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На обложке — фрагмент скульптуры «Доктор и больной», автор — академик И.Я. Гинцбург (1859–1939), добрый друг Юлии Ароновны Менделевой (ректора ЛПМИ с 01.04.1925 по 1949 г.) и ее семьи.

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EDITORIAL

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APPLICATION OF INFORMATICS IN THE WORK OF A PATHOLOGIST: GUIDELINES FOR LEARNING HOW TO CREATE AND USE A DIGITAL ARCHIVE OF GROSS IMAGES

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Pathology informatics has been developing as a response to a large amount of diagnostically relevant morphological information and attempt to the best store and use it. The main components of pathology informatics include digital images of histological slides and gross photographs, telepathology, and electronic data collection. Photo documentation of gross specimens is an integral part for efficient work of a pathologist. Currently, many grossing stations are equipped with continuously recording video cameras. A logical and detailed description of the macroscopic specimens, supported by properly obtained digital photographs, should be the standard of a modern pathology report. However, with the increasing workload of the pathologists, they have less and less time to take gross photographs. That is why, in our opinion, it is important to ask questions such as: what is necessary to photograph, how to take a photo of the gross specimen, and in which order? There are only a few publications on this topic in both domestic and foreign literature. This paper attempts to summarize the literary data on this topic, based on which a list of medical use cases that require a mandatory photo documentation has been created. Practical recommendations have been developed and are outlined for gross photographs. In the context of widespread use of digital photography as a resource for deep learning of neural networks and digital analysis, this article will be useful not only for postgraduate education of pathologists, but also for physicians of other specialties.

Keywords: postgraduate medical education; pathology informatics; digital gross photography; pathological anatomy; training of neural networks.

ПРИМЕНЕНИЕ ИНФОРМАТИКИ В РАБОТЕ ПАТОЛОГОАНАТОМА: ОБУЧЕНИЕ СОСТАВЛЕНИЮ И ИСПОЛЬЗОВАНИЮ ЦИФРОВОГО АРХИВА ИЗОБРАЖЕНИЙ МАКРОПРЕПАРАТОВ

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Патоморфологическая информатика возникла как ответ на огромное количество диагностически значимой морфологической информации и попытку наилучшего ее хранения и использования. Основными составляю-

щими патоморфологической информатики можно считать цифровые изображения макро- и микропрепаратов, телепатологию и сбор электронных данных. Фотодокументация макропрепаратов — неотъемлемая часть эффективной работы врача-патологоанатома. В настоящее время многие станции вырезки снабжены камерами непрерывной видеосъемки. Логичное и детальное описание макропрепарата, подкрепленное правильно выполненными цифровыми фотографиями, должно быть стандартом современного патологоанатомического заключения. Однако в условиях повсеместно возрастающей рабочей нагрузки на врачей-патологоанатомов времени для занятий фотосъемкой остается все меньше. Поэтому очень важными, на наш взгляд, являются вопросы: что необходимо фотографировать обязательно, как фотографировать макропрепарат, и в какой последовательности? Публикации на эту тему и в отечественной, и в зарубежной литературе немногочисленны. В этой работе сделана попытка обобщения литературных данных по данной теме, и на основе этих данных составлен перечень медицинских случаев, которые требуют обязательной фотодокументации; разработаны практические рекомендации по проведению съемки макропрепаратов; дана оценка возможностей использования цифровой фотографии макропрепарата для дифференциальной диагностики. В условиях широкого использования цифровой фотографии как ресурса для глубокого обучения нейросетей и цифрового анализа эта статья будет полезна не только для последипломного образования патологоанатомов, но и для врачей других специальностей.

Ключевые слова: последипломное медицинское образование; патоморфологическая информатика; цифровая фотография; макропрепарат; патологическая анатомия; обучение нейросетей.

Today, most educated people are aware of informatics as a science about the methods and processes of collecting, storing, processing, transferring, analyzing, and evaluating information using computer technologies that allow its use for decision-making [5]. Medical informatics is a branch of science that focuses on biomedical information. It studies the patterns and methods of obtaining, storing, processing, and using knowledge in medical science and practice to prevent and treat diseases. However, nowadays, the rapidly developing branch of informatics in the field of pathological anatomy ("pathology informatics") remains in progress in the Russian healthcare system. Therefore, not every doctor is even familiar with the term "pathology informatics" or pathomorphological informatics. In Russia, researchers such as I.M. Vorontsov, E.V. Gubler, M.O. Ioffe, I.P. Kulbush, N.N. Melnikov, V.G. Chasnyk, V.V. Shapovalov, and V.V. Yuriev implemented informatics and pathological anatomy, in specific, into medical practice [2, 3].

Unfortunately, at that time, their ideas were not widely adopted by pathoanatomists for use in their practices. Pathology informatics arose due to a considerable amount of diagnostically important morphological information and an attempt to store and use it optimally. Digital imagery, teleconsultation, and mining or electronic data collection can be considered the main components of pathology informatics. Digital images of gross specimens or histological preparations represent a vast archive of data on pathological anatomy in electronic format. These images are used for education, diagnostics, consultation, and research. As a branch of telemedicine, telepathology has already become an integral part of the work of pathoanatomists worldwide. However, in current practice, when it comes to "digital pathology," the work with a digital image of histological micro preparations is mainly implied. Much less attention is paid to the digital images of gross specimens. In our opinion, this preference seems completely unfounded since a photograph of a clinical tissue sample is an integral part of an anatomic pathology report and electronic medical case history. Also, it is part of a legal document since it is integrated into the laboratory information system [7, 11].

Many digital systems for documenting autopsy materials and surgical specimens are integrated into modern cutting stations. These systems enable continuous video and audio recording during the entire macroscopic examination process. Some experts consider it to be sufficient [18].

We disagree with this point of view. The considerable amount of digital video information recorded at the cutting station requires vast storage space and consumes a great deal of viewing time. In most cases, this laborious use of resources is entirely unreasonable. Moreover, not all gross specimens require conventional digital photography, particularly video documentation [13]. According to the authors of the article, in the context of the ubiquitously increasing workload on the pathologist, questions about what is necessary to photograph, how to photograph, and in what sequence are very significant.

Our study aims to perform the following:

1) A critical analysis of modern literature on photographing gross specimens in pathological anatomy and compiling a list of medical cases that require mandatory photographic documentation;

2) Develop practical recommendations for imaging of gross specimens;

3) Assess the possibilities of using digital photography of a gross specimen for differential diagnostics based on digital analysis.

The literature on this subject is scarce in the Russian language and is mainly represented by works on forensic photography [4, 6, 19].

The international literature on photography regarding the practice of a pathologist is mainly focused on photography equipment, and various hardware and software used to transfer and store digital photographs [10, 14, 16].

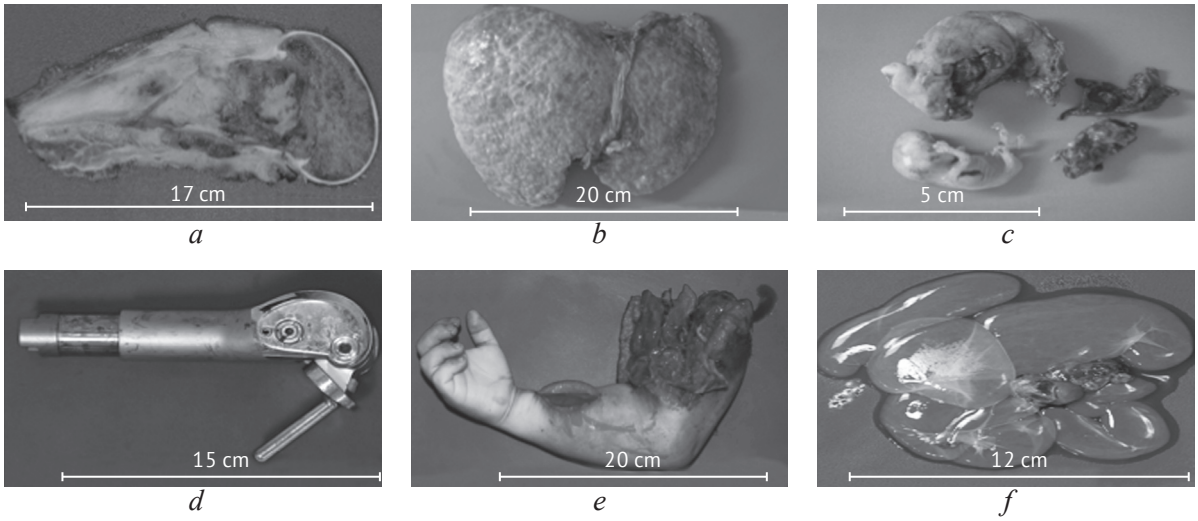
Only a few works focused on the technique and strategy to obtain high-quality imaging of gross specimens [8, 15, 17, 20].

By combining literature data and many years of our experience into a single array, we offer the following list of cases requiring mandatory photo documentation:

1) All findings associated with a tumor process (Fig. 1, *a*) and a pronounced inflammatory process (Crohn's disease);

2) All gross specimens during transplantation surgeries (Fig. 1, *b*) of organs (prostheses of heart valves, explanted organs);

3) The absence of any findings while anticipating them by clinicians (the absence of a tumor in the gross specimen during the anatomicopathological examination of the surgical material sent for tumor removal); gross specimens with disruption of continuity (Fig. 1, *c*) of anatomical structures



a *b* *c*

d *e* *f*

Fig. 1. A macroscopic photograph: *a* – the right femoral segmental resection specimen for osteosarcoma. The central slab of the bone is longitudinally sectioned in the sagittal plane. The macroscopic photograph demonstrates a tumor with massive structure-less areas of necrosis and hemorrhagic infiltration. The tumor involves the diaphysis, metaphysis, intramedullary space, cortical bone, and partially soft tissue. There is no gross evidence of tumor at the inked margins; *b* – an external view of the explanted native liver due to cirrhosis specimen; *c* – a specimen composed of fragmented parts of the fallopian tube and fetus due to disrupted ectopic pregnancy; *d* – a total femoral prosthesis hardware removed due to being worn out. The specimen is for gross examination only and photo documentation; *e* – a specimen resulting from an above elbow amputation of the right upper extremity. The skin, soft tissue, and bone margins are irregularly-shaped and hemorrhagic consistent with traumatic amputation. There is a previously opened defect of skin and underlying soft tissue consistent with a surgical incision on the anterior aspect of the forearm; *f* – a macroscopic photograph of a rare mesothelial cyst of the abdominal cavity

Рис. 1. Макропрепараты: *a* — сегментарная резекция правого бедра по поводу остеосаркомы. Центральная костная пластина, выпиленная в сагиттальной плоскости. На фотографии видна опухоль с массивным бесструктурным участком некроза и геморрагической инфильтрации. Опухоль захватывает диафиз, метафиз, интрамедуллярное пространство, кортикальную часть кости и частично мягкие ткани. Маркированные края резекции без видимого опухолевого роста; *b* — макропрепарат удаленного нативного органа с выраженным циррозом при операции по трансплантации печени; *c* — фрагментированные части маточной трубы и плод при прервавшейся эктопической беременности; *d* — дистальный феморальный протез, извлеченный вследствие износа. Препарат доставлен для макроскопического исследования и фотодокументации; *e* — макропрепарат травматической ампутации правой верхней конечности на уровне средней трети плеча при автомобильной травме. Края кожи на уровне ампутации неровные, мягкие ткани размозжены, отмечается геморрагическая инфильтрация. Визуализируется оскольчатый перелом плечевой кости. На внутренней поверхности предплечья послеоперационная рана; *f* — препарат мезотелиальной кисты брюшной полости

(fragmented organs, preparations in the presence of hemorrhages, ruptures);

4) Gross specimens that require only a macroscopic examination (Fig. 1, *d*) without subsequent histological analysis (excised Phyto- or trichobezoars, medical devices, endoprostheses);

5) Gross specimens of cases (Fig. 1, *e*) that may be the cause of court proceedings (foreign bodies, traumatic organ amputations); unusual findings (Fig. 1, *f*) and rare cases (mesothelial, fetus in fetu, others).

When working, a simple rule must be borne in mind. A set of macro photographs for a given case should form a single picture that enables answering the questions raised by the clinician and leads to the correct clinical and morphological conclusion.

In the daily practice of a pathoanatomist, many different models of digital cameras can be used for photography. If a camera is not available, subject to patient data confidentiality, a mobile telephone can also be used. Several practical recommendations that will help improve the imaging quality of gross specimens are provided below.

1. The choice of imaging mode (manual or automatic) depends on the experience and skills of the camera user. For indoor photography, a ring flash is useful, the design of which provides uniform illumination of small objects and is ideal for shooting gross specimens. At the start of shooting, the gross specimen is photographed in the form it was delivered for research. Then, its sectional view is photographed. If serial sections are made in the form of a "book." then the picture should be taken before parts of the sample have been displaced relative to each other. This is necessary to recreate the integral anatomical structure of the sample and see the contact boundaries of its parts. If separate serial cuts are made, then the plates should be laid out sequentially. All parts must be included entirely while ensuring that no cut edges of one or another fragment are in the frame. When shooting, it is recommended to take several pictures at different magnifications. This practice can be useful in further work for drawing up the so-called schematic map for the layout of tissue fragments of the sample in cassettes and macro-microscopic comparisons [1].

2. It is essential to choose the background for macro photography. It must be clean and have a suitable color. For example, black is not preferable when photographing dark brown and dark red specimens. Yellow, red, and brown are not very good backgrounds for photography of gross specimens, while light blue and green are the most suitable colors.

3. A digital photograph of a gross specimen is a legal document. A lack of scaling and labeling can ultimately devalue all the efforts and diagnostic value of this image. Therefore, macrophotography must necessarily contain labeling with the identification number of the sample and a scale bar with the units of measurement. It is better to place the scale bar closer to the sample, and labeling should be in the corner of the frame. They should not be located on the specimen or overlap its parts. This arrangement enables removing the photo identification number and using the photo for a conference, training, or scientific presentation. All objects in one photo (gross specimen, scale bar, and labeling) must be in focus.

