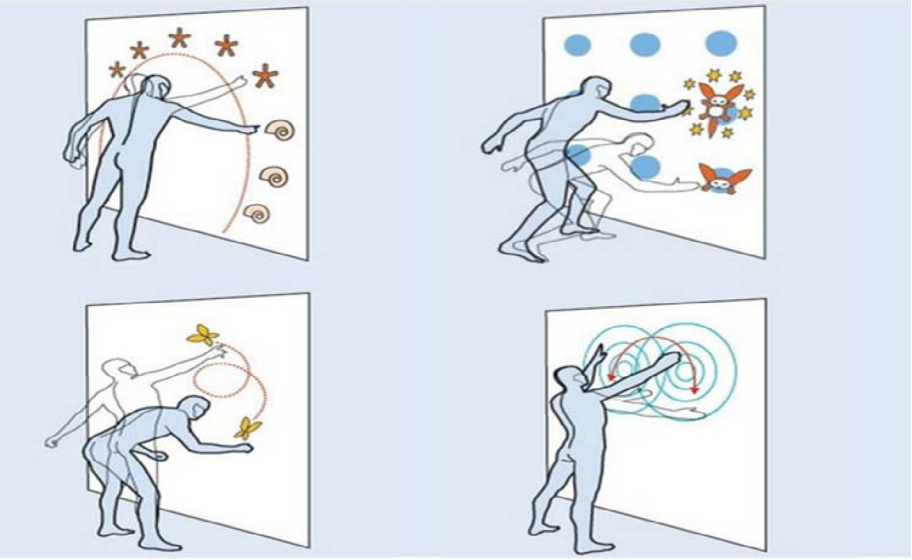
memory and ability to concentrate, reduces fatigue, symptoms of depression, etc.) and the correction of motor disorders. According to the study, it was proved that memantine can improve the metabolism of neurons, which is an important step to stabilize or prevent damage to neurons. These results emphasize the need for longer studies to assess the full potential of neuroprotective agents [17]. The drug was prescribed once, regardless of food intake, in an initial dose of 5 mg / day, followed by a dose increase of 5 mg per day every 7 days until the maximum daily dose of 20 mg / day was reached. In addition to HAART and memantine hydrochloride, patients of the main group (85 patients) underwent neurorehabilitation using the NIRVANA virtual reality system (https://www.btsbioengineering.com/nirvana/). NIRVANA - is an outstanding therapeutic method for the rehabilitation of neurological diseases and impaired motor skills of patients of all ages. A wide selection of tasks of varying complexity is offered to stimulate motor skills and cognitive abilities. Exercises can be carried out both individually and in groups [18]. Interactive virtual reality system for patients with neuromotor impairment NIRVANA is the first system in the world that provides full sensory immersion (acoustic and visual) in virtual reality. NIRVANA reproduces scenarios that can be projected on horizontal and vertical surfaces: the patient can interact with the virtual environment naturally, moving against the background of the projected images. NIRVANA is applicable to any rehabilitation institution that provides therapeutic treatment for patients with cognitive and motor deficiencies of the lower and upper extremities. NIRVANA is a really effective remedy for rehabilitation after lesions of the central nervous system (for example, as a result of a stroke of a head injury, encephalopathy) or in chronic and progressive neurological diseases (for example, Parkinson's disease or multiple sclerosis). The system includes a predefined set of exercises for the upper and lower extremities and body to help physicians. Some exercises aimed at restoring motor function control and rehabilitation can be used in combination with several disorders, such as Parkinson's disease, multiple sclerosis and unilateral paralysis. In addition to several modes and increasing levels of difficulty, each task is determined by multiple feedback sensory connections: in comparison with the traditional therapeutic approach, the patient receives powerful cognitive and motor stimuli, which increases his motivation to perform more complex exercises. The completely non-invasive system, immersed in a visual, acoustic and olfactory interactive virtual environment, is incredibly impressive and leaves an unforgettable experience. The system, based on the optoelectronic infrared markerless technology of motion recognition, creates virtual images on horizontal and vertical surfaces, with which the patient interacts absolutely naturally. Additionally, a sound environment is created, smells are reproduced;

NIRVANA is an outstanding therapeutic method for the rehabilitation of neurological diseases and impaired motor skills of patients of all ages. A wide selection of tasks of varying complexity is suggested to stimulate motor skills and cognitive abilities. Exercises can be carried out both individually and in groups. Classes can be of various types: perceptive, aimed at perceiving the environment, aimed at achieving a goal (following an animal or walking along a line), motor (an event occurs when the patient crosses an object) or game (football, balloons, etc.). (https://www.btsbioengineering.com/nirvana/).

Picture 1

Thus, with the help of the NIRVANA system it is possible to carry out training of locomotion, balance, arm movements and their coordination. At the same time, developing virtual reality technologies are becoming more accessible, and the use of game consoles as such systems allows the patient to continue training at home. The patient performs exercises in a virtual environment through movements performed on an interactive screen. Movements allow you to move or manipulate specific objects in different directions (for example, balls, colors and butterflies) or create specific associations (for example, number of colors) with dynamic interaction in a virtual environment. When a patient touches virtual objects, he / she determines the audio and video feedback (using the sprite action). In particular, the subject can perform ideomotor sequences under the guidance of a therapist, numerical processing, inhibition control and arithmetic operations; can evaluate the numerical quantity and classification; perform deductive logical reasoning using specific virtual tasks.

The patient selects / explores some elements (colors, music, geometric shapes, animals, etc.) observed in a virtual environment. These elements remain visible to the observer for various times determined by the interaction between the virtual system, the therapist, and the patient. The patient touches the virtual target at a specific time; this action causes a visual change with typical audio / video feedback (positive influence); otherwise, the element disappears (negative reinforcement).



Picture 2

Sessions were held every other day. The rehabilitation course was 20 sessions. Exercises were selected individually depending on the prevailing neurological symptoms.

The follow-up period was 6 weeks, at the end of which a re-study was carried out, including the Raven's scale, a questionnaire on the quality of life, a test for identifying praxis disorders and motor disorders.

All data was entered into Excell summary tables to calculate average values and their standard deviations. Intergroup difference was evaluated using Student's t-test for 2 comparisons. Frequency comparison was carried out using the chi- chi-square table criterion. The dynamics of the indicators was evaluated as a relative change in the initial indicator, expressed as a percentage.

Research results and discussion.

In the course of the study, it was found that the applied treatment schemes contributed to a significant improvement in motor function in the aspect of pyramidal extra pyramidal disorders (the scoring decreased by 21.70%, $p < 0.001$ with the initial data, Table 1) and praxis (-10.79%, $p < 0.001$). The level of intellectual development also increased statistically significantly, although clinically insignificantly (+ 2.53%, $p < 0.001$). As a result, the number of patients with an average level of intelligence increased from 8 (5.19%) to 13 (8.44%, frequency difference

chi square = 1.33, nd). All aspects of the quality of life also showed a clinically insignificant, but statistically significant tendency to improve: thus, the difficulty score for physical activity decreased by 1.03% ($p < 0.01$), emotional activity - by 2.20% ($p < 0.001$), social activity by 1.34% ($p < 0.01$), school activity by 0.44% ($p < 0.05$). Such statistical reliability with minimal changes indicates a persistent unidirectional tendency to positive changes in a large number of patients, though by a small amount.

Table 1 – Neuropsychological testing of children with HIV encephalopathy during 6 weeks therapy

scales	initial	6 weeks
Screening assessment of motor impairment	3,20±0,99	2,51±0,97***
Screening assessment of praxis disorders	2,58±0,88	2,22±0,83***
Raven scale	18,68±4,51	19,08±4,60***
PedsQL physical activity	18,30±4,91	18,09±4,78**
PedsQL emotional activity	15,50±2,23	15,17±2,56***
PedsQL social activity	14,10±2,93	13,89±2,87**
PedsQL school activity	19,29±1,23	19,21±1,34*

*Note: the significance of differences with the source data is *. One symbol- $p < 0.05$, two symbol - $p < 0.01$, three symbol - $p < 0.001$.*