4. When shooting, it is recommended to avoid getting your hands in the frame. A metal probe or tweezers can be used to point to a specific area in the sample.

5. After photographing, the quality of the photographs should be checked to ensure that they fully meet the requirements of the researcher and are saved. The most common file format for saving digital images is JPEG (Joint Photographic Experts Group). However, it has a disadvantage manifested as the deletion of part of the information during the shooting process; when an image is opened in the editing program and saved as a JPEG, part is deleted. The RAW format is the optimal format since it preserves the maximum image quality [6].

6. The creative approach of this specialty enables obtaining an image with a greater depth of field from a series of conventional macro photographs and software for merging focal digital planes (z-stacking) [12]. Such digital images will illustrate the anatomic pathology report and be used in the educational process.

Several studies have already demonstrated success with using digital photographs of gross specimens for in-depth learning of neural networks and the use of neural network analysis in the future for recognizing various organs [9].

The next step is using neural network analysis of digital images of gross specimens for macroscopic differential diagnostics of pathological processes. Today, creating a high-quality and well-annotated digital image repository of gross specimens and their metadata should be considered. This endeavor is a time-consuming and labor-intensive process. Such annotations in our work were created using the publicly available software QuPath. This pro-

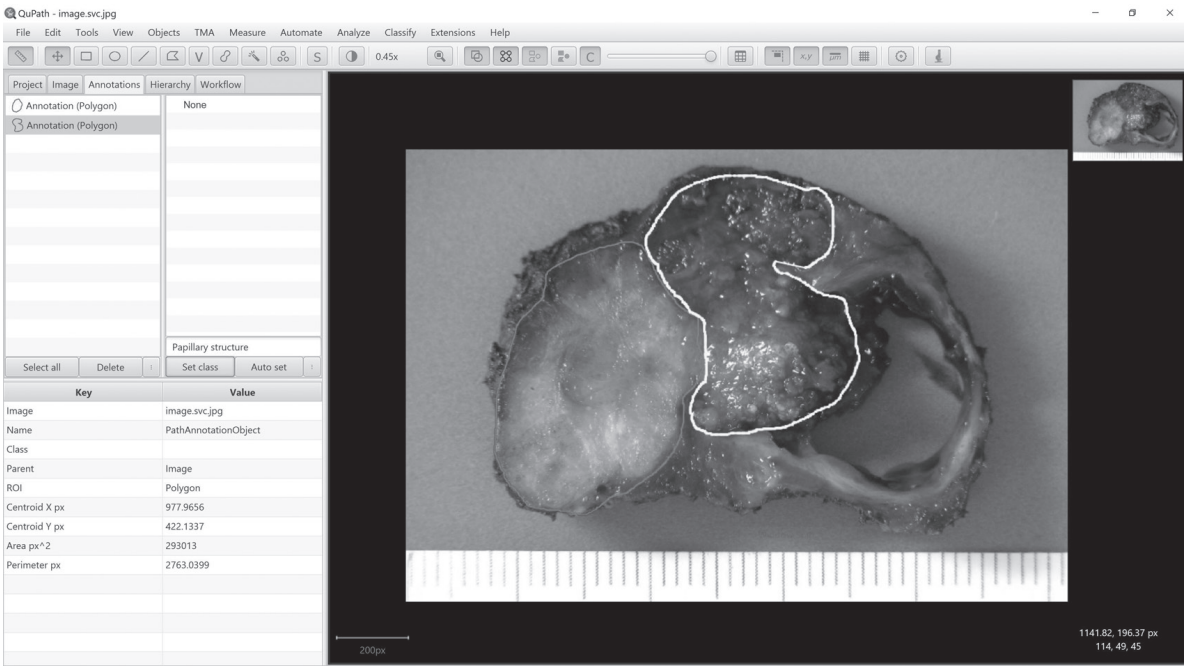


Fig. 2. An example of work with QuPath software for annotation digital gross photograph of the thyroid gland tumor
Рис. 2. Пример работы с программным обеспечением QuPath для аннотации цифрового изображения макропрепарата опухоли щитовидной железы

gram allows for object detection, classification, and image segmentation (Fig. 2).

Thus, even today, with a minimum expenditure of material resources and having certain knowledge of and skills in digital photography, a pathoanatomist can significantly improve the quality of the anatomic pathology report and create the necessary base for conducting computer-assisted differential diagnostics based on digital images.

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INFLUENCE OF PAIN ON THE DEVELOPMENT IN PRETERM INFANTS

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Introduction. The influence of uncontrolled exposure to pain in newborns in the first days of life on the long-term consequences for both the brain and the development of the nervous system as a whole is of interest.

The aim of the study was to assess the intensity of pain in preterm infants who need respiratory care in the early neonatal period and to determine its impact on the development of the child by the end of the first month of life.

Materials and methods. From December 2018 to December 2019, 92 preterm infants requiring respiratory support in the early neonatal period were examined. Pain intensity was assessed on the EDIN6 scale, and neuro-muscular maturity was assessed on the J. Ballard scale. The preterm infants were divided into 2 groups: Group I – 34 children who underwent invasive ventilation (body weight 1120 [865; 1390] g, gestational age 29 [26; 31] weeks); group II – 58 newborns who used non-invasive respiratory therapy (CPAP) (body weight 1160 [875; 1400] g, gestational age 29 [28; 31] weeks). Group I newborns had a lower Apgar score at 5 minutes ($p = 0.001$) and a higher Silverman score ($p = 0.001$).

Results and discussions. In all newborns, the maximum pain intensity score on the EDIN6 scale was registered on the 3rd day of life: in group I, it was 9, and in group II – points ($p = 0.041$), which corresponds to moderate pain. Group I children underwent more manipulations (20.8 ± 2.14 vs 17.7 ± 2.05; $p = 0.016$). An increase in the average airway pressure of ⩾10 cm H_2O in group I children and ⩾6.5 cm H_2O in group II patients is accompanied by an increase in the intensity of pain to severe and moderate, respectively. In both groups of children, an inverse correlation was found between the number of manipulations, head circumference ($R = -0.64$; $p = 0.004$) and the J. Ballard score on the 28th day of life ($R = -0.57$; $p = 0.008$). The number of painful manipulations in the early neonatal period, exceeding 21 procedures per day, increases the risk of delayed child development by more than 3.5 ($p = 0.009$; OR = 3.68; CI = 1.12–8.36).

Conclusion. The number of manipulations performed and the value of the average airway pressure are the main factors affecting the intensity of pain in preterm infants and determining their development in the neonatal period.

Keywords: preterm infants; pain level; neuromuscular and physical development.

ВЛИЯНИЕ БОЛИ НА РАЗВИТИЕ ГЛУБОКО НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ

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Введение. Исследование долгосрочных последствий неконтролируемого воздействия боли у новорожденных первых дней жизни для развития нервной системы в целом и головного мозга в частности представляет научный и клинический интерес.

Цель исследования — оценить интенсивность боли у глубоко недоношенных новорожденных, нуждающихся в респираторной поддержке в раннем неонатальном периоде, и установить ее влияние на развитие ребенка к концу первого месяца жизни.

Материалы и методы. Обследовано 92 глубоко недоношенных новорожденных, нуждающихся в респираторной поддержке в раннем неонатальном периоде. Оценку интенсивности боли проводили по шкале EDIN6, оценку нейромышечной зрелости — по шкале J. Ballard. Новорожденные были разделены на 2 группы: I группа — 34 ребенка,

которым проводилась инвазивная ИВЛ (масса тела 1120 [865; 1390] г, срок гестации 29 [26; 31] недель); II группа — 58 новорожденных, у которых использовалась неинвазивная респираторная поддержка (НИП/CPAP) (масса тела 1160 [875; 1400] г, срок гестации 29 [28; 31] недель). Новорожденные I группы имели более низкую оценку по шкале Апгар на 5-й минуте (p = 0,001) и более высокую — по шкале Сильвермана (p = 0,001).

Результаты и обсуждение. У всех новорожденных максимальная оценка интенсивности боли по шкале EDIN6 была зарегистрирована на 3-и сутки жизни: в I группе она составила 9, а во II — 8 баллов (p = 0,041), что соответствует умеренной боли. Детям I группы было проведено большее количество манипуляций (20,8 ± 2,14 vs 17,7 ± 2,05; p = 0,016). Увеличение среднего давления в дыхательных путях ⩾10 см H_2O у детей I группы и ⩾6,5 см H_2O у пациентов II группы сопровождается увеличением интенсивности боли до сильной и умеренной соответственно. У детей обеих групп выявлена обратная корреляционная зависимость между количеством манипуляций, окружностью головы (R = –0,64; p = 0,004) и оценкой по шкале J. Ballard на 28-е сутки жизни (R = –0,57; p = 0,008). Количество болезненных манипуляций в раннем неонатальном периоде, превышающее 21 процедуру в сутки, увеличивает риск задержки развития ребенка более чем в 3,5 раза (p = 0,009; OR = 3,68; CI = 1,12–8,36).

Заключение. Количество выполняемых манипуляций и величина среднего давления в дыхательных путях — основные факторы, влияющие на интенсивность боли у глубоко недоношенных новорожденных, определяющие их развитие в неонатальном периоде.

Ключевые слова: глубоко недоношенные новорожденные; уровень боли; нейромышечное и физическое развитие.

Due to a significant increase in the survival rate of extremely premature infants, considerable attention is currently paid to reducing neurological deficits and long-term adverse consequences associated with immaturity of the central nervous system (CNS) and stress during the first days of life [17]. Since all extremely premature newborns require care and treatment in resuscitation and intensive care units (RICU), they require numerous diagnostic and therapeutic procedures much more frequently, many of which are very painful. All this happens in the presence of stress caused by the weaning of the child from the mother. The role of long-term exposure to stress and pain experienced by extremely premature infants in RICU remains unclear and requires detailed study. Although the CNS of extremely premature infants during the early neonatal period is in a critical period of development, it is apparent that these children can perceive pain [7]. Considering that the tactile sense threshold is lower, and the descending inhibitory pathways are immature, premature infants, especially extremely premature infants, are even more sensitive to painful stimuli [22].

Early life pain in newborns has long-term effects on both the developing brain and the nervous system. Experimental studies on animals have established that chronic stress in the mother during pregnancy causes excitotoxic brain damage in newborn mice [20]. In addition, several studies that attempted to create an environment aimed to reduce stress in premature infants showed improved short-term and long-term outcomes [5, 6]. Excessive pain can alter the structure and function of the developing brain in premature infants by contracting the white matter and the subcortical gray matter [8]. Therefore, such adverse effects may be associated with subsequent changes in the IQ levels of schoolchildren, which are mediated by microstructural changes in the brain [23]. Smith et al. [21] demonstrated that premature infants are exposed to many potentially stressful factors. The increased exposure to these factors in RICU is associated with decreases in the sizes of the frontal and parietal brain regions and changes in the microstructure in the temporal lobes. Also, developmental psychomotor disorders have been associated with early exposure to stress [21].

The study aims to assess pain intensity in extremely premature infants who require respiratory support during the early neonatal period and establish its effect on child development by the end of the first month of life.

MATERIALS AND METHODS

A non-randomized controlled comparative cohort study was performed from December 2018 to December 2019. The study included 92 extremely premature infants in the neonatal RICU of the V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, the Ministry of Health of Russia. The study was approved by the local Ethics Committee (Protocol No. 2 of November 24, 2018), and the infants' parents signed a voluntary informed consent to participate in the study.

The study included children with respiratory distress syndrome, with a gestational age of 29 [range, 27–31] weeks and birth weight of 1150 [range, 875–1400] grams. All children received respiratory support in the early neonatal period, namely con-

tinuous positive airway pressure (CPAP) therapy or invasive artificial pulmonary ventilation (APV) [2]. The exclusion criteria for the mother were narcotic drug intake and alcohol abuse during pregnancy. Exclusions for the child were the presence of congenital malformations and diseases requiring surgical intervention, and severe hemorrhagic lesions of the CNS (degree III–IV intraventricular hemorrhage), and degree III cerebral ischemia in the early neonatal period, a change in the strategy of respiratory support. All children enrolled in the study had a NEOMOD score of 2 [range, 1–3] points to remove the influence of comorbidity and the presence/progression of multiple organ failure on pain intensity [15].

The degree of respiratory impairment was measured using the Silverman scale. The duration of respiratory support was also assessed. The follow-up of children was performed daily, including clinical, laboratory, and instrumental assessment of the state of organs and systems. Neuromuscular and physical maturity was assessed using the Ballard Scale on the first day of life and then every seven days until the end of the neonatal period. The pain level was assessed daily using the modified EDIN6 (Echelle Douleur Inconfort Nouveau-Né, 6) pain and discomfort scale in newborns [12, 19]. The number of manipulations performed was also counted daily. On day seven of life, children underwent an assessment of anthropometric data and neuromuscular and physical maturity according to the Ballard Scale.

Concerning the various methods of respiratory support, newborns were distributed into two groups. Group I consisted of 34 children who underwent invasive APV, and group II included 58 newborns, where CPAP therapy was used.

Table 1 presents the characteristics of the groups. The patients were comparable regarding anthropo-

Table 1 / Таблица 1

Characteristics of the examined preterm infants
Характеристика обследованных новорожденных

Indications / Показатели	Group I / Группа I (n = 34)	Group II / Группа II (n = 58)	p
Female/male, *n* / Женский/мужской пол, *n*	15/19	30/28	–
Gestational age, weeks / Гестационный возраст, нед.	29 [26; 31]	29 [28; 31]	0.081
Weight, g / Вес тела при рождении, г	1120 [865; 1390]	1160 [875; 1400]	0.320
Length, cm / Длина, см	36 [33; 39]	37 [34; 40]	0.071
Head circumference, cm / Окружность головы, см	26 [24; 28]	27 [25; 28]	0.067
Without prevention of RDS, *n* / Без профилактики респираторного дистресс-синдрома плода, *n*	16 (47.0%)	23 (39.7%)	0.480
Apgar score for 1 min, points / Оценка по шкале Апгар на 1-й минуте, балл	4 [3; 5]	4 [4; 5]	0.078
Apgar score for 5 min, points / Оценка по шкале Апгар на 5-й минуте, балл	5 [4; 6]	6 [5; 6]	0.001
Score for scale Silverman, points / Оценка по шкале Сильвермана, балл	6 [6; 7]	5 [5; 6]	0.001
Total time of primary resuscitation, min / Длительность первичной реанимации, мин	10 [10; 12]	5 [5; 10]	0.001
$FiO_{2\ max}$ when performing respiratory support in the delivery room / $FiO_{2\ max}$ при проведении респираторной поддержки в родильном зале	0.42 [0.3; 0.5]	0.21 [0.21; 0.3]	0.001

Note. $FiO_{2\ max}$ – the maximum fraction of oxygen in the oxygen-air mixture.
Примечание. $FiO_{2\ max}$ — максимальная фракция кислорода в кислородно-воздушной смеси.

metric parameters, gestational age, and antenatal prevention of fetal respiratory distress syndrome. The mothers' medical history was also comparable. Newborns of group I had a lower Apgar score at minute five ($p = 0.001$) and a higher score on the Silverman scale, which indicated that they had severe respiratory failure ($p = 0.001$).

Primary resuscitation care in the delivery room was provided according to current recommendations [2, 3]. In group I children, exogenous surfactant was administered through an additional port on the endotracheal tube in the delivery room. In contrast, the less invasive surfactant administration was used for children in group II.

Statistical data processing was performed using the Statistica v. 10.0 software package (Statsoft Ink, USA), the Open Epi system (http://www.openepi.com). Quantitative characteristics were presented as *Me* [Q_{25}; Q_{75}] for nonparametric samples and $M \pm m$ for parametric samples. The normal distribution of attribute values was tested using the Shapiro–Wilk *W*-test. The differences were assessed by the Mann–Whitney test for unconjugated samples, and Fisher's exact test was used for small samples. Correlation analysis was performed using Spearman's correlation coefficient. Differences were considered statistically significant at $p < 0.05$. The influence of individual risk factors on the studied groups was assessed by calculating the odds ratio (OR) with a 95% confidence interval (95% CI).

RESULTS

Analysis of primary resuscitation measures in the delivery room in children of group I revealed a significantly longer duration of primary resuscitation measures ($p = 0.001$). For children of group I from the first minutes of life, APV was started through an endotracheal tube, and CPAP was performed for the group II children. With respiratory support in newborns of group I, a significantly higher ($p = 0.001$) maximum oxygen fraction in the oxygen-air mixture ($FiO_{2\ max}$) was required. No children in either group required closed-chest cardiac massage or medication.

Upon admission to the RICU, all children continued respiratory therapy, the parameters of which are presented in Table 2. The maximum oxygen concentration in the oxygen-air mixture during APV in children of group I was statistically significantly higher ($p = 0.001$) than those in group II. Also, children in group I had a significantly longer duration of respiratory support ($p = 0.001$) than in children in group II.

Suppression syndrome was registered in the neurological status of children in both groups. The majority (67.6% in group I and 60.3% in group II) of infants had a delay in neuromuscular and physical development ($p > 0.05$) on the initial assessment with the Ballard Scale. Development corresponding to the gestational age was only 26.5% of newborns in group I and 29.3% in group II. The level of development exceeding the gestational age was registered in 5.9% of newborns in group I and 10.3% of patients in group II ($p > 0.05$).

From day 14 of life, newborns in group I had a statistically significant delay in neuromuscular and physical development according to the Ballard scale ($p = 0.002$). This tendency persisted until the end of the neonatal period ($p = 0.001$) (Fig. 1).

Table 2 / Таблица 2

The parameters of respiratory support for premature infants in the NICU in the early neonatal period
Параметры респираторной поддержки глубоко недоношенных новорожденных в отделении реанимации и интенсивной терапии в раннем неонатальном периоде

Indications / Показатели	Group I / Группа I ($n = 34$)	Group II / Группа II ($n = 58$)	*p*
$FiO_{2\ max}$	0.42 [0.3; 0.65]	0.25 [0.21; 0.3]	0.001
V_{te}, ml / V_{te}, мл	7 [6; 10]	–	–
MAP, cm H_2O / MAP, см вод. ст.	9 [8; 10]	6 [6; 7]	0.001
Duration of respiratory support, hours / Длительность респираторной поддержки, ч	185 [96; 297]	72 [48; 92]	0.001

Note. $FiO_{2\ max}$ – the maximum fraction of oxygen in the oxygen-air mixture; V_{te} – expiratory respiratory volume; MAP – average airway pressure.

Примечание. $FiO_{2\ max}$ — максимальная фракция кислорода в кислородо-воздушной смеси; V_{te} — экспираторный дыхательный объем; MAP — среднее давление в дыхательных путях.

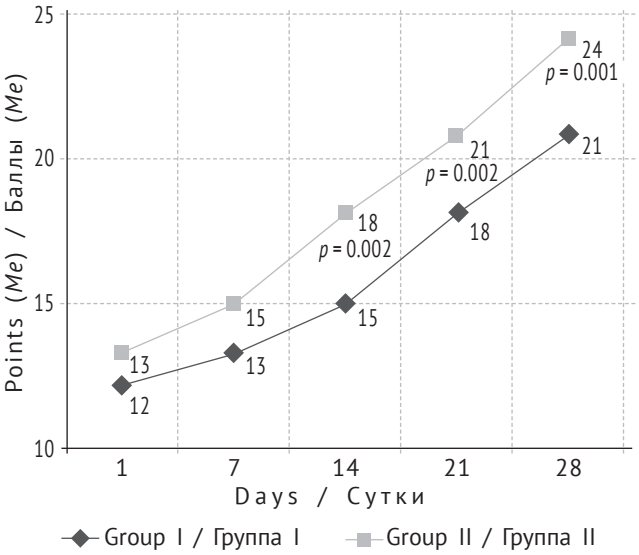

Fig. 1. Dynamics of neuromuscular and physical maturity in preterm infants according to the J. Ballard scale

Рис. 1. Динамика нейромышечной и физической зрелости у глубоко недоношенных новорожденных по шкале J. Ballard

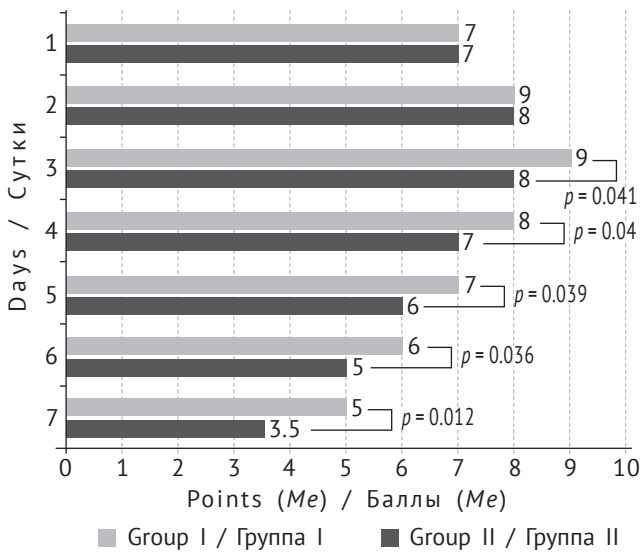

Fig. 2. Pain level on the EDIN6 scale in preterm infants in the early neonatal period

Рис. 2. Уровень боли по шкале EDIN6 у глубоко недоношенных новорожденных в раннем неонатальном периоде

The pain level on the first day of life was 7 [range, 7–9] points in group I and 7 [range, 6–9] points in group II ($p > 0.05$), which is interpreted as moderate pain. The daily assessment of pain intensity in extremely premature infants throughout the early neonatal period is presented in Fig. 2.

In the first two days, the pain level in patients of both groups was also statistically indistinguishable ($p > 0.05$). The maximum pain intensity in children of the group I was noted on the third day of life, and the EDIN6 score was 9. Starting from the third day of life until the end of the early neonatal period, the intensity of pain was significantly higher in children of group I ($p < 0.05$).

When analyzing the frequency of painful manipulations, children of group I in the early neonatal period underwent a significantly greater number of manipulations (20.8 ± 2.14 manipulations per day in group I versus 17.7 ± 2.05 manipulations per day in group II; $p = 0.016$) that caused pain or exerted stress. The most frequent procedures (% of the total number of manipulations) causing acute pain in extremely premature infants were changing baby linens and diapers (43%), changing body position (21%), puncturing the skin for taking tests (12%), manipulations for correct fixing the interface to provide CPAP therapy (9%), cleaning the trachea (6%), weighing (4%), cleansing the oral cavity and nasal passages (4%), inserting a naso- or orogastric tube for feeding children (3%), and others (10%). In addition, all newborns experienced the background effects of pain and/or stress during respiratory support using CPAP or APV. Depending on the group, these effects occurred from the placement of an endotracheal tube for APV in children of group I, the constant presence of an orogastric tube during respiratory support, continuous infusion through the deep venous line, and phototherapy.

The analysis of respiratory support revealed that in those children who, during APV (group I) required a mean airway pressure (MAP) of 10 cm H_2O or higher [$n = 6$ (17.6%)], the pain level was 11 [range, 10–11] points, which meets the criteria of severe pain on the EDIN6 scale and is significantly higher ($p = 0.001$) than in children on APV with a MAP lower than 10 cm H_2O (Fig. 3).

It was established that in children who required a MAP level of 6.5 cm H_2O or higher [$n = 9$ (15.5%)] for CPAP therapy, the pain level was recorded as an 8 [range, 7–9] points, the highest in the group, and met the criteria for moderate pain (Fig. 4).

Monitoring children over time showed that at the end of the neonatal period, body weight was 1450 [range, 1130–1610] g in children of group I, and 1520 [range, 1150–1650] g in children of group II ($p > 0.05$); body length of newborns was 35 [range, 31–38] cm in group I and 36 [range, 31–39] cm in children of group II ($p > 0.05$); head circumference was 28 [range, 27–31] cm in children of group II, and 27 [range, 26–29] cm

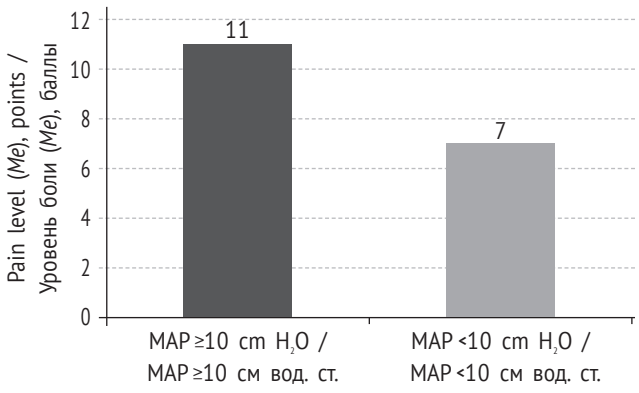

Fig. 3. The level of pain in preterm infants with mechanical ventilation (group I) depending on the MAP

Рис. 3. Уровень боли у детей, которым проводится ИВЛ (I группа), в зависимости от MAP

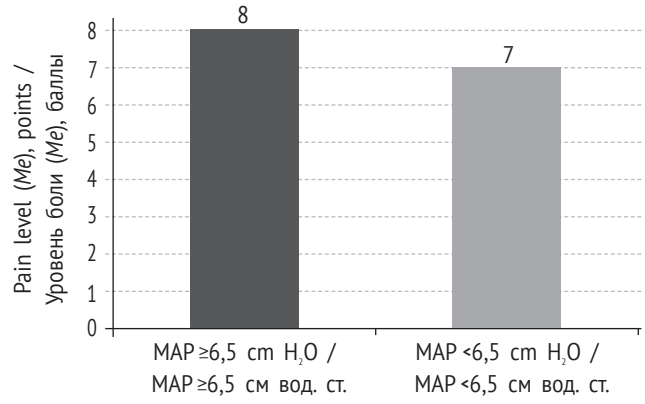

Fig. 4. The level of pain in preterm infants with CPAP (group II) depending on the MAP

Рис. 4. Уровень боли у детей, получающих CPAP (II группа) в зависимости от MAP

in children of group I ($p = 0.043$). A statistically smaller head circumference in children of group I at the end of the neonatal period may indicate significant influences of various factors acting in the early neonatal period (the presence of invasive ventilation, duration of APV, $FiO_{2\ max}$ during respiratory support, others), including the pain intensity.

An inverse correlation was revealed between the average number of manipulations in the early neonatal period in extremely premature infants of both groups and the head circumference by day 28 of life ($R = –0.64$; $p = 0.004$), and an inverse relationship between the average number of manipulations in the early neonatal period in extremely premature infants of both groups with a Ballard Score on day 28 of life ($R = –0.57$; $p = 0.008$).

DISCUSSION

Within the implementation of the concept of developing care for extremely premature newborns, much attention is paid to preserve the child's life successfully and reducing the incidence of late developmental disorders. Also, the influence of manipulations and actions of medical personnel during the first days of life affect long-term disease outcomes.

The study results demonstrated that the total number of painful procedures during the early neonatal period in extremely premature infants who received respiratory support averaged 18.8 ± 1.6 per day. The results obtained are comparable with the results of other authors, demonstrating that newborns can experience 10–18 painful manipulations per day [9, 11]. Although many procedures that we consider painful (diaper change, skin treatment in cases of local infection, use of nasal cannulas) are common in the neonatal RICU and most often are not defined as stressful by most doctors, their ability to influence other outcomes, in particular, the psychoneurological development of the child, must be considered in the future [1, 18, 25].