The distribution of patients by therapeutic groups revealed that in both groups there was a positive dynamics of all the studied parameters (table 2). At the same time, although the relative dynamics of the indicators was comparable in both therapeutic groups, in the main group of patients, all the studied parameters changed more pronounced (the dynamics of the score of motor disorders in the main group was -23.61% ($p < 0.001$ with the initial data) versus -19, 78% in the comparison group ($p < 0.001$ with initial data), ; praxis disorder score -13.58% ($p < 0.001$ with initial data) versus 7.99% ($p < 0.001$ with initial data); score for Raven's scale + 3.49% ($p < 0.001$ with the initial data) versus 1.56% ($p < 0.01$ with the initial data), ; difficulty points for assessing the quality of life in terms of physical activity -1.24% ($p < 0.05$ with the initial data) versus -0.82 ($p < 0.05$ with the initial data), emotional activity -3.42% ($p < 0$, 05 with initial data) versus -0.97% ($p < 0.05$ with initial data), social activity -1.94% ($p < 0.05$ with initial data) versus -0.75, school activity -0, 54% versus -0.33%, all aspects – i.d.). As a result, with initial comparable indicators in the groups, by the end of the observation period, the average score of praxis disorders in the main group was significantly lower than in the comparison group ($p < 0.05$).

The NIRVANA virtual reality modulation system was created to increase the effectiveness of neurorehabilitation in patients with consequences of acute cerebrovascular accidents, paralysis, consequences of myocardial infarction, paresis (weakening of muscle strength), consequences of craniocerebral trauma, cerebral palsy, consequences of injuries to hands and feet [19]. We attempted to use this method in children with HIV encephalopathy - a progressive HIV-associated damage to the nervous system, the outcome of which is an irreversible damage to the nervous system and a deep neurological and cognitive deficit. The study showed the effectiveness of the method in preventing the progression of pathology and reducing the scoring of neurological deficiency.

In order to protect the nervous system in patients with progressive diseases, various medications are used, but so far there is no evidence base testifying to the effectiveness of medical measures. In this work, we investigated the effectiveness of memantine hydrochloride. A positive effect of the drug in the aspect of impaired movement and praxis was found, as well as a weak but persistent positive effect in terms of the level of intelligence and quality of life associated with difficulties in physical and emotional functioning.

Table 2 – Indicators of the neuropsychological status of children with HIV encephalopathy on the background of 6-week therapy, including memantine and the NIRVANA virtual reality method (in the numerator, the initial data, in the denominator, after 6 weeks of observation).

Scale	Main group (n = 77)	Comparison group (n = 77)
Screening assessment of motor impairment	3,18±0,98 2,44±1,01***	3,22±1,00 2,57±0,94***
Screening assessment of praxis disorders	2,58±0,88 2,08±0,75***	2,59±0,88 2,37±0,89^***
Raven scale	18,64±4,54 19,17±4,63***	18,71±4,52 19,00±4,60**
PedsQL physical activity	18,32±4,92 18,04±4,68*	18,29±4,93 18,14±4,91*
PedsQL emotional activity	15,49±2,23 14,99±2,76*	15,51±2,24 15,36±2,34*
PedsQL социальная активность	14,04±2,92 13,74±2,85*	14,16±2,95 14,04±2,91
PedsQLschool activity	19,25±1,26 19,14±1,36	19,33±1,20 19,28±1,32

Note: *the significance of the difference with the initial data is *, the significance of the difference between therapeutic groups ^. One symbol- p <0.05, two symbols - p <0.01, three symbols - p <0.001.*

Conclusion

This study revealed that in children with HIV encephalopathy, the use of memantine significantly improves motor impairment and praxis disorders, as well as a persistent tendency to improve the intellectual level and quality of life, physical and emotional activity. The additional use of the NIRVANA neurorehabilitation system, based on immersing the patient in virtual reality (visually and acoustically) and game motivation, is associated with an increase in the positive effect of therapy, mostly to praxis disorders.

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We invite to cooperation teachers, doctoral students, undergraduates, employees of scientific, educational and practical medical institutions.

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With respect and gratitude for your cooperation,

Executive Secretary
Abzaliyeva Symbat Abulkhairovna
abzaliyeva.symbat@gmail.com
symbat.abzalieva@kaznu.kz
+7(727) 377 33 33 (вн.1959) 8(777)232-29-78

Technical secretary
Nasyrova Nargiza Batyrhankyzy
nassyrova.n94@gmail.com; nargiza.mashurova@mail.ru
+7(727) 377 33 33 (вн.1958) 8(747)896-84-07

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