Particular attention should be paid during the first two days of life since there was no significant difference in pain intensity in children of both groups. The maximum pain intensity was noted in all children on the third day of life. Therefore, during the first two days of life, in extremely premature infants, protective mechanisms are activated, including the production of opioid peptides with analgesic and sedative effects and the presence of endogenous glucocorticoids [4, 14, 16]. However, in the presence of severe pathology, compensatory mechanisms are quickly depleted, and the pain intensity increases. The concentrations of endogenous active substances in extremely premature infants requiring respiratory support decrease over time. Therefore, one of the main tasks of the RICU personnel on the third day of life consists of controlling pain intensity by expanding the measures aimed at eliminating it [14, 16].

By the end of the early neonatal period, pain intensity tended to decrease in both groups ($p = 0.003$ and $p = 0.001$, respectively). In contrast, the mean values in group II on the seventh day of life bordered moderate and minimal pain levels. This result is probably due to the stabilization of patients and regression of the primary pathological process during therapeutic measures by the end of the early neonatal period. In children who underwent invasive APV, the intensity of pain, starting from the third day of life, was significantly higher

($p = 0.001$) than in newborns on CPAP therapy. Differences were revealed in pain intensity depending on the average airway pressure.

We believe that in the presence of signs of severe pain (an EDIN6 score greater than 10 points), both drug and non-drug methods of analgesia must be used to eliminate it [10, 16].

In children who required the MAP level of 6.5 cm H_2O or higher during CPAP therapy, pain intensity was recorded as the highest in the group ("moderate" pain on the EDIN6 scale). This can be explained by the negative effect of high flow and medium pressure on irritated receptors of the nasal passages [16].

When assessing neuromuscular and physical maturity according to the Ballard Scale (Fig. 1), a minimum increase ($p = 0.047$ in group I and $p = 0.031$ in group II) in points was registered in both groups by the end of the early neonatal period. This increase might be explained by the severity of the condition in children requiring intensive care. Also, there was further significant ($p = 0.001$ in both groups) improvement in development by day 28 of life. According to the results of the correlation analysis, many manipulations performed by extremely premature newborns contributed to a decrease in the increment in head circumference and a reduction in neuromuscular and physical development by the end of the neonatal period. Studies have revealed [13] that stressful events predict poorer development of motor skills, strength, and orientation in premature infants. Many painful procedures were directly associated with the subsequent decrease in head circumference growth and brain function in extremely premature infants. Also, recurring pain during the stabilization period can activate a stress signaling cascade that affects subsequent growth and development [24, 25]. The revealed differences in anthropometric parameters and the dynamics of neuromuscular and physical development (according to the Ballard Scale) of the newborns examined, depending on the pain level, will be necessary for the further neuropsychic development of an extremely premature child.

Based on the study, we calculated the risk of slowing down neuromuscular and physical development by day 28 of life in extremely premature infants who require respiratory support. When the number of painful manipulations during the early neonatal period exceeds 21 procedures per day, the risk of delayed development in a child increases by more than 3.5 times ($p = 0.009$; OR = 3.68; CI = 1.12–8.36).

CONCLUSIONS

1. The total number of painful manipulations in extremely premature infants requiring respiratory support is 18.8 ± 1.6 per day. The maximum pain intensity in the early neonatal period is typical for three days of life when most invasive procedures are performed.

2. Pain intensity in extremely premature infants requiring respiratory support is moderate, with the maximum EDIN6 score in infants requiring invasive APV.

3. MAP is one of the main factors determining pain intensity in extremely premature infants who require respiratory support. When conducting invasive APV, the "critical" MAP value is considered to be 10 cm H_2O or higher, and in patients who received CPAP therapy, it was 6.5 cm H_2O or higher.

ADDITIONAL INFORMATION

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CHANGES OF MORPHOFUNCTIONAL STATE OF CARDIOVASCULAR SYSTEM IN ADOLESCENTS WITH METABOLIC SYNDROME MANIFESTATIONS

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The results of investigation of features of morphofunctional state of cardiovascular system in adolescents with manifestations of metabolic syndrome depending on presence of hyperuricemia are presented. In the cardiorheumatology department of the hospital, 34 adolescent patients were observed. Criteria for inclusion in the study: the presence of increased blood pressure levels, increased body mass index values. Depending on serum uric acid levels, patients were divided into two groups: group 1 – patients without hyperuricemia ($n = 18$) and group 2 – patients with hyperuricemia ($n = 16$). Functional diagnostic methods were used: standard 12-channel electrocardiography, transtoral echocardiography, daily Holter monitoring. The main attention was paid to the study of the parameters of the left ventricle. Student's *t*-test was used to determine the significance of the differences, the results at $p < 0.05$ were considered reliable. It was established that adolescents with hyperuricemia were more often diagnosed with primary and secondary arterial hypertension, less often with labile arterial hypertension and autonomic dysfunction syndrome by hypertensive type, and adolescents without hyperuricemia were equally often diagnosed with primary arterial hypertension and labile arterial hypertension, autonomic dysfunction syndrome by hypertensive type. Signs of left ventricular remodeling according to echocardiography were more often noted in boys without hyperuricemia (62.5% of cases) than in girls without hyperuricemia (10%; $p < 0.01$) and in boys with hyperuricemia (26.7%; $p > 0,05$). The findings indicated more significant changes in the morphofunctional state of the cardiovascular system in adolescents with hypertensive conditions and manifestations of metabolic syndrome without hyperuricemia, which requires further study.

Keywords: cardiovascular system; morphofunctional state; adolescents; metabolic syndrome; hyperuricemia.

ИЗМЕНЕНИЯ МОРФОФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ У ПОДРОСТКОВ С ПРОЯВЛЕНИЯМИ МЕТАБОЛИЧЕСКОГО СИНДРОМА

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Представлены результаты исследования особенностей морфофункционального состояния сердечно-сосудистой системы у подростков с проявлениями метаболического синдрома в зависимости от наличия гиперурикемии. В кардиоревматологическом отделении наблюдали 34 пациента подросткового возраста. Критерии включения

в исследование: наличие повышенных значений уровня артериального давления и индекса массы тела. В зависимости от значений уровня мочевой кислоты в сыворотке крови пациенты были разделены на две группы: группа 1 — пациенты без гиперурикемии ($n = 18$) и группа 2 — пациенты с гиперурикемией ($n = 16$). Использовались функциональные методы диагностики: стандартная 12-канальная электрокардиография, трансторакальная эхокардиография, суточное холтеровское мониторирование. Основное внимание уделяли изучению параметров левого желудочка. Для определения значимости различий использовали *t*-критерий Стьюдента, достоверными считали результаты при $p < 0,05$. Установлено, что у подростков с гиперурикемией чаще диагностировали первичную и вторичную артериальную гипертензию, реже — лабильную артериальную гипертензию и синдром вегетативной дисфункции по гипертоническому типу, а у подростков без гиперурикемии одинаково часто диагностировали первичную артериальную гипертензию и лабильную артериальную гипертензию, синдром вегетативной дисфункции по гипертоническому типу. У мальчиков без гиперурикемии превалировала лабильная артериальная гипертензия, а у девочек — синдром вегетативной дисфункции по гипертоническому типу. Признаки ремоделирования левого желудочка по данным эхокардиографии чаще отмечали у мальчиков без гиперурикемии (62,5 % случаев), чем у девочек без гиперурикемии (10 %; $p < 0,01$) и у мальчиков с гиперурикемией (26,7 %; $p > 0,05$). Полученные данные свидетельствуют о более значимых изменениях морфофункционального состояния сердечно-сосудистой системы у подростков с гипертензивными состояниями и проявлениями метаболического синдрома без гиперурикемии, что требует дальнейшего изучения.

Ключевые слова: сердечно-сосудистая система; морфофункциональное состояние; подростки; метаболический синдром; гиперурикемия.

BACKGROUND

Arterial hypertension is recognized as a component of metabolic syndrome (MS) in the adult population and is considered a significant and independent risk factor for cardiovascular pathology [2]. The urgency of this problem has recently prompted studies of MS-associated comorbid conditions in adolescents, despite numerous disagreements and disputes over the diagnostic criteria for MS and its clinical significance [3, 4, 12]. The concept of MS has not been specified in the ICD-10 and is not subject to statistical accounting. However, in real life, it is constantly discussed by doctors and the population regarding preventing adverse medical consequences, such as atherosclerosis and type 2 diabetes mellitus. MS is considered a "disease of abundance," which clinically presents as obesity with dyslipidemia and arterial hypertension. At the same time, hyperuricemia in adults is recognized as an integral component of MS since it is often combined with insulin resistance and lipid metabolism disorders [13]. Evidence indicates that arterial hypertension and abdominal obesity in adolescents contribute to the deterioration of cardiovascular system functional characteristics. This deterioration manifests as an increase in the frequency of left ventricular myocardial remodeling in the form of concentric hypertrophy with initial manifestations of diastolic dysfunction [14]. The effect of hyperuricemia in adolescents with MS on the cardiovascular system morphofunctional parameters has not been adequately studied.

This study aims to determine the aspects of the cardiovascular system morphofunctional condition in adolescents with manifestations of MS, depending on the presence of hyperuricemia.

PATIENTS AND METHODS

From 2018 to 2019, 34 adolescent patients ($M \pm \sigma = 15.4 \pm 1.9$ years) were under follow to up in the cardio-rheumatology department of St. Petersburg St. Mary Magdalene Children's City Hospital No. 2 (chief physician A.G. Mikava). They were consistently admitted for examination and treatment of increased blood pressure (BP) values.

The criteria for enrolling patients in the study were elevated BP values and increased body mass index (BMI) values.

The decision about the increase in BP was made considering the clinical recommendations "Arterial hypertension in children" of the Ministry of Health of the Russian Federation (2016) [6]. The systolic (SBP, mm Hg) and diastolic blood pressure (DBP, mm Hg) were determined based on the centile distribution of the patient's height. The assessment categories were defined in points, where 0 conditional points indicated normal BP, 1 point meant high normal BP, and 2 points implied arterial hypertension. Body weight was measured and assessed by height (in points according to centile tables). Height was measured and determined by patient age (in points according to centile tables), and BMI (kg/m^2) was calculated. BMI values were considered increased if they were not lower than the 75 centile level, corresponding to assessments of 6, 7, or 8 points.

Depending on the values of uric acid levels in the blood serum (more than 400 μmol/L for boys and more than 300 μmol/L for girls), the patients were distributed into two groups: group 1 consisted of patients without hyperuricemia ($n = 18$; 52.9%) and group 2 included patients with hy-

peruricemia (n = 16; 47.1%). Although the groups were comparable regarding age, they had gender differences, as boys comprised the majority (n = 23; 67.6%).

All patients underwent general clinical blood and urine tests; biochemical blood test with the determination of parameters of fat and carbohydrate metabolism [cholesterol, low-density lipoproteins (LDL) and high-density lipoproteins (HDL), atherogenic index, triglycerides, glucose], with an assessment of the thyroid profile [total T3, free T4, thyroid-stimulating hormone (TSH)]. Additionally, the blood levels of creatinine and cortisol were determined.

The examination protocol included functional and radiation diagnostic methods, namely standard 12-lead electrocardiography (ECG) (Shiller and Fucuda), transthoracic echocardiography (Echo-CG) (Toshiba Aplio500CV and Vivid 7 Pro), 24-hour Holter monitoring (HM), ECG (Kardiotehnika 07 Inkart), ultrasound examination (US) of the thyroid gland and abdominal organs, and examination of the fundus. When analyzing the ECG to determine the signs of left ventricular myocardial hypertrophy (LVMH), the Sokolow–Lyon index was also determined. The percentile distribution of the Echo-CG values was determined depending on body weight according to the tables of Belozerov and Bolbikov [1] and expressed in points. At the same time, the evaluation of echo-CG indicators of 1 point corresponding to values less than 3 percentiles, 2 points corresponding to values from 3 to 10, 3 points corresponding to values from 10 to 25, 4 points corresponding to values from 25 to 50, 5 points corresponding to values from 50 to 75, 6 points corresponding to values from 75 to 90, 7 points corresponding to values from 90 to 97, and 8 points corresponded to values more than 97 percentiles. The mean values of the echo-CG parameters and their percentile distribution were calculated depending on the body weight in the patient groups.

Considering that in adolescents, arterial hypertension and abdominal obesity (as components of MS) contribute to the deterioration of the functional characteristics of the cardiovascular system, which is primarily manifested by remodeling of the left ventricle (LV), most attention was paid to echo-CG parameters of the LV. The end-systolic (ESD, cm) and end-diastolic (EDD, cm) dimensions of the LV were measured and evaluated. The LV myocardium mass (LVMM, g), LV myocardial mass index (LVMMI, g/m^2), the thickness of the interventricular septum (IVS, mm), the thickness of the LV posterior wall (LVPW, mm), and the LV wall relative thickness (LVWRT) were evaluated [9, 16]. The echo-CG criterion for LVMH in boys was considered to be LVMMI at least 47.58 g/m^2, and in girls, these were LVMMI values of at least 44.38 g/m^2, corresponding to the value of the 99th percentile of the population distribution curve of LVMMI. Variants of LV myocardial changes (norm, concentric remodeling, concentric hypertrophy, eccentric hypertrophy with or without dilatation) were assessed according to the echo-CG indicators, namely LVMM (LVMMI), LVWRT, ESD, and EDD of the LV [6].

Based on generally accepted diagnostic criteria, the patients were diagnosed with essential (primary) arterial hypertension (ICD-10 code I10); symptomatic (secondary) arterial hypertension in relation to endocrine disorders (ICD-10 code I15.2); labile arterial hypertension, and autonomic dysfunction syndrome of the hypertensive type (the latter are not defined by ICD-10 as independent nosological units).

Data collection, storage, and primary grouping were performed using MS Office tools. Also, statistical data analysis was performed. The incidence of the attribute, the mean value of the indicator (M), and the standard deviation (σ) were calculated. Considering the normal distribution of the sample (quantitative data were checked for normality of distribution using the Shapiro–Wilk test), Student's t-test was used to determine the significance of differences. The results were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Analysis of the gender composition of patients in groups revealed that in group 1, the quantities of boys and girls did not differ significantly ($p > 0.05$). In contrast, in group 2, boys represented the absolute majority (93.8%; $p < 0.05$), confirming known data on the prevalence of males among patients with hyperuricemia [5]. The average age of boys in the groups did not differ significantly, just as the average age of boys and girls in group 1 did not differ significantly (Table 1).

When studying the absolute and relative values of anthropometric indicators in the patient groups, boys in group 2 were taller without differences in its relative values (Table 2).

An analysis of the established clinical diagnoses showed that primary arterial hypertension was diagnosed more often in group 1 than in group 2. In contrast, secondary arterial hypertension was diagnosed more often in group 2. Labile arterial

Table 1 / Таблица 1

Sex composition and mean age of patients in groups
Половой состав и средний возраст пациентов в группах

Sex composition and average age of patients / Половой состав и средний возраст пациентов		Group 1 / Группа 1 (n = 18)	Group 2 / Группа 2 (n = 16)
Boys / Мальчики, лет		8 (44.4%)	15 (93.8%)
Girls / Девочки, лет		10 (55.6%)	1 (6.2%)
Middle age, years ($M \pm \sigma$) / Средний возраст, лет ($M \pm \sigma$)	boys / мальчики	15.3 ± 1.9	16.2 ± 0.9
	girls / девочки	14.6 ± 2.5	14

Table 2 / Таблица 2

Absolute and relative values of anthropometric measures and blood pressure in boys and girls of observed groups
Абсолютные и относительные значения антропометрических показателей и артериального давления у мальчиков и девочек наблюдаемых групп

Indicators / Показатели	Group 1 / Группа 1		Group 2 / Группа 2	
	boys / мальчики (n = 8)	girls / девочки (n = 10)	boys / мальчики (n = 15)	girls / девочки (n = 1)
Body weight, kg / Масса тела, кг	86.1 ± 13.8	71.1 ± 21.1	92.5 ± 15.2	127
Body weight estimate by height, point / Оценка массы тела по росту, балл	6.6 ± 0.7	6.0 ± 1.2	6.6 ± 1.1	7
Height, cm / Рост, см	171.9 ± 5.9	163.0 ± 11.6	178.6 ± 6.6*	170
Age growth score, point / Оценка роста по возрасту, балл	5.0 ± 2.4	5.7 ± 1.4	5.5 ± 1.6	6
BMI (kg/m^2) / Индекс массы тела, кг/м^2	29.4 ± 5.4	26.0 ± 5.3	29.1 ± 4.1	43.8
BMI assessment, point / Оценка индекса массы тела балл	7.8 ± 0.5	7.3 ± 1.0	7.5 ± 1.0	8
Assessment of systolic blood pressure level, conditional point / Оценка уровня систолического АД, усл. балл	2 ± 0	1.6 ± 0.8	2 ± 0	2
Assessment of diastolic blood pressure level, conditional point / Оценка уровня диастолического АД, усл. балл	1.5 ± 0.8	1.4 ± 0.8	1.7 ± 0.6	2

* t = 2.4; $p < 0.05$ (Student ratio and rate of difference between Group 1 and Group 2 boys).
* t = 2,4; $p < 0,05$ (коэффициент Стьюдента и уровень различий показателя между мальчиками группы 1 и группы 2).

hypertension was detected more often in boys of group 1 than in boys of group 2. The autonomic dysfunction syndrome of the hypertensive type was detected more often in girls of group 1 (Table 3).

The data obtained indicate that among patients of group 2, primary and secondary arterial hypertension prevailed in relation to labile arterial hypertension and autonomic dysfunction syndrome of hypertensive type., Among patients of group 1, there was an equal ratio of primary arterial hypertension (50% of cases) and labile arterial hypertension, autonomic dysfunction syndrome of the hypertensive type (50% of cases in total). In boys of group 1, labile arterial hypertension prevailed, and in girls, the autonomic dysfunction syndrome of the hypertensive type prevailed.

Analysis of complaints presented by boys and girls in group 1 showed a rarer incidence of vertigo, 25% versus 90% in girls (t = –3.39; $p < 0.01$). Vertigo was clinically assessed as a manifestation of autonomic dysfunction syndrome, which was significantly more common in girls of group 1. Differences in the frequency of complaints of headaches, sleep disturbances, and heart failure was not significant. An increase in appetite was noted in 75% of boys and only 30% of girls (t = 2.01; $p > 0.05$). A decrease in physical performance was revealed in 25% of boys and 30% of girls. When compa-

Table 3 / Таблица 3

Clinical diagnosis options in boys and girls in observed groups
Варианты клинического диагноза у мальчиков и девочек в наблюдаемых группах

Clinical diagnosis options / Варианты клинических диагнозов	Group 1 / Группа 1		Group 2 / Группа 2	
	boys / мальчики (n = 8)	girls / девочки (n = 10)	boys / мальчики (n = 15)	girls / девочки (n = 1)
Primary arterial hypertension / Первичная артериальная гипертензия	4 (50%)	5 (50%)	3 (20%)	0
Secondary arterial hypertension / Вторичная артериальная гипертензия	0 (0%)	0 (0%)	7 (46.7%)	1 (100%)
Labile arterial hypertension / Лабильная артериальная гипертензия	3 (37.5%)	1 (10%)	2 (13.3%)	0
Autonomic dysfunction syndrome by hypertensive type / Синдром вегетативной дисфункции по гипертоническому типу	1 (12.5%)	4 (40%)	3 (20%)	0

Table 4 / Таблица 4

Values of biochemical metabolic indices in patients of observed groups
Значения биохимических показателей обмена веществ у пациентов наблюдаемых групп

Indicators of biochemical blood analysis / Показатели биохимического анализа крови	Group 1 / Группа 1		Group, 2 boys / Группа 2, мальчики (n = 15)
	boys / мальчики (n = 8)	girls / девочки (n = 10)	
Cholesterol, mmol/L / Холестерин, ммоль/л	4.4 ± 0.7	4.7 ± 1.0	4.6 ± 1.2
Low density lipoproteins, mmol/L / Липопротеиды низкой плотности, ммоль/л	2.1 ± 0.4	2.3 ± 0.7	2.2 ± 0.6
High density lipoproteins, mmol/L / Липопротеиды высокой плотности, ммоль/л	1.4 ± 0.4	1.3 ± 0.3	1.2 ± 0.4
Atherogenicity factor/ Коэффициент атерогенности	2.3 ± 1.0	2.6 ± 1.2	2.9 ± 1.2
Triglycerides, mmol/L / Триглицериды, ммоль/л	1.8 ± 0.7	1.4 ± 0.9	1.4 ± 0.5
Glucose, mmol/L / Глюкоза, ммоль/л	5.2 ± 0.3	4.5 ± 0.4*	5.0 ± 0.5
Creatinine, μmol/L / Креатинин, мкмоль/л	77.4 ± 15.7	62.0 ± 16.4	88.7 ± 11.5

* t = 2.4; p < 0.001 (Student ratio and rate of difference in group 1 boys and girls)
* t = 2,4; p < 0,001 (коэффициент Стьюдента и уровень различий показателей у мальчиков и девочек группы 1).

ring the frequency of complaints of vertigo, headaches, sleep disturbances, and heart failure in boys of groups 1 and 2, no significant differences were detected. An increase in appetite was registered in 75% of boys of group 1 and 80% of group 2. At the same time, a decrease in physical performance was noted more often in boys of group 2 (60%) than in boys of group 1 (25%; t = –1.9; p > 0.05).

The hereditary burden of cardiovascular pathology was registered equally often in boys of both groups (62.5% of cases each) and exceeded that value in girls of group 1 (40% of cases; p > 0.05).

The average values of lipid metabolism in patients of the groups under study did not differ significantly. However, the atherogenic index was higher in boys of group 2, and the level was higher in boys of group 1 (Table 4). The fasting blood glucose level in boys of group 1 was within the normal range but significantly higher than in girls, indirectly indicating a relative decrease in glucose tolerance. Increased BP values, increased blood glucose levels, and obesity are interrelated components of MS in adolescents [5]. Data analysis of biochemical metabolism parameters revealed more distinct changes in boys, as noted earlier [8].

Table 5 / Таблица 5

Structure and frequency of heart rhythm disorders in patient groups
Структура и частота нарушений ритма сердца в группах пациентов

Types of heart rhythm disorders / Виды нарушений ритма сердца	Group 1 / Группа 1		Group 2 / Группа 2	
	boys / мальчики (n = 8)	girls / девочки (n = 10)	boys / мальчики (n = 15)	girls / девочки (n = 1)
Sinus tachycardia / Синусовая тахикардия	3 (37.5%)	3 (30%)	4 (26.7%)	0
Sinus bradycardia / Синусовая брадикардия	2 (25%)	0	1 (6.7%)	0
Unstable supraventricular tachycardia / Неустойчивая суправентрикулярная тахикардия	0	0	1 (6.7%)	0
Single ventricular extrasystoles / Одиночные желудочковые экстрасистолы	1 (12.5%)	0	1 (6.7%)	1 (100%)
Transient AV blockade of 1 degree / Транзиторная АВ-блокада 1-й степени	0	1 (10%)	1 (6.7%)	0

According to the US, signs of fatty hepatosis were detected in 25% of boys and 10% of girls of group 1, and 53.3% of boys in group 2 ($p > 0.05$). Signs of pancreatic steatosis were revealed in 25% of boys and 30% of girls in group 1, and 60% of boys in group 2 ($p > 0.05$). Signs of hypomotor dysfunction of the biliary tract were seen in 25% of boys in group 1 and 66.7% of boys in group 2 ($t = 2.02$; $p > 0.05$). The data obtained indicated slightly more frequent morphofunctional changes in the hepato-pancreato-biliary system in boys of group 2 than in group 1.

The average values of T3, T4, TSH, and cortisol in the patient groups were within the normal range and did not differ significantly. Autoimmune thyroiditis was diagnosed in one (12.5%) boy of group 1, and secondary (postoperative) hypothyroidism was diagnosed in one (6.7%) boy of group 2.

Evaluation of ECG signs of LVMH revealed no significant differences in the values of the Sokolow–Lyon index in boys and girls of group 1 (27.8 ± 7.0 and 29.2 ± 5.6 mm, respectively), as well as in boys of both groups (27.8 ± 7.0 and 29.0 ± 8.3 mm, respectively). At the same four children (one boy and one girl of group 1, and in two boys of group 2). Moreover, LV myocardial hypertrophy was confirmed by echo-CG data in only one patient.

According to the HM ECG data, the average values of the circadian index in the groups did not differ significantly. However, the enhanced circadian profile of the heart rate (confidence interval (CI) > 1.45), indicated the increased sensitivity of the heart rate to sympathetic influences, was more often detected in girls of group 1 (50%) than in boys of group 1 (12.5%; $p > 0.05$) and group 2 (13.3%; $p > 0.05$). A decrease in CI, which has a prognostically unfavorable value at a level of less than 1.22 [10, 11], the so-called rigid circadian profile of heart rate, was noted in one patient (12.5%) of group 1 with secondary arterial hypertension.

The average values of the minimum heart rate during the day and at night in the groups of patients did not differ significantly. This finding partially coincided with the data of the authors who studied the heart rate variability in adult patients with arterial hypertension [11]. Cardiac arrhythmias were more often registered in boys of group 1 (75% of cases) than in boys of group 2 (53.3%; $p > 0.05$) and in girls of group 1 (40%; $p > 0.05$) (Table 5). The cardiac arrhythmias identified were primarily due to an imbalance of the autonomic nervous system.

Echo-CG study revealed signs of LVMH in five (62.5%) boys of group 1, in one (10%) girl of group 1 ($t = 2.5$; $p < 0.01$), in four (26.7%) boys of group 2 ($p > 0.05$), and in one (100%) girl of group 2. It should be noted that the frequency of diagnosing LVMH according to ECG and echo-CG data does not coincide, which coincides with the data of other authors [7, 15].

Minor heart anomalies (additional LV chord, mitral valve prolapse) in group 1 were detected in 12.5% of boys and 60% of girls ($t = –2.3$; $p < 0.05$), and in 33.3% boys of group 2 ($p > 0.05$). Degree 1 aortic valve (AV) insufficiency of group 1 was di-

agnosed in one (10%) girl. Degree 1 mitral valve (MV) insufficiency was diagnosed in three (30%) girls of group 1 and in six (66.7%) boys of group 2 ($p > 0.05$). Degree 1 pulmonary artery (PA) regurgitation was revealed in one (12.5%) boy and four (40%) girls of group 1 ($p > 0.05$), and in seven (46.7%) boys and one (100%) girl of group 2.

The average values of echo-CG indicators and their percentile distribution depending on body weight (in points) in patients of the groups under study are presented in Table 6.

Evaluation of LV morphological aspects according to echo-CG data in boys of groups 1 and 2 (Table 6) revealed significantly higher values of

Table 6 / Таблица 6

Mean values and percentiles of echocardiographic scores in boys and girls in observed groups
Средние значения и процентили эхокардиографических показателей у мальчиков и девочек в наблюдаемых группах

Indicators and percentiles / Показатели и их процентили	Group 1 / Группа 1		Group 2 / Группа 2	
	boys / мальчики ($n = 8$)	girls / девочки ($n = 10$)	boys / мальчики ($n = 15$)	girls / девочки ($n = 1$)
Left ventricular anterior wall thickness, mm / Толщина передней стенки левого желудочка, мм	3.8 ± 0.5	3.6 ± 0.5	3.8 ± 0.4	5.0
Right ventricular diameter in diastole, mm / Диаметр правого желудочка в диастолу, мм	22 ± 3	24 ± 4	24 ± 4	28
Thickness of the ventricular septum in diastole, mm / Толщина межжелудочковой перегородки в диастолу, мм	10.0 ± 0.7	8.1 ± 0.9**	9.3 ± 0.9	10
Percentile of the thickness of the ventricular septum, point / Процентиль толщины межжелудочковой перегородки, балл	7.6 ± 0.5	6.0 ± 0.9**	7.0 ± 0.7♦	8
Left ventricular posterior wall thickness, mm / Толщина задней стенки левого желудочка, мм	9.9 ± 0.6	8.1 ± 1.1**	9.4 ± 0.9	12
Percentile of left ventricular posterior wall thickness, points / Процентиль толщины задней стенки левого желудочка, балл	7.6 ± 0.5	6.1 ± 1.8*	7.1 ± 0.6	8
Final diastolic diameter of the left ventricle, mm / Конечный диастолический диаметр левого желудочка, мм	50 ± 4	43 ± 3**	48 ± 3	55
Percentile of left ventricular thickness to diastole, point / Процентиль толщины левого желудочка в диастолу, балл	5.8 ± 1.8	3.8 ± 2.5	4.8 ± 1.7	8
Final systolic diameter of the left stomach, mm / Конечный систолический диаметр левого желудочка, мм	33 ± 2	28 ± 2***	31 ± 1♦♦	31
Left ventricular myocardial mass, g / Масса миокарда левого желудочка, г	184.0 ± 28.3	108.5 ± 24.4***	162.8 ± 33.0	247.3
Left ventricular myocardial mass index relative to body area / Индекс массы миокарда левого желудочка относительно площади тела	92.9 ± 15.5	62.5 ± 11.4 ***	77.2 ± 13.0♦	106.1
Relative thickness of left ventricular wall / Относительная толщина стенки левого желудочка	4.0 ± 0.4	3.8 ± 0.5	3.9 ± 0.3	4.4
Thoracic aortic diameter, mm / Диаметр грудной аорты, мм	30 ± 4	27 ± 2*	28 ± 4	29
Percentile of thoracic aortic diameter, points / Процентиль диаметра грудной аорты, баллов	6.6 ± 1.8	5.6 ± 1.2	5.3 ± 2.2	7
Anterior-posterior size of the left atrium, mm / Переднезадний размер левого предсердия, мм	36 ± 2	33 ± 3*	35 ± 3	39
Right atrial anterior-posterior percentile, point/ Процентиль переднезаднего размера левого предсердия, балл	7.9 ± 0.4	7.4 ± 1.3	7.3 ± 1.5	8
Right atrial diameter, mm / Диаметр правого предсердия, мм	40 ± 4	33 ± 5**	36 ± 3♦	32
Pulmonary artery diameter, mm / Диаметр легочной артерии, мм	22 ± 1	20 ± 1***	21 ± 1♦	23

Table 6 (continued) / Продолжение таблицы 6

Indicators and percentiles / Показатели и их процентили	Group 1 / Группа 1		Group 2 / Группа 2	
	boys / мальчики (n = 8)	girls / девочки (n = 10)	boys / мальчики (n = 15)	girls / девочки (n = 1)
Emission fraction, % / Фракция выброса, %	66.0 ± 3.6	68.4 ± 3.9	68.3 ± 4.9	72
Global left ventricular longitudinal deformation, % / Глобальная продольная деформация левого желудочка, %	34.4 ± 1.7	37.2 ± 3.2*	37.4 ± 3.9	41
Maximum aortic blood flow rate, m/s / Максимальная скорость аортального кровотока, м/с	1.2 ± 0.1	1.0 ± 0.1**	1.1 ± 0.1♦	1.1
Pressure gradient on aortic valve, mm Hg / Градиент давления на аортальный кровоток, мм рт. ст.	6.7 ± 1.9	5.6 ± 0.6	5.4 ± 0.6♦	–
Maximum mitral blood flow rate, m/s / Максимальная скорость митрального кровотока, м/с	0.9 ± 0.2	0.9 ± 0.1	0.9 ± 0.1	0.7
Mitral valve pressure gradient, mm Hg / Градиент давления на митральный кровоток, мм рт. ст.	2.9 ± 1.0	2.6 ± 1.1	2.6 ± 0.7	–
Maximum pulmonary artery speed, m/s / Максимальная скорость в легочной артериии, м/с	1.0 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	0.8
Pulmonary artery pressure gradient, mm Hg / Градиент давления в легочной артериии, мм рт. ст.	4.0 ± 0.8	3.3 ± 0.5*	3.7 ± 0.5	–
Maximum tricuspid blood flow rate, m/s / Максимальная скорость трикуспидального кровотока, м/с	0.6 ± 0.1	0.7 ± 0.1	0.7 ± 0.1♦	0.9
Pressure gradient on tricuspid valve, mm Hg / Градиент давления на трикуспидальный клапан, мм рт. ст.	1.4 ± 0.3	2.2 ± 0.4***	1.8 ± 0.5♦	1.0
Systolic pressure in the pulmonary artery, mm Hg / Систолическое давление в легочной артерии, мм рт. ст.	14.8 ± 1.0	14.8 ± 0.8	15.3 ± 1.7	16

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (level of differences in values of indicators for boys and girls of group 1); ♦ $p < 0.05$; ♦♦ $p < 0.01$ (level of difference of values of indicators in boys of group 1 and group 2).
* $p < 0,05$; ** $p < 0,01$; *** $p < 0,001$ (уровень различий значений показателей у мальчиков и девочек группы 1); ♦ $p < 0,05$; ♦♦ $p < 0,01$ (уровень различий значений показателей у мальчиков группы 1 и группы 2).

the percentile of the IVS thickness, LV end-systolic dimension, LVMM index relative to body area in favor of group 1, which could indicate the course of the LV remodeling process. These changes influenced the parameters of the maximum aortic blood flow velocity and pressure gradient in the AV.

Comparing the average values of echo-CG indicators in boys and girls of group 1 revealed significant differences in most of the studied morphological and functional characteristics caused by sexual factors. At the same time, the absence of signs of systolic dysfunction of the right ventricle was registered, according to significantly higher values of fractional changes in the right ventricle area.

CONCLUSION

As a result of the studies, it was established that adolescents with hyperuricemia were more often diagnosed with primary and secondary arterial hypertension and other manifestations of MS, less often with labile arterial hypertension and the hypertensive type autonomic dysfunction syndrome. In contrast, adolescents without hyperuricemia were equally often diagnosed with primary arterial hypertension and labile arterial hypertension, and autonomic dysfunction syndrome of hypertensive type.

In boys, in the group of patients without hyperuricemia, labile arterial hypertension prevailed, and in girls, the autonomic dysfunction syndrome according to the hypertensive type, was more frequent. The hereditary burden of cardiovascular disease was registered more often in boys (62.5% of cases) than in girls (40% of cases; $p > 0.05$). More pronounced manifestations of metabolic disorders, accompanied by morphofunctional changes in the hepato-pancreato-biliary system, revealed by the US, were detected in boys with hyperuricemia. Cardiac arrhythmias were noted more often in boys of group 1 (75% of cases) than in boys of group 2 (53.3%; $p > 0.05$) and girls of group 1 (40%; $p > 0.05$).

Signs of LV remodeling according to Echo-CG data were registered more often in boys without hyperuricemia (62.5% of cases) than in girls without hyperuricemia (10%; $p < 0.01$) and in boys with hyperuricemia (26.7%; $p > 0.05$). The data obtained indicate more significant changes in the morphofunctional condition of the cardiovascular system in adolescents with hypertensive states and manifestations of MS without hyperuricemia, which requires further study.

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BASIC PRINCIPLES OF EARLY INTERVENTION FOR CHILDREN WITH HEARING LOSS

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Hearing loss is a common birth problem that can affect a baby's ability to develop speech, language and social skills in lack of comprehensive early intervention. Early intervention occurring within the first 6 months has higher effectiveness for hearing impaired children. The introduction of universal newborn hearing screening programs allowed to identify hearing loss in the first months of life. That determines the need of immediate comprehensive early intervention for children identified with hearing loss. The main approaches of such intervention have been described in detail in the literature. However there are not well-developed, evidence-based, well-documented recommendations for family-centred early intervention for children who are deaf or hard of hearing. Similar problems are noted in many countries, that is why in 2012, within the framework of an international conference, specialists and parents of deaf and hard of hearing children developed a document (international consensus statement). The experts arrived at consensus on 10 principles guiding family-centred early intervention. These principles are presented in the article as well as a brief description of their implementation in various countries. The consensus statement has become an important document which is intended to provide a framework for professionals over the world. Knowledge of these principles allows specialists to apply evidence-based approaches working with children who are deaf of hard of hearing.

Keywords: children; hearing loss; early intervention program; principles; consensus.

ОСНОВНЫЕ ПРИНЦИПЫ СИСТЕМЫ РАННЕЙ ПОМОЩИ ДЕТЯМ С НАРУШЕНИЯМИ СЛУХА

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Нарушение слуха — часто встречающаяся проблема у детей раннего возраста. При отсутствии качественной программы помощи данная патология оказывает выраженное негативное влияние на развитие ребенка. При врожденной тугоухости наиболее эффективными являются программы помощи, начатые до возраста 6 мес. Внедрение всеобщего аудиологического скрининга новорожденных позволило выявлять и диагностировать нарушения слуха на первых месяцах жизни. Выявленные нарушения слуха требуют незамедлительного начала всесторонней программы помощи. Основные подходы к оказанию такой программы подробно представлены в отечественной литературе. Однако в настоящий момент отсутствуют единые, хорошо отработанные, задокументированные рекомендации по составлению и реализации программ помощи для детей раннего возраста с проблемами слуха. Сходные трудности отмечаются во многих странах мира, что послужило причиной объединения усилий специалистами из разных стран.

В 2012 г. в рамках международной конференции специалистами и родителями глухих и слабослышащих детей был выработан документ (международный консенсус), регламентирующий основные принципы семейно-центрированной системы ранней помощи детям с нарушениями слуха, соответствующие этим принципам программы и требования к специалистам. В статье представлены данные принципы, а также приведено краткое описание их реализации в различных странах. Данное консенсусное заявление стало важным документом в работе специалистов всего мира. Знание этих принципов позволяет специалистам применять доказательные подходы при работе с глухими и слабослышащими детьми.

Ключевые слова: дети; нарушение слуха; раннее вмешательство; программа помощи; принципы; консенсус.

INTRODUCTION

Sound is very significant in a person's life and perception of the surrounding environment. Each sound carries certain information. During the day, we hear and focus on many everyday sounds, danger signals warn us, music gives great pleasure and enjoyment, but the most critical sound signal for a person is speech, which is the basis of our communication with other people. That is why any hearing impairment can harm a child's development. Especially significant problems can arise with congenital hearing impairment. In the absence of a timely, high-quality program of assistance, the central departments of the auditory system do not receive the necessary acoustic stimulation in the first years of life, which disrupts their formation, leading to irreversible consequences. Hearing impairment is the most common pathology of the sensory systems and, according to the World Health Organization, there are approximately 34 million children with hearing impairment in the world. At the same time, approximately 2–3 children out of 1000 are born with congenital hearing abnormalities, and during the first years of life, another 1–2 babies out of 1000 acquire bradyacuasia [11, 16, 19].

Approaches to detecting hearing pathology in children based on the analysis of only risk factors are not highly effective since only approximately 50% of hearing-impaired children are at risk of hearing disorders. That is why in many countries, including Russia, compulsory audiological screening is currently performed, covering all newborns. This enables to suspect bradyacuasia very early (in the first weeks of life) and perform the necessary diagnostic procedures already in the first months of life. The methods of screening and diagnostic examinations in children of the first year of life have been studied well, described, and standardized [3, 16]. Such examinations are implemented in most countries in accordance with national recommendations. In the Russian Federation, they are presented in the form of Clinical Recommendations of the Ministry of Health [5]. Undoubtedly, there are still several issues to improve the efficiency of both primary audiological screening and the diagnostic stage. However, in general, the introduction of the existing hearing screening system in newborns has solved the early detection of congenital bradyacuasia. Currently, the average age for diagnosing congenital hearing impairments in Russia is seven months [12, 13].

Identification of hearing impairment requires a comprehensive program of assistance for hearing-impaired and deaf children as soon as the problem is discovered. The main issues of implementing assistance programs in Russia are presented in the literature by various specialists and parents of deaf and hard-of-hearing children [1, 2, 4, 6–9, 14]. However, at the same time, there are no uniform, well-developed programs to help young children with hearing problems. A similar situation is noted in many countries of the world, which was why the pooling of knowledge and efforts of specialists from different countries and parents of children with hearing impairments.

In June 2012, in Bad Ischl, Austria, the first International Family-Centered Early Intervention Conference for Children who are Deaf or Hard of Hearing was held. Later this conference became traditional. During the conference, hearing professionals, program managers, early intervention specialists, and parents of children with hearing impairments discussed the principles of family-centered early care systems and the methods of their implementation in different countries. Based on the discussion results, these principles were clarified, and a consensus was reached in determining the most effective approaches in early assistance to deaf and hard-of-hearing children. A document (international consensus statement) regulating the principles themselves, the programs corresponding to them, and the requirements for specialists were drawn up. The document was signed by representatives from different countries by Professor I.V. Koroleva on the part of the Russian Federation [17]. Since its publication in 2013, this consensus statement has become an essential document for hearing professionals worldwide.

Being aware of these principles, specialists (pediatricians, neurologists, audiologists, teachers of

the deaf and hard of hearing, speech therapists, social workers, special educators, others) can apply comprehensive, evidence-based approaches in working with families with deaf and hard-of-hearing children. The main provisions of the consensus are summarized below, and a brief description of the implementation of its principles in various countries. The full text of the consensus is presented in the publication by M.R. Moeller et al. [17].

INTERNATIONAL CONSENSUS STATEMENT FOR FAMILY-CENTERED EARLY ASSISTANCE FOR DEAF AND HARD-OF-HEARING CHILDREN

Principle 1: Early, timely, and equitable access to services. This regulation prescribes timely audiological screening of newborns and diagnostic examination by qualified personnel in accordance with accepted recommendations; immediate inclusion of the family in the early assistance program when a child's hearing pathology is detected. It provides the family with comprehensive support regardless of the socio-economic status of the family, income, or geographic location. The continuity of the various stages should be monitored, namely the transition from screening to diagnostic procedures, the timely implementation of the assistance program, and other activities.

Principle 2: Collaboration between family and early care professionals. The family-centered early care model aims to develop balanced partnerships between family and professionals. Collaboration between the family and the family service provider must be characterized by interaction, mutual trust, respect, honesty, shared goals, and open communication.

Principle 3: Conscious choice and decision making. It is the right of the family to make decisions. Specialists help the family obtain the necessary information, knowledge, and experience. Families are trained to make informed decisions based on the information obtained. Families need to be aware of the possible outcomes, potential benefits, and challenges of using different approaches.

Principle 4: Social and emotional support for the family. Families can receive the necessary support, knowledge, and experience in official organizations/associations (professional, parental) and public organizations, from friends, relatives, and groups united by religious views and other principles. Professionals should appreciate the importance of family well-being for the child's development, provide social support and encouragement to the family, facilitate obtaining necessary support, and refer to mental health professionals.

Principle 5: Interaction between family and child. The family and professionals cooperate to create the optimal environment for the child's communication and language development. For this purpose, everyday activities, games, and communication with the child are used. Adults provide the child with an action-packed language environment in communication with all family members, adapting their language in accordance with the child's development. The specialists respect and support the communication method chosen by the family (oral approach, kinetic speech).

Principle 6: Use of assistive technology and communications tools. Professionals working with a family with a hearing-impaired child should be aware of current technical devices to help improve the child's hearing (hearing aids, implantable systems, FM systems), provide visual support, and alternative and complementary communication. Professionals should inform families about the existing technical means and technologies used in the educational process (portable microphones, interactive whiteboards, computer and web technologies, others).

Principle 7: Qualification of professionals. Specialists should be well trained, have the necessary qualifications, and specialized knowledge and skills related to working with deaf and hard-of-hearing children of various ages and their families. Families should be able to have access to professionals with specialized knowledge and skills.

Principle 8: Teamwork. An optimally formed family-centered early intervention transdisciplinary team focuses on the family. It includes professionals experienced in supporting early assistance programs for deaf and hard-of-hearing children. The team is formed depending on the needs of the child and family. It might include specialists working in early intervention programs, specialists with knowledge and skills in working with deaf and hard-of-hearing children, including teachers of the deaf and hard of hearing, speech therapists, audiologists, social workers, and psychologists. If necessary, a physical therapist, an occupational therapist, such narrow specialists as a developmental pediatrician, a neurologist, a psychiatrist, a visual impairment specialist, and others can be included. The family is considered an equal rights member of the team.

Principle 9: Tracking the progress of the child's development. Regular monitoring is required to assess the child's individual development, family satisfaction and well-being, and the efficiency of the assistance program. If necessary,

based on the results obtained, the approaches and strategies used are modified.

Principle 10: **Control of program functioning**. The monitoring of the quality control of all the program elements is required, and monitoring the extent to which specialists adhere to accepted international standards and practices in their work.

EXAMPLES OF IMPLEMENTING THE PRINCIPLES OF EARLY ASSISTANCE FOR DEAF AND HARD-OF-HEARING CHILDREN

There is a wide variety in the planning and implementing family-centered early childhood assistance programs in different countries. This document has been applied both by professionals in countries with well-developed early care services and emerging programs. Examples of implementing this document's recommendations in some countries, namely in Upper Austria* and the United States from 2012 to 2014, are presented below [20]. This information indicates very clearly the difficulties that the colleagues from these countries faced and their solutions.

Implementation of principle 1 on ensuring early, timely, and equitable access to services. Despite the introduction of universal screening for newborn hearing in 1990 in Austria, for 20 years after that, no follow-up system was established for children who had poor screening results or failed to undergo it. In response, Upper Austrian health officials organized meetings. They collected and analyzed data on the age of deaf and hard-of-hearing children at the time of diagnosis establishment and the age of inclusion in early childhood care programs. As a result, a family tracking procedure was developed and implemented in case of an unsatisfactory result of the initial screening in the maternity hospital. If the parents do not attend an appointment, the otorhinolaryngologist contacts them. If the hearing impairment is confirmed by a diagnostic examination, then the information is immediately transmitted to the early assistance service. Finally, the specialist of this service contacts the family within 48 h.

In 2012, in the United States, 96.6% of 3,953,986 newborns were screened for primary hearing. However, 35.9% of these infants did not attend diagnostic audiological examinations, or their documents were lost. Approximately a quarter of children who should have been provided with early assistance programs were not included in them in a timely manner.

The UK audiological screening program requires at least 95% of newborns to undergo primary screening in the first month of life (age corrected for premature infants). The diagnostic stage must be completed for at least 90% of children within four weeks after their referral for diagnostics. Data from 4,645,823 children born in the UK from 2004 to 2013 showed a continuous improvement in the quality of implementation of this program. Thus, for children born in 2012–2013, primary hearing screening was performed in the first month of life for 97.5% of newborns. The average age of the diagnostic stage was 30 days; the median age for inclusion of children with hearing impairments in the care program was 50 days nationwide. Primary hearing aid for children with confirmed bilateral bradyacuasia was performed on average at 82 days of age. These data demonstrate the high efficiency of conducting initial audiological screening in the UK and follow-up measures up to the initial steps of the assistance program, such as selection and fitting hearing aids [18].

Implementation of principle 2: ensuring a partnership between family and early childhood care providers. Each of the 50 states in the USA has established and operates advisory councils to provide early assistance to deaf and hard-of-hearing children. These advisory councils include parents in most cases. The responsibilities, structure, accountability, and allocation of financial resources of these advisory councils might vary and depend on the laws of the state of their location.

Implementation of principle 3: ensuring informed choices and decision making. The assurance of this principle remains unclear. Interviews with parents and questionnaires of parents did not determine whether this principle is being implemented in any system.

Implementation of principle 4: provision of social and emotional support to the family. This support can be provided in a variety of ways by different professionals. An essential role in supporting families is played by specialists and other parents with deaf and hard-of-hearing children. In Upper Austria, parents who provide professional support to parents and immediate family members have been included in the early assistance program. They attend the initial meeting when the family is included in the program. The seminars-meetings are held, organized by psychologists and experienced parents, where issues such as "living with a child with bradyacuasia," "family communication," "brothers and sisters," and others are discussed. Regular meetings provide an opportunity to establish informal communication. Many parents

*Upper Austria is a federal state of Northern Austria

exchange contacts and visit each other. The assistance program regularly surveys the needs and well-being of parents.

In the USA, many states provide parent-to-parent support. In most cases, this support is provided immediately after the diagnosis establishment, and in some situations, after the initial screening. The Disability Research Distribution Center, as part of the National Early Childhood Assessment Project: Deaf/Hard of Hearing (NECAP), performs assessment and collection of data on the development of deaf and hard-of-hearing young children. Monitoring of the social and emotional well-being of families with deaf and hard-of-hearing young children is implemented in many countries. However, there are no standard approaches to such assessments.

Implementation of principle 5: ensuring interaction between the family and the infant. The early childhood care program helps parents create the optimal language learning environment for their children through everyday family routines. In Upper Austria, early assistance providers were trained to be more aware of the family's living conditions. An automated speech recognition device (Language Environment Analysis, LENA) can assess the quantity and quality of speech that the child hears throughout the day and vocalizations of the child [15]. This is necessary for parents to understand the quality of communication they provide to their children during a typical day. Early assistance specialists have compiled a list of strategies to improve communication. If the family chooses kinetic speech to communicate, then the early assistance professional should be fluent in kinetic speech communication skills. All early assistance professionals are required to complete a two-year kinetic speech course. Together with preschool institutions for deaf and hard-of-hearing children, kinetic speech courses are regularly held, adapted to the needs of parents of young children. In the USA, some states provide a professional who is fluent in kinetic speech and can teach kinetic speech to parents and family relatives who choose to communicate with kinetic speech.

Implementation of principle 6: use of assistive technology and communication tools. In Upper Austria, the child must be provided with devices for adequate hearing correction if the family has chosen spoken language as their primary mode of communication. Hearing aid and implant manufacturers regularly hold seminars for early care specialists on the latest advances in hearing aids. Hearing aids/implants are provided to all children in the USA. Only a small number of young children have access to assistive devices such as FM systems.

Implementation of principle 7: ensuring the qualifications of specialists. Assessment of the qualifications of early care providers is challenging. Some NECAP states in the USA are currently collecting and analyzing data related to the training of early childhood care providers. Some states require all professionals to receive specific training in hearing impairment in young children. However, so far, few states have implemented programs that guarantee the core competencies of professionals.

Implementation of principle 8: ensuring teamwork. The most effective results in the development of deaf and hard-of-hearing children can be achieved only if specialists in health care, education, and the social sphere collaborate. Upper Austria and many states in the USA have a single network of early childhood care professionals, audiologists, otorhinolaryngologists, pediatricians, preschool and school educators, and representatives of parental associations and societies for the deaf.

Implementation of principle 9: Tracking the progress of a child's development. In the USA, the NECAP project monitors developmental outcomes for deaf and hard-of-hearing children in several states. When analyzing the data within the project, it was revealed that the average coefficient of development of deaf and hard-of-hearing children is within the standard values of hearing children, while the data of the three language indicators are below the average values. However, they are within the reference limits. It has been established that the factors such as early inclusion in the assistance program (up to the age of 6 months), milder hearing loss, lack of concomitant impairment in the child, or a family with deaf or hard-of-hearing parents have a positive effect on the results of language development.

Implementation of Principle 10: Maintenance of the program control. This principle is an essential component but not widely adopted in the United States. In some states, such as Colorado, programs are monitored by an early care system using reports and expert supervision.

CONCLUSION

An international consensus statement describing these 10 principles has been translated into many world languages, including Russian [10]. This contributes to its distribution and implementation among specialists around the world. Many factors affect a child's development, including language and speech development, social and communication skills, academic performance, and mental health. Awareness of specialists working with children with hearing impairments with this document and

adherence to the principles set out allows the most effective planning and implementation of a comprehensive assistance program, thereby leveling the possible negative consequences of hearing impairment. In addition, the study of the global situation regarding the implementation of these principles is required. The document provides a framework for program collaboration worldwide to collect and analyze data that will improve the efficiency of early assistance programs for deaf and hard-of-hearing children.

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PRECOCIOUS PUBERTY IN GIRLS: A CLINICAL CASE OF IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY

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Central precocious puberty occupies an important place in the practice of a pediatric endocrinologist. If the patient reveals signs of premature sexual development, the diagnostic search is aimed at eliminating the tumor origin of both false (peripheral) and gonadotropin-dependent, or central, precocious puberty, as well as gonadotropin-independent forms of premature sexual development. Oncological alertness is important in the work of not only a pediatric endocrinologist, but also a pediatrician. In the treatment of all non-tumor forms of central precocious puberty, drugs of the group of analogues of gonadotropin-releasing hormone are used, which allows to stop the progression of sexual development, reduce the rate of bone maturation and, thereby, increase the final growth of the child. The most common idiopathic variant of central precocious puberty. The article presents a clinical case of observing a patient with an idiopathic variant of central premature sexual development during therapy with a drug from the group of analogues of gonadotropin releasing hormone of prolonged action. The classical course of the idiopathic variant of central precocious puberty with typical diagnostic difficulties in the onset of the disease, good compensation against the background of therapy with a drug from the group of agonists of gonadotropin-releasing hormone and normal puberty 6–12 months after cancellation of the therapy is demonstrated. The latter is explained by the proven reversibility of the effects of this group of drugs. The description of this clinical case, in the authors' opinion, should be of interest to doctors at the local pediatricians and pediatricians working in the medical care departments for children in educational institutions.

Keywords: precocious puberty; idiopathic central precocious puberty; GnRH agonist treatment; triptorelin.

ПРЕЖДЕВРЕМЕННОЕ ПОЛОВОЕ РАЗВИТИЕ У ДЕВОЧЕК: КЛИНИЧЕСКИЙ СЛУЧАЙ ИСТИННОГО ИДИОПАТИЧЕСКОГО ПРЕЖДЕВРЕМЕННОГО ПОЛОВОГО РАЗВИТИЯ

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Преждевременное половое развитие занимает важное место в практике детского эндокринолога. При выявлении у пациента признаков преждевременного полового развития диагностический поиск направлен на исключение опухолевого генеза как ложного (периферического), так и истинного, или центрального, преждевременного полового развития, а также гонадотропин-независимых форм преждевременного полового развития. Онкологическая настороженность важна в работе не только детского эндокринолога, но и врача-педиатра. В лечении пациентов

со всеми неопухолевыми формами центрального преждевременного полового развития используют препараты группы аналогов гонадотропин-рилизинг-гормона, что позволяет остановить прогрессирование полового развития, снизить темпы костного созревания и, тем самым, увеличить конечный рост ребенка. Наиболее часто встречается идиопатический вариант центрального преждевременного полового развития. В статье представлено клиническое наблюдение пациентки с идиопатическим вариантом центрального преждевременного полового развития. Изложено классическое течение идиопатического варианта центрального преждевременного полового развития с типичными сложностями диагностики в дебюте заболевания, хорошей компенсацией на фоне терапии препаратом из группы агонистов гонадотропин-рилизинг-гормона и нормальным половым созреванием через 6–12 мес. после отмены терапии. Описание данного клинического случая может быть интересно педиатрам и эндокринологам.

Ключевые слова: преждевременное половое развитие; идиопатическое центральное преждевременное половое развитие; лечение агонистами гонадотропин-рилизинг-гормона; трипторелин.

Precocious puberty (PP) in girls is diagnosed when all or some secondary sexual characteristics appear before eight years old. According to the current classification, there are true PP, false PP, and incomplete PP (premature thelarche, premature adrenarche, and premature menarche). The cause of true PP is the premature activation of the hypothalamic-pituitary (HT-P) system, which may be due to tumors of the central nervous system (CNS), pineal gland, organic non-neoplastic lesions of the CNS, irradiation of the brain, pathology of migration of gonadotropin-releasing hormone-secreting neurons, genetic syndromes such as Russell-Silver syndrome, or neurofibromatosis type I. Untreated primary hypothyroidism and late treatment with an excess of sex hormones in false PP also lead to true PP [16]. If the above causal factors are excluded, true idiopathic PP is diagnosed in the patient with laboratory-proven HT-P activation of ovarian function. True PP can be complete if the patient has developed all secondary sexual characteristics (enlargement of the mammary glands, hair growth in the pubic area, armpits, and the onset of menarche). True PP is considered incomplete if not all secondary sexual characteristics have appeared yet.

False PP is caused by hypersecretion of sex hormones (androgens or estrogens) without activating the HT-P system. Autonomous hypersecretion of estrogens can be caused by a tumor of the ovaries or adrenal glands or exogenous administration of estrogens. In this case, PP develops in an isosexual manner. The development of heterosexual false PP causes an excess of androgens caused by androgen-producing tumors of the ovaries or adrenal glands or impaired adrenal steroidogenesis due to various enzymatic defects, as in congenital suprarenal cortex hyperplasia (CSCH) [15].

Until a specific time, generally, before reaching the "pubertal" bone age, the McCune–Albright–Braitsev syndrome belongs to the variant of false PP. The pathology is caused by the autonomous functioning of ovarian follicular cysts. Estrogen production is associated with the pre-pubertal structure of luteinizing hormone (LH) secretion with no response to gonadotropin-releasing hormone (GRH). Later, usually with the onset of ovulatory cycles, gonadotropin-dependent puberty occurs [6, 7, 16]. McCune–Albright–Braitsev syndrome is a rare genetic disorder based on somatic mutations in the GNAS gene. Clinical signs of the disease include light brown spots with clear boundaries, localized usually on the hips, back, lower back, chest, and in places of bone deformities, and fibrous dysplasia and hyperfunction of the endocrine glands [13]. McCune–Albright–Braitsev syndrome and persistent follicular cysts in girls are classified as a separate group of gonadotropin-independent PP caused by the activation of steroid-secreting elements of the genital glands without the involvement of gonadotropins [8].

In most cases, both true and false PP, there is a significant acceleration of bone age. In the absence of timely diagnosis and therapy in patients, the growth zones are rapidly closed, which results in the formation of short stature in adulthood [4, 8, 12].

Separately, it is required to highlight such incomplete forms of PP, as premature thelarche and premature adrenarche. Premature thelarche is represented by a unilateral or bilateral development of the mammary glands that starts in infancy, more often at two years. It is not accompanied by other symptoms of sexual development. There can rarely be the development of mammillae, vaginal mucosa thickening, and estrogen-induced enlargement of the uterus. This condition is usually benign and is associated with the secretion of follicle-stimulating hormone (FSH) and the development of antral follicles to a greater extent than in the pre-pubertal control group. Unstimulated and GRH-stimulated plasma LH levels correspond to the values typical for the pre-pubertal period [6].

The diagnosis of premature adrenarche is established after ruling out false and true PP.

The term adrenarche implies a physiological process that starts in healthy individuals at the age of 6–8 years, as a rule, two years or more before activating the HT-P system and an increase in gonadotropin secretion. At this age, the secretion of dehydroepiandrosterone and androstenedione, synthesized in the reticular zone of the adrenal cortex, increases, which is not clinically manifested, except as a minor increase in the growth rate and increased secretion of apocrine sweat glands. In some children, an increase in the activity of 17,20-lyase and 17-α-hydroxylase results in the premature appearance of pubarche (hair growth in the pubic region) and terminal hair in the axillary region, which is premature adrenarche. In the international literature, this term is interpreted as excessive adrenarche [10]. Most girls with premature adrenarche have a moderate acceleration of bone age, and the level of 17-hydroxyprogesterone (17-OHP) may exceed the norm in children in the pre-pubertal period, which necessitates differential diagnostics of premature adrenarche and nonclassical form of CSCH [1, 9, 14, 17]. Despite the increase in growth rate and bone age, the final height with premature adrenarche does not change. However, the probability of polycystic ovary syndrome in adulthood is increased [6, 19]. According to Russian authors, the hormonal marker of premature adrenarche is an increased level of androstenedione [2].

According to the Federal Clinical Guidelines for the Management of Patients with PP, PP is diagnosed in stages. At stage 1, it is required to establish the presence of PP, to identify a group of incomplete forms (premature thelarche and premature adrenarche). At stage 2, it is necessary to establish a nosological variant in patients with confirmed PP to determine the therapeutic approach [8].

Modern diagnostic standards require a short-acting GRH stimulation test. This test enables the differentiation of gonadotropin-dependent forms of PP from gonadotropin-independent and isolated thelarche in girls. In treating all variants of gonadotropin-dependent PP, including true idiopathic PP, drugs from the group of GRH analogs with prolonged action are effectively used, which desensitize the pituitary gland to the stimulating effect of its gonadotropin-releasing hormone. The drugs from this group, such as Diferelin 3.75 mg, Diferelin 11.25 mg, Decapeptil depot 3.75 mg with triptorelin as an active ingredient, and Lyukrin 3.75 mg and Lyukrin depot 11.25 mg (active ingredient leuprorelin), are registered in Russia.

After magnetic resonance imaging (MRI) of the brain and pituitary gland, organic tumor causes of PP and hamartoma of the hypothalamic region can be ruled out [5]. It should be noted that hypothalamic hamartoma is not a tumor but is a congenital ectopia of hypothalamic tissue and causes PP in 70% of cases. In addition to PP, hamartomas of hypothalamic localization are accompanied by neurological disorders and behavioral disorders and can cause diabetes insipidus [8].

The drug of choice in the treatment of true idiopathic PP was triptorelin 3.75 mg, which suppresses effectively the secretion of gonadotropins and sex steroid hormones, which, in turn, stops the development of secondary sexual characteristics and leads in some patients to their regression, contributes to the regulation of patient behavior. Long-term therapy with triptorelin effectively regulates bone age in patients and ensures optimal stature in children with true PP [3, 8, 18].

The criteria for the efficiency of therapy with drugs from the group of long-acting analogs of GRH, which include triptorelin (3.75 mg), can be considered as a decrease in the growth rate to the age norm, the absence of progression of sexual development, or regression of secondary sexual characteristics, an increase in bone age by no more than one year within the current year. Low basal levels of LH and estradiol in girls may be considered the efficiency criterion initially elevated levels of these hormones. With the low efficiency, 3–6 months after the start of treatment, the test with short-acting triptorelin is repeated with anticipated LH release of no more than 4 U/L during the test [8].

As an example of a differential diagnostic algorithm, selection of treatment, and further follow-up monitoring of premature sexual development in girls, we present a clinical case of a patient with true idiopathic PP. The results of follow-up monitoring of patients with true PP in St. Petersburg revealed that the idiopathic variant accounts for 50% of cases with this pathology [11].

Patient P., 7.5 years old, was admitted for examination at the endocrine department of the clinic due to the premature appearance and progression of secondary sexual characteristics.

At the time of hospitalization, the case history revealed an increase in mammary glands in the girl since the age of 4.5 years old, which at the outpatient stage was regarded as an incomplete form of PP, namely isolated thelarche. At the age of 6.5 years old, due to a gradual increase in the mammary glands, an ultrasound scan of the pelvic organs was performed and showed the size of the uterus and ovaries corresponding to 11 years. Hormonal examination revealed basal LH 1.5 mMu/ml,

FSH 5.26 mMu/ml, and estradiol 49.6 pmol/l, corresponding to stage II of puberty on the Tanner scale. Hospitalization in the pediatric endocrine department was recommended. With the appearance and progression of pubarche, the patient was immediately hospitalized.

Upon admission, height was 134 cm (+2.5 SDS), body weight was 30.5 kg (+0.25 SDS weight for height). Body mass index (BMI) was 16.9 kg/m^2 (±1 SDS). Sexual formula on the Tanner scale was AI PII–III MaIII Me (–). The growth rate was 14 cm per year. Bone age corresponded to 9.5 years. Ultrasound examination (US) of the pelvic organs (uterus 4.5 × 1.8 × 1.5 cm; left ovary 2.0–1.4–1.9 cm, 4–5 follicles up to 3 mm; right ovary 2.0–1.4–1.8 cm, 3–5 follicles up to 4 mm), which corresponded to 11 years. Hormonal examination showed the basal level of LH hormones 3.3 mIU/ml, FSH 4.9 mIU/ml, and estradiol 62 pmol/l, 17-OHP 0.85 ng/ml. There were no indications for an adrenocorticotropic hormone test to rule out the nonclassical form of CSCH based on the 17-OHP value obtained. Ultrasound of the adrenal glands revealed no pathology.

The standard for diagnosing true PP is a short-acting GRH test [8, 15]. After a stimulation diagnostic test (0.1 mg of triptorelin was injected subcutaneously), the maximum increase in the levels of the hormones under study was LH 67.9 mMe/ml and FSH 21.1 mMe/ml.

MRI of the brain and pituitary gland showed no MRI data on the presence of space-occupying paraplasms in the chiasmo-sellar region. True idiopathic PP was diagnosed in the patient.

In a patient with clinical manifestations of PP, the diagnosis of true idiopathic premature puberty was established at 7.5 years, and therapy with a drug from the group of long-acting GRH analogs triptorelin (3.75 mg) was started according to the scheme at a dose of 3.75 mg intramuscularly one time in 28 days. The conditions for treatment with a long-acting triptorelin drug are continuity of therapy, calendaring, and adherence to the injection regimen. The patient did not violate the recommended triptorelin injection regimen.

Subsequently, the patient was examined on an outpatient basis. The case follow-up showed that the patient stopped the progression of secondary sexual characteristics; with palpation of the mammary glands, the gland tissue was slightly increased, mainly due to the fatty component. On day 26, after administration of triptorelin (3.75 mg), LH level was 0.2 mIU/ml, FSH was 0.6 mIU/ml, which indicated a positive effect of therapy. Ultrasound of the pelvic organs showed that the size of the uterus and ovaries corresponded to the age of 9 years. In the first year of treatment, the growth rate was 6.5 cm. The progression of bone age slowed down, which after one year of therapy corresponded to 10 years.

In the subsequent second year of therapy, the patient's growth rate was 4.5 cm per year. Bone age corresponded to 10.5 years. Sexual formula on the Tanner scale was AI PIII Ma II–III Me (–). Since androgenization has increased, and the growth rate over the past six months of follow-up was 1 cm, it was decided to cancel hormonal therapy. At the time of completion of treatment, the girl was nine years old and nine months old. Her physical development was assessed as high and harmonious, with a height of 146 cm (+2.5 SDS), a bodyweight of 40.5 kg (+0.9 SDS weight for height), and a BMI of 18.9 kg/m^2 (+1.2 SDS).

One year after the end of therapy with triptorelin, an ultrasound scan of the pelvic organs revealed the size of the uterus and ovaries corresponding to 9 years. X-ray data of her hands showed the bone age corresponding to 11.5 years. Her sex hormone levels (LH 5.45 mIU/ml, FSH 7.16 mIU/ml, and estradiol 49.5 pmol/L) corresponded to stage III of puberty by the Tanner scale (AIII PIV Ma III Me (–)). Her growth rate was 8 cm/year. Menarche was registered 15 months after discontinuation of therapy.

A control medical examination, which was performed 30 months after completion of therapy with triptorelin (3.75 mg), when the girl was 12 years old and three months, showed that the patient's menstrual function became regular 10–12 months after menarche. The levels of sex hormones taken on day 5 of the menstrual cycle were 2.61 mIU/ml of LH, 6.9 mIU/ml of FSH, and 26.1 pmol/l of estradiol. Ultrasound of the pelvic organs showed that the size of the uterus and ovaries corresponded to 12.5 years; single follicles with a diameter of up to 5 mm were located in the ovaries along the periphery. The physical development of the patient was assessed as above average and harmonious. Her height was 160 (+1.6 SDS), and her body weight was 50.5 kg (+0.1 SDS). A feminine physique was formed. Sexual development was AIII PIV Ma IV Me (+). Regular menstruation after 28–30 days corresponded to stage IV on the Tanner scale.

The initiation of therapy with a long-acting triptorelin drug in our patient enabled us to block the progression of the gonadarche and slow down the early closure of bone growth zones. The duration of therapy was two years, three months. At the end of therapy, the child's height was two years ahead

of the average height by age and balanced with bone age. After completion of therapy, gradual development of secondary sexual characteristics was registered. Menarche appeared 15 months after completion of therapy with triptorelin (3.75 mg). Then, 2.5 years after the completion of therapy, the patient's physical and sexual development and the results of hormonal and instrumental research methods corresponded to her passport age.

CONCLUSION

Thus, true idiopathic PP was diagnosed in the patient with the onset of PP at 4.5 years of age and the progression of the disease from 6.5 years of age. Timely diagnostics and efficient and safe therapy contributed to the normalization of the physiological parameters of growth and sexual development of the child. The latter is explained by the proven reversibility of a group of drugs of GRH agonists in treating central forms of PP, including true idiopathic PP. The concern is that some other forms of gonadotropin-dependent PP at the onset start to manifest in the same way as true idiopathic PP. Unfortunately, there is faster disease progression, the closure of growth zones, and the risk of short stature in adulthood. Pediatricians, in the course of scheduled follow-up monitoring, may notice the period of initial manifestations of PP in children, manifested by an increase in mammary glands in girls, an increase in the size of testicles in boys, and a pronounced acceleration of the growth rate, which is very important for early disease diagnosis.

